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SYSTEMIC MANIFESTATIONS OF SJÖGREN'S SYNDROME

SISTEMSKE MANIFESTACIJE SJÖGRENVOG SINDROMA

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ABSTRACT

Sjögren's syndrome (SS) is a heterogeneous disease which, in the majority of cases, includes a mild clinical course. However, in some patients it takes on a severe form with numerous systemic manifestations and results in an adverse outcome. Systemic manifestations occur in approximately 25% of patients with primary Sjögren's syndrome (pSS). The clinical presentation of systemic manifestations of SS is very diverse and can involve any organ system. Systemic manifestations can occur due to lymphocytic infiltration of organs or proliferation of B lymphocytes and deposition of immune complexes.

Fatigue is the most common systemic manifestation. The most significant cutaneous manifestations of the disease are palpable purpura, ulcerations, urticarial vasculitis and leukocytoclastic vasculitis. Musculoskeletal manifestations can range from arthralgias to erosive arthritis. Pulmonary involvement may include symptoms such as nonspecific interstitial pneumonia with fibrosis and tracheobronchial disease. Renal changes are observed in 10% to 30% of patients with SS. Tubulointerstitial nephritis, type 1 renal tubular acidosis and nephrogenic diabetes insipidus can develop as a consequence of lymphocytic infiltration. Less often, the inflammatory process affects the glomeruli which leads to glomerulonephritis. Liver diseases are found in approximately 20% of patients with SS and their symptoms usually include inflammation of intrahepatic bile ducts resembling primary biliary cirrhosis. The manifestations of peripheral nervous system involvement include sensorimotor axonal polyneuropathy, mononeuritis multiplex, neuropathies and radiculopathies. Optic neuropathy, hemiparesis, movement disorders, cerebellar syndromes, transient ischemic attacks, transverse myelitis (less commonly), and progressive myelopathy have been described as central nervous system changes. Symptoms of vasculitis can range from mononeuritis multiplex to intestinal ischemia and dysfunction of the affected organs. The development of non-Hodgkin's B-cell lymphoma is a major complication of the disease which occurs in 5%–7% of patients with SS.

KEYWORDS: Sjögren's syndrome, systemic manifestations

SAŽETAK

Sjögrenov sindrom (SS) je heterogena bolest koja se najčešće prezentira blagim kliničkim tijekom. Međutim, u manjeg dijela bolesnika poprima teški oblik bolesti s brojnim sistemskim manifestacijama i mogućim lošim ishodom. Sistemske manifestacije se pojavljuju u približno 25% bolesnika s primarnim Sjögrenovim sindromom (pSS). Klinička prezentacija sistemskih očitovanja SS-a vrlo je raznolika i može zahvatiti bilo koji organski sustav. Mogu nastati uslijed limfocitne infiltracije organa ili proliferacije limfocita B i odlaganja imunih kompleksa.

Umor je najčešća sistemska manifestacija. Najznačajnije dermatološke manifestacije bolesti su palpabilna purpura, ulceracije, urtikarijalni i leukocitoklastični vaskulitis. Koštano-mišićne manifestacije u bolesnika s pSS-om pojavljuju se u širokom rasponu od artralgija do erozivnog artritisa. Zahvaćenost pluća može se očitovati kao nespeci-

fična intersticijska pneumonija s fibrozom i traheobronhalna bolest s povećanom reaktivnošću bronha, bronhiektazijama, bronhiolitom ili ponavljajućim respiratornim infekcijama. Bubrežne promjene se uočavaju u 10–30% bolesnika sa SS-om. Kao posljedica limfocitne infiltracije razvija se tubularni intersticijski nefritis, renalna tubularna acidoza tipa I, nefrogeni dijabetes insipidus i ostali poremećaji tubularne funkcije. Znatno rjeđe upalni proces zahvaća glomerule dovodeći do glomerulonefritisa. Jetreni poremećaji se nalaze u oko 20% bolesnika sa SS-om, a najčešće se očituju upalnim promjenama intrahepatalnih žučnih vodova nalikujući primarnoj bilijarnoj cirozi. Zahvaćenost perifernoga živčanog sustava manifestira se senzomotornom aksonalnom polineuropatijom, senzornom ataksičnom i autonomnom neuropatijom, mononeuritisom multipleks, kranijalnim neuropatijama i radikulopatijama. Od promjena središnjega živčanog sustava opisuju se optička neuropatija, hemipareza, poremećaji pokreta, cerebelarni sindromi, tranzitorne ishemijske atake, rjeđe transverzalni mijelitis i progresivna mijelopatija. Simptomi vaskulitisa mogu varirati od mononeuritisa multipleksa do ishemije crijeva i disfunkcije zahvaćenih organa. Razvoj non-Hodgkinovog limfoma B-stanica predstavlja glavnu komplikaciju bolesti i pojavljuje se u 5–7% bolesnika sa Sjögrenovim sindromom.

KLJUČNE RIJEČI: Sjögrenov sindrom, sistemske manifestacije

INTRODUCTION

Sjögren's syndrome (SS) is a chronic autoimmune disease of the exocrine glands characterised by lymphocytic infiltration of the affected glands. The disease can occur independently, and, in that case, it is known as primary Sjögren's syndrome (pSS). It is a heterogeneous autoimmune disease which includes a broad range of clinical features, from the dryness syndrome, as the main feature of the disease, to numerous systemic or extraglandular manifestations (1). When it occurs as part of other autoimmune diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) or progressive systemic sclerosis (SSc), it is called secondary Sjögren's syndrome.

The clinical presentation of systemic manifestations of pSS is very diverse, as any organ system can be involved (2). Systemic manifestations occur in approximately 25% of patients with pSS (3), and may arise as a result of lymphocytic infiltration of organs or proliferation of B lymphocytes and deposition of immune complexes (4). While the dryness syndrome primarily affects quality of life and localised complications, systemic involvement determines disease prognosis (5).

Musculoskeletal system

Articular involvement occurs in approximately 30%–60% of patients with pSS. Arthritis is mostly polyarticular, peripheral and symmetrical. It is usually not deforming or erosive, and it affects the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints and wrists, while changes such as Jaccoud arthropathy (Figure 1) or sacroiliitis are much less common. Synovitis is generally mild; however, articular involvement is a predictor of other systemic involvement (6, 7). Myalgia and weakness are common symptoms in patients with pSS, but clinically significant myositis is rare. In the study conducted by Lindvall et al., (8) myalgia was described in approximately 30% of patients with pSS and it was determined that 27% of patients fulfil the diagnostic criteria for fibromyalgia,

UVOD

Sjögrenov sindrom (SS) je kronična autoimuna bolest žlijezda s vanjskim izlučivanjem obilježena limfocitnim nakupinama u zahvaćenim žlijezdama. Bolest se može javiti samostalno i tada se naziva primarni Sjögrenov sindrom (pSS). Radi se o heterogenoj autoimunoj bolesti sa širokim rasponom kliničkih obilježja, od sindroma suhoće kao glavne odlike bolesti do brojnih sistemskih odnosno izvanžljezdanih manifestacija (1). Kada se javlja u sklopu drugih autoimunih bolesti poput reumatoidnog artritisa (RA), sistemskog eritemskog lupusa (SLE) ili progresivne sistemske skleroze (SSc) naziva se sekundarnim Sjögrenovim sindromom.

Klinička prezentacija sistemskih očitovanja pSS-a vrlo je raznolika jer može biti zahvaćen bilo koji organski sustav (2). Sistemske manifestacije se pojavljuju u približno 25% bolesnika s pSS-om (3), a mogu nastati uslijed limfocitne infiltracije organa ili proliferacije limfocita B i odlaganja imunih kompleksa (4). Dok sindrom suhoće primarno utječe na kvalitetu života i lokalizirane komplikacije, sustavna zahvaćenost određuje prognozu bolesti (5).

Koštano-mišićni sustav

Zglobovi su zahvaćeni u 30–60% bolesnika s pSS-om. Artritis je uglavnom poliartikularan, periferan i simetričan. Obično nije deformirajući niti eroziv, a zahvaća metakarpofalangealne (MCP), proksimalne interfalangealne (PIP) zglobove i zapešća, dok su promjene poput Jaccoudove artropatije (slika 1) ili sakroileitisa znatno rjeđe. Sinovitis je općenito blag, međutim, zahvaćenost zglobova je prediktor za druga sustavna zahvaćanja (6, 7). Mijalgija i slabost česti su simptomi u bolesnika s pSS-om, ali klinički značajan miozitis je rijedak. U istraživanju Lindvall i sur. (8) mijalgija je opisana u oko 30% bolesnika s pSS-om i utvrđeno je da 27% bolesnika ispunjava dijagnostičke kriterije za fibromijalgiju, dok su Moerman i sur. dokazali polimiozitis u tek oko 4% bolesnika (9). Dokazana je i

while Moerman et al. have proved the occurrence of polymyositis in only about 4% of patients (9). An increased frequency of SS among patients with fibromyalgia has also been proven (10).

Cutaneous manifestations

Cutaneous manifestations of SS include the dryness syndrome, immune-mediated inflammatory diseases such as vasculitis, and other associated disorders. The symptom of dry skin was observed in 50% of patients with SS and it is unclear whether it occurs due to lymphocytic infiltration of the glands or sweating dysfunction (11). Annular erythema is one of the most specific cutaneous manifestations of SS. It occurs in approximately 9% of patients and is clinically identical to erythema in patients with subacute cutaneous lupus erythematosus (SCLE) (12). It has sharply demarcated borders with central clearing, it is photosensitive and usually located on the head and upper body. It heals without scarring and atrophy, but hypopigmented lesions may remain. Perivascular lymphocytic infiltrates, less frequent epidermal changes and positive indirect immunofluorescence are detected through histopathology (13). Raynaud's phenomenon is another manifestation of SS, with a prevalence of approximately 30%, and it can occur years before the diagnosis (14). The manifestations of cutaneous vasculitis include palpable purpura (Figure 2), leukocytoclastic or urticarial vasculitis, and the lesions are predominantly located on the lower limbs (15). Leukocytoclastic vasculitis, hypocomplementemia and hepatitis C are associated with the presence of cryoglobulins in the serum of patients with pSS (16). Vasculitis occurs in approximately 10% of patients with SS (17), and in the study conducted by Kyle et al. it was found that approximately half of all patients from a large group of patients with hyperglobulinemic purpura were diagnosed with SS (18). Cutaneous purpura in patients with SS is associated with the involvement of the central nervous system (CNS), as well as pulmonary involvement, development of lymphoma and increased mortality.(19, 20).

Pulmonary involvement

Pulmonary involvement is defined by the presence of respiratory symptoms, mainly chronic cough or dyspnoea, which are associated with altered pulmonary diagnostic tests (pulmonary function tests and radiographic testing). The frequency of respiratory symptoms in patients with SS varies from 9% to 75%, while clinically significant manifestations occur in 9% to 12% of patients. Respiratory symptoms may occur as a result of glandular damage or diffuse lymphocytic infiltration of the respiratory tract. The reduction or disappearance of secretions in the respiratory tract causes



FIGURE 1. Jaccoud arthropathy in a patient with Sjögren's syndrome

SLIKA 1. Jaccoudova artropatija u bolesnice sa Sjögrenovim sindromom



FIGURE 2. Purpura in a patient with Sjögren's syndrome

SLIKA 2. Purpura u bolesnica sa Sjögrenovim sindromom.

povećana učestalost SS-a među oboljelima od fibromijalgije (10).

Koža

Kožne manifestacije SS-a uključuju sindrom suhoće, imunološki posredovana upalna stanja poput vaskulitisa te druge pridružene poremećaje. Suha koža je zabilježena u 50% bolesnika sa SS-om i nejasno je nastaje li uslijed limfocitne infiltracije žlijezda ili disfunkcionalnog znojenja (11). Prstenasti (anularni) eritem jedno je od najspecifičnijih kožnih obilježja SS-a, pojavljuje se u oko 9% oboljelih i klinički je identičan eritemu u bolesnika sa subakutnim kožnim sistemskim lupusom (scLE) (12). Oštro je ograničen sa središnjom blijedom zonom, fotosenzitivan i obično smješten na glavi i gornjem dijelu tijela. Zacijeljuje bez stvaranja ožiljka i atrofije, ali mogu zaostati hipopigmentacije. Histopatološki se otkrivaju perivaskularni limfocitni infiltrati, rjeđe epidermalne promjene i pozitivna indirektna imunofluorescencija (13). Raynaudov fenomen je još jedno obilježje SS-a, s prevalencijom od oko 30%, a može se pojaviti godinama prije postavljanja dijagnoze bolesti (14). Kožni vaskulitis se može manifestirati palpabilnom purpustom (slika 2), leukocitoklastičnim ili urtikarijalnim vaskulitisom, a lezije su pretežno smještene na donjim udovima (15). Leukocitoklastični vaskulitis, hipokomplementemija i hepatitis C povezani su s pri-

damage to the mucociliary apparatus and difficult expectoration, which can lead to infections. Consequently, bronchiectasis, bronchiolitis, recurrent respiratory infections or bronchial hyperresponsiveness may occur. Interstitial lung disease (ILD) occurs in 8%–38% of patients with SS (21). The most common manifestation of ILD is nonspecific interstitial pneumonia with fibrosis (NSIP). Changes such as bronchiolitis obliterans organizing pneumonia (BOOP), usual interstitial pneumonia (UIP) and lymphocytic interstitial pneumonia (LIP) are less common. Through high-resolution computed tomography (HRCT) of the lungs, bronchiectasis, bronchiolar deformations, and interstitial changes such as ground-glass opacity are most often detected, while nodules, interlobular septal thickening, and reticular pattern are less frequently observed. The presence of signs of lung involvement detected through HRCT or abnormalities found through pulmonary function tests present a risk factor for mortality in patients with SS. (22).

Renal involvement

Studies of renal involvement in SS show significant differences in prevalence and indicate that the level of renal involvement ranges from 4.2% to 67%, which can be explained by differences in diagnostic criteria and research protocols. Tubulointerstitial nephritis (TIN), which is histopathologically characterised by peritubular lymphocyte infiltration and fibrosis, is the most common renal manifestation in patients with SS which rarely leads to renal failure. Renal tubular acidosis (RTA) is the main clinical presentation of TIN and is caused by damage to the renal tubules resulting in acid retention or bicarbonate loss. Its main manifestations include weakness or paralysis due to potassium loss, renal colic due to nephrocalcinosis and polyuria/polydipsia due to nephrogenic diabetes insipidus (NDI) (23). Glomerular disease is most often the result of immune complex deposition in the kidneys and is more often associated with the development of lymphoma than it is with the occurrence of tubulointerstitial disease. (24). Clinical presentations of glomerulonephritis include proteinuria, nephrotic syndrome, haematuria, arterial hypertension, and renal failure. Histopathological findings of kidney biopsies mainly reveal membranoproliferative, proliferative or membranous glomerulonephritis. The presence of glomerulonephritis in patients with SS significantly contributes to the increase in morbidity and mortality rates and affects disease prognosis(25).

GI system involvement

Gastrointestinal manifestations in patients with SS include dysphagia, dyspepsia, nausea, and epigastric

sutnošću krioglobulina u serumu oboljelih od pSS-a (16). Vaskulitis se pojavljuje u oko 10% bolesnika sa SS-om (17), a Kylea i sur. su utvrdili da među velikom skupinom bolesnika s hiperglobulinemijskom purpustom oko polovica boluje od SS-a (18). Kožna purpura se u bolesnika sa SS-om povezuje sa zahvaćanjem središnjega živčanog sustava (CNS), pluća, razvojem limfoma i povećanom smrtnošću (19, 20).

Pluća

Zahvaćenost pluća se definira prisutnošću respiratornih simptoma, uglavnom kroničnog kašlja ili zaduhe, koji su povezani s promijenjenim plućnim dijagnostičkim testovima (funkcionalnim i radiografskim). Učestalost respiratornih simptoma u bolesnika sa SS-om varira od 9 do 75%, dok se klinički značajne manifestacije pojavljuju u 9 do 12% bolesnika. Do pojave respiratornih simptoma može doći uslijed žljezdastog oštećenja ili difuzne limfocitne infiltracije dišnih puteva. Smanjenje ili nestanak sekreta u dišnim putovima uzrokuje oštećenje mukocilijarnog aparata i otežano iskašljavanje, što pogoduje infekcijama. Posljedično se mogu javiti bronhiektazije, bronhiolitis, ponavljane respiratorne infekcije ili bronhalne hiperreaktivnosti. Intersticijska bolest pluća (ILD) javlja se u 8–38% bolesnika sa SS-om (21). Najčešća manifestacija ILD-a je nespecifična intersticijska pneumonija s fibroznim promjenama (NSIP). Promjene poput organizirane upale pluća (BOOP), uobičajene intersticijske upale pluća (UIP) i limfocitnoga intersticijskog pneumonitisa (LIP) su rjeđe. Na kompjutoriziranoj tomografiji pluća visoke rezolucije (HRCT) najčešće se opisuju bronhiektazije, bronhiolarne deformacije i promjene intersticija poput „mliječnog stakla“, dok se čvorići, interlobularna septalna zadebljanja i retikularni crtež rjeđe opisuju. Prisutnost znakova zahvaćenosti pluća na HRCT-u ili poremećaj plućnih funkcionalnih testova predstavlja čimbenik rizika smrtnog ishoda u bolesnika sa SS-om (22).

Bubrezi

Istraživanja zahvaćenosti bubrega u SS-u pokazuju velike razlike u prevalenciji te pokazuju da su bubrezi zahvaćeni od 4,2 do 67%, što se objašnjava razlikama u dijagnostičkim kriterijima i protokolima istraživanja. Tubularni intersticijski nefritis (TIN), koji je histopatološki obilježen peritubularnom infiltracijom limfocita i fibrozom, najčešća je bubrežna manifestacija u bolesnika sa SS-om i rijetko dovodi do zatajivanja bubrežne funkcije. Renalna tubularna acidoza (RTA) jest glavna klinička prezentacija TIN-a, a nastaje zbog oštećenja bubrežnih tubula koje za posljedicu ima zadržavanje kiselina ili gubitak bikarbonata. Uglavnom se očituje slabošću ili paralizom zbog gubitka kalija, bubrežnim kolikama zbog nefrokalcinoze te poliuri-

pain, which may be associated with hyposalivation, decreased oesophageal motility, gastritis, and decreased stomach acid production. Patients with SS are more susceptible to gastroesophageal reflux disease (GERD) due to the lack of saliva, which has a neutralising effect on stomach acid (26). In patients with SS and patients who experience symptoms of gastritis, *Helicobacter pylori* infection should be ruled out, especially due to the connection with MALT lymphoma (extranodal marginal zone lymphoma) (27). Abnormal values of liver enzymes, after excluding the hepatotoxic effect of drugs and fatty liver, are most often associated with disorders such as hepatitis C virus (HCV) infection, autoimmune hepatitis, primary biliary cirrhosis, or nonspecific hepatitis (28). Distinguishing between viral and autoimmune aetiology of liver disease in these patients is extremely important since they require different therapeutic approaches and have different prognoses. Chronic HCV infection is the main cause of hepatic involvement in patients from the Mediterranean region, while chronic hepatitis B virus (HBV) infection is a more common cause of hepatic involvement in patients from Asian countries (29, 30). After the exclusion of viral hepatitis, the second most common cause of liver disease in pSS is primary biliary cirrhosis (PBC) (31). It is believed that immune-mediated injury to the epithelium of the bile ducts occurs, which is histologically characterised by inflammation composed of clusters of lymphoid cells and/or granulomas. The prevalence of primary biliary cirrhosis (PBC) in patients with pSS is high and ranges from 4% to 9%. This may lead to the conclusion that both diseases share common etiopathogenetic mechanisms, which is why they are described as autoimmune epithelitis (32). The presence of antimitochondrial antibodies (AMA) in the serum of patients with SS is a risk factor for the development of PBC during a five-year period (31).

Nervous system involvement

Neurological complications are observed in approximately 20% of patients with pSS, they are manifested by involvement of the peripheral and central nervous system and may be associated with vasculitis (33). The prevalence of peripheral neuropathy varies from 20% to 60% and may precede the diagnosis of the syndrome. Its most common form is peripheral sensory neuropathy (PSN) and it is considered a characteristic neurological feature of SS. Patients report symmetric and distal paresthesias, neuropathic pain and a burning sensation in the feet, while reduced or absent deep tendon reflexes can be detected through clinical examination (34). Cranial nerves can also be damaged. The cochlear nerve is often affected, resulting in hearing loss

jom/polidipsijom zbog nefrogenog dijabetesa insipidusa (23). Glomerularna bolest je najčešće rezultat odlaganja imunokompleksa u bubrežima i češće je povezana s razvojem limfoma od tubulointersticijske bolesti (24). Kliničke prezentacije glomerulonefritisa uključuju proteinuriju, nefrotski sindrom, hematuriju, arterijsku hipertenziju i zatajivanje funkcije bubrega. Patohistološki nalazi bioptata bubrega uglavnom otkrivaju membranoproliferativni, proliferativni ili membranski glomerulonefritis. Prisutnost glomerulonefritisa u bolesnika sa SS-om značajno pridonosi povećanju stope morbiditeta i mortaliteta te utječe na prognozu bolesti (25).

Probavni sustav

Gastrointestinalne manifestacije u bolesnika sa SS-om uključuju disfagiju, dispepsiju, mučninu i bol u epigastriju, što može biti povezano s hiposalivacijom, smanjenim motilitetom jednjaka, gastritisom i smanjenom proizvodnjom želučane kiseline. Bolesnici sa SS-om podložniji su nastanku gastroezofagealnog refluksa zbog nedostatka sline koja ima neutralizirajući učinak na želučanu kiselinu (26). U bolesnika sa SS-om i simptomima gastritisa potrebno je isključiti infekciju *Helicobacterom pylori*, osobito zbog povezanosti s MALT limfomom (ekstranodalni limfom marginalne zone) (27). Poremećene vrijednosti jetrenih enzima, nakon isključenja hepatotoksičnog učinka lijekova i masne jetre, najčešće su povezane s poremećajima poput infekcije virusom hepatitisa C (HCV), autoimunog hepatitisa, primarne bilijarne ciroze ili nespecifičnog hepatitisa (28). Razlučivanje virusne i autoimune etiologije bolesti jetre u ovih bolesnika izuzetno je važno, budući da zahtijevaju različite terapijske pristupe i imaju različite prognoze. Kronična HCV infekcija glavni je uzrok zahvaćenosti jetre u bolesnika s područja Mediterana, dok je kronična infekcija virusom hepatitisa B (HBV) češći uzrok zahvaćenosti jetre u bolesnika iz azijskih zemalja (29, 30). Nakon isključenja virusnog hepatitisa, primarna bilijarna ciroza (PBC) jest sljedeći najčešći uzrok bolesti jetre u pSS-u (31). Smatra se da dolazi do imunološki posredovanog oštećenja epitela žučnih kanala, što je histološki obilježeno upalom koja se sastoji od nakupina limfoidnih stanica i/ili granuloma. Prevalencija PBC-a u bolesnika s pSS-om je visoka i kreće se od 4% do 9%. To može upućivati na zaključak da obje bolesti dijele zajedničke etiopatogenetske mehanizme, zbog čega se opisuju kao autoimuni epitelitis (32). Prisutnost antimitochondrijskih protutijela (AMA) u serumu bolesnika sa SS-om predstavlja rizični čimbenik razvoja PBC-a tijekom petogodišnjeg razdoblja (31).

Živčani sustav

Neurološke komplikacije opažene su u oko 20% bolesnika s pSS-om, a očituju se zahvaćanjem perifernog

and vestibular symptoms, and disorders of the trigeminal and facial nerves are common. Other neurological manifestations in SS include painful sensory neuropathy, multiple mononeuropathy, polyradiculopathy, and autonomic neuropathy. Central nervous system manifestations include diffuse and focal brain and spinal cord lesions, subacute aseptic meningitis, chorea, and optic neuritis. Estimates of the prevalence of these manifestations range widely from 8% to 40%. Patients with pSS often show cognitive changes with poor concentration and memory as well as visual-spatial disorders and long-term or short-term memory loss with often present depressive disorders (33).

Haematological system involvement

Haematologic diseases are observed in approximately 5%–15% of patients with pSS and they most often include leukopenia and thrombocytopenia, and haemolytic anaemia with a positive direct antiglobulin (Coombs) test can also be observed (35). Lymphomas occur in approximately 5% of patients, and it is considered that patients with SS have a 20 to 40 times higher risk of lymphoma than those that do not have SS. Non-Hodgkin's lymphoma is considered the most severe SS complication (36), and in a study conducted by Ioannidis et al. it was found that 20% of mortality cases in patients with pSS can be attributed to lymphoma (20). According to some studies, various infectious agents, such as *Helicobacter pylori*, human herpesvirus and Epstein-Barr virus, are associated with the development of lymphoma in patients with pSS (1). Lymphoproliferative neoplasms are almost exclusively of B cell lineage. Most lymphomas are extranodal, such as lymphoma connected with mucosa-associated lymphoid tissue (MALT – extranodal marginal zone B-cell lymphoma), and salivary glands are the most common target. Permanent enlargement of the parotid gland, peripheral lymphadenopathy, palpable purpura, cryoglobulinemia and low complement C4 levels are predictors of the development of lymphoma, and their simultaneous presence further increases the risk of its occurrence (37). With regard to the risk of developing lymphoma, it was proposed that patients with SS be divided into two groups. The first group includes low-risk patients without simultaneous presence of palpable purpura and low complement C4 levels. The second group that includes patients with simultaneous presence of the mentioned features has a high risk of developing lymphoma and an adverse prognosis (20).

CONCLUSION

Sjögren's syndrome is a relatively prevalent autoimmune disease with a broad range of clinical manifesta-

i središnjeg živčanog sustava te mogu biti povezane s vaskulitisom (33). Prevalencija periferne neuropatije varira od 20 do 60% i može prethoditi dijagnozi sindroma. Najčešći oblik je periferna senzorna neuropatija (PSN) i smatra se karakterističnim neurološkim obilježjem SS-a. Bolesnici prijavljuju simetrične i distalne parestezije, neuropatsku bol i osjećaj pečenja stopala, dok se kliničkim pregledom mogu dokazati smanjeni ili odsutni duboki tetivni refleksi (34). Kranijalni živci također mogu biti oštećeni. Kohlearni živac je često zahvaćen, što rezultira gubitkom sluha i vestibularnim simptomima, a često se javljaju poremećaji trigeminalnog i ličnog živca. Ostale neurološke manifestacije u SS-u uključuju bolnu senzornu neuropatiju, multiplu mononeuropatiju, poliradiculopatiju i autonomnu neuropatiju. Manifestacije središnjega živčanog sustava uključuju difuzne i fokalne lezije mozga i leđne moždine, subakutni aseptični meningitis, koreju i optički neuritis. Procjene prevalencije ovih manifestacija kreću se u širokom rasponu od 8% do 40%. Bolesnici s pSS-om često pokazuju kognitivne promjene s lošom koncentracijom i pamćenjem te vizualno-prostornim poremećajima i deficite dugotrajnog ili kratkoročnog pamćenja uz često prisutne depresivne poremećaje (33).

Hematološki sustav

Hematološki poremećaji uočeni su u približno 5–15% bolesnika s pSS-om i najčešće uključuju leukopeniju i trombocitopeniju, a može se uočiti i hemolitička anemija s pozitivnim izravnim antiglobulinskim (Coombsovim) testom (35). Limfomi se pojavljuju u oko 5% bolesnika te se smatra da bolesnici sa SS-om imaju 20 do 40 puta veći rizik od limfoma od onih bez SS-a. Non-Hodgkinov limfom smatra se najtežom komplikacijom SS-a (36), a Ioannidis i sur. su otkrili da se 20% smrtnosti u bolesnika s pSS-om može pripisati limfomu (20). Prema nekim istraživanjima, različiti se infektivni uzročnici, poput *Helicobacteria pylori*, humanog herpesvirusa i Epstein-Barrova virusa povezuju s nastankom limfoma u bolesnika s pSS-om (1). Limfoproliferativne neoplazme su gotovo isključivo B-stanične linije. Većina limfoma je ekstranodalna, poput limfoma povezanog s limfnim tkivom sluznice (MALT – ekstranodalni B-stanični limfom marginalne zone, engl. *mucosa-associated lymphoid tissue*), a najčešće sijelo su žlijezde slinovnice. Trajno uvećanje parotida, periferna limfadenopatija, palpabilna purpura, krio-globulinemija i niske vrijednosti C4 komponente komplemента predskazatelji su razvoja limfoma, a njihova istodobna prisutnost dodatno povećava rizik njegova nastanka (37). S obzirom na rizik razvoja limfoma predložena je podjela oboljelih od SS-a u dvije skupine. Prva skupina uključuje bolesnike s niskim rizikom, u kojih nije istodobno prisutna palpabilna purpura i niske vrijednosti C4 komponente komplemента. Dru-

tions and significant morbidity, which, in the majority of cases, includes a mild clinical course. Disease prognosis depends on the presence of extraglandular forms of the disease, the occurrence of lymphoproliferative neoplasia or the clinical manifestation and activity of the associated autoimmune disease in secondary Sjögren's syndrome. To improve the care of these patients, it is necessary to conduct a comprehensive assessment of the condition and the involvement of the target organs, and it is extremely important to take a multidisciplinary approach and raise awareness of the complexity of this disease.

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ga skupina s istodobnom prisutnošću navedenih obilježja ima visoki rizik za razvoj limfoma i lošiju prognozu (20).

ZAKLJUČAK

Sjögrenov sindrom je relativno česta autoimuna bolest sa širokim rasponom kliničkih manifestacija i značajnim morbiditetom koja se ipak najčešće prezentira blagim kliničkim tijekom. Prognoza bolesti ovisi o prisutnosti izvanžljezdanih oblika bolesti, pojavi limfoproliferativne neoplazije ili kliničkom očitovanju i aktivnosti pridružene autoimune bolesti u sekundarnom Sjögrenovom sindromu. Za poboljšanje skrbi ovih bolesnika potrebna je sveobuhvatna procjena stanja i zahvaćenosti ciljnih organa, a svakako je neophodan multidisciplinarni pristup i podizanje svjesnosti o složenosti ove bolesti.

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ANTICOAGULATION: AN OVERVIEW OF PHARMACOLOGICAL AGENTS AND THERAPEUTIC IMPLICATIONS IN RHEUMATOLOGY

ANTIKOAGULACIJA: PREGLED FARMAKOLOŠKIH SREDSTAVA I TERAPIJSKIH IMPLIKACIJA U REUMATOLOGIJI

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ABSTRACT

The use of anticoagulant therapy is a part of the daily work of clinicians and a reason for fear, primarily due to the risk of bleeding. The use of anticoagulant drugs in rheumatology remains a challenge. First, a large number of clinicians consider rheumatic conditions as a hypercoagulable state, which often leads to wrong decisions. Second, the use of drugs in the treatment of rheumatic diseases may be associated with an increased risk of venous thromboembolism (VTE), and they can have effect on dose of anticoagulant agent. The aim of this paper is to present the properties of anticoagulant therapy through the prism of rheumatological pathology.

KEYWORDS: Anticoagulants, Rheumatology, Treatment

SAŽETAK

Primjena antikoagulantne terapije dio je svakodnevnog rada kliničara i postupak koji izaziva strah, prvenstveno zbog opasnosti od krvarenja. Primjena antikoagulantnih lijekova u reumatologiji i dalje je izazovan postupak. Kao prvo, velik broj kliničara smatra reumatska stanja hiperkoagulabilnim stanjima, što često dovodi do donošenja pogrešnih odluka. Kao drugo, primjena lijekova u liječenju reumatskih bolesti može biti povezana s povećanim rizikom od venske tromboembolije (VTE) te lijekovi mogu utjecati na dozu antikoagulansa. Cilj je ovog rada prikazati svojstva antikoagulantne terapije kroz prizmu patologije reumatskih bolesti.

KLJUČNE RIJEČI: antikoagulansi, reumatologija, liječenje

INTRODUCTION

Anticoagulant treatment in rheumatology is a field that still remains unexplored, primarily due to the risk of bleeding (1). However, the risk (and fear) of bleeding should not be a reason not to include anticoagulant therapy (1,2). The CHADS2 score (established in 2010) and then the revised CHA2DS2-VASc score (in 2012) have been used in practice since the first guidelines for

UVOD

Antikoagulantna terapija u reumatologiji još je uvijek neistraženo područje, prvenstveno zbog rizika od krvarenja (1). Međutim, rizik (i strah) od krvarenja ne bi trebao biti razlog da se antikoagulantna terapija ne uvede u liječenje (1,2). Bodovni sustav CHADS2 (uspostavljen 2010.), a potom i revidirani bodovni sustav CHA2DS2-VASc (uspostavljen 2012.) u praksi se upo-

the treatment of atrial fibrillation (AF), and they serve to assess the risk of stroke in patients with non-rheumatic AF, common and severe cardiac arrhythmias associated with thromboembolic stroke, and to determine whether or not treatment with anticoagulant therapy or anti-aggregation therapy is required (3,4). Assessing the risk of bleeding (HAS-BLED, ATRIA, ABC, ORBIT, HEMORR2HAGE score) is an important part of deciding on a therapeutic modality, but it should not be an eliminatory step in the initiation of anticoagulant therapy (5). Scores are a simple and indispensable tool in optimizing the therapeutic modality of patients with AF, along with imperative knowledge of the pharmacodynamic and pharmacokinetic properties of the pharmacological agent (5). The literature states that in the case of adequate thromboprophylaxis, about 185,255 cases of venous thromboembolism (VTE) per year worldwide could be prevented (6). In 70% of cases, deep vein thrombosis (DVT) occurs in patients hospitalized for acute medical conditions such as acute myocardial infarction, acute heart failure, oncological pathology, or pneumonia (6). A risk assessment in accordance with the PADUA score is recommended (as well as the IMPROVE-DD score), as well as a bleeding risk assessment according to the IMPROVE score (7). All hospitalized patients over 40 years of age with active pathology and reduced mobility, and one of the associated comorbidities (acute heart failure, respiratory disease, active malignancy, acute infectious condition, thrombophilia, rheumatic disease, ischemic stroke, acute myocardial infarction) are candidates for thromboprophylaxis, both in rheumatology and complete internal medicine (7). It is crucial to take into account the patient's medical history (positive family history for coagulopathy or coagulation-related gene polymorphism) and any additional data that could predispose to VTE (electrocardiogram (ECG) Holter monitoring findings, if not indicative of atrial fibrillation, but verifies a great number of supraventricular extrasystoles, is also alarming regarding anticoagulation) (8).

AIM

The aim of this paper is to present the properties of anticoagulant therapy through the prism of rheumatological pathology.

ANTICOAGULANT AGENTS

Pharmacological anticoagulants are differentiated into heparin (low molecular weight, unfractionated), warfarin derivatives (vitamin K antagonists), new oral anticoagulants (NOACs), and fondaparinux (9). According to the method of administration, they are divided into parenteral and oral. The use of anticoagu-

trebljavaju od pojave prvih smjernica za liječenje atrijske fibrilacije (AF), a služe za procjenu rizika od moždanog udara u bolesnika s nereumatskom AF, uobičajenim i teškim srčanim aritmijama povezanim s tromboembolijskim moždanim udarom te kako bi se utvrdilo je li potrebno liječenje antikoagulantnom terapijom ili antiagregacijskom terapijom (3,4). Procjena rizika od krvarenja (bodovni sustavi HAS-BLED, ATRIA, ABC, ORBIT, HEMORR2HAGE) važan je dio odlučivanja o terapijskom modalitetu, ali ne smije biti eliminacijski korak u započinjanju antikoagulantne terapije (5). Bodovni su sustavi, uz obavezno poznavanje farmakodinamičkih i farmakokinetičkih svojstava farmakološkog sredstva, jednostavan i nezaobilazan alat u optimizaciji terapijskog modaliteta bolesnika s AF (5). U literaturi se navodi da bi se, primjenom odgovarajuće trombopofilakse, godišnje u svijetu moglo spriječiti oko 185.255 slučajeva venske tromboembolije (VTE) (6). U 70% slučajeva duboka venska tromboza (DVT) javlja se u bolesnika hospitaliziranih zbog akutnih zdravstvenih stanja kao što su akutni infarkt miokarda, akutno zatajenje srca, onkološka patologija ili upala pluća (6). Preporučuje se procjena rizika prema bodovnom sustavu PADUA, to jest, The Padua Prediction Score (kao i prema bodovnom sustavu IMPROVE-DD) te procjena rizika od krvarenja prema bodovnom sustavu IMPROVE (7). Kandidate za trombopofilaksu, kako u reumatologiji, tako i u internoj medicini, predstavljaju svi hospitalizirani bolesnici stariji od 40 godina s aktivnom patologijom i smanjenom pokretljivošću te jednim od pridruženih komorbiditeta (akutno zatajenje srca, respiratorna bolest, aktivna maligna bolest, akutno infektivno stanje, trombofilija, reumatska bolest, ishemijski moždani udar, akutni infarkt miokarda) (7). Ključno je uzeti u obzir bolesnikovu anamnezu (pozitivna obiteljska anamneza na koagulopatiju ili polimorfizam gena povezan s koagulacijom) i sve dodatne podatke koji bi mogli predstavljati predispoziciju za VTE (nalazi Holter elektrokardiograma [EKG] također su alarmantni u pogledu antikoagulacije ako ne ukazuju na atrijsku fibrilaciju, ali potvrđuju velik broj supraventrikulskih ekstrasistola) (8).

CILJ

Cilj je ovog rada prikazati svojstva antikoagulantne terapije kroz prizmu patologije reumatskih bolesti.

ANTIKOAGULANTNA SREDSTVA

Farmakološki antikoagulansi dijele se na heparin (niskomolekularni, nefrakcionirani), derivate varfarina (antagonisti vitamina K), nove oralne antikoagulanse (NOAK) i fondaparinux (9). Prema načinu primjene dijele se na parenteralne i oralne. Primjena antikoagulantne terapije indicirana je u profilaksi venske

TABLE 1. Properties of unfractionated heparin and LMWH (10)

TABLICA 1. Svojstva nefrakcioniranog heparina i NMH-a (10)

Heparin	Advantages / Prednosti	Disadvantages / Nedostatci
Unfractionated / Nefrakcionirani	Rapid onset, greater flexibility for the dose titration, as well as the discontinuation of therapy, the ability to monitor the effect through monitoring aPTT and anti-factor Xa activity, activated platelet aggregation time, usage independent of renal function, the presence of antidotes in the form of protamine sulfate. / Brz početak djelovanja, veća fleksibilnost za titraciju doze, kao i prekid terapije, mogućnost praćenja učinka praćenjem APTV-a i antifaktora Xa aktivnosti, aktivirano vrijeme agregacije trombocita, uporaba neovisna o funkciji bubrega, prisutnost antidota u obliku protamin sulfata.	Short plasma half-life, need for continuous infusion administration, the requirement of frequent activity monitoring through laboratory parameters, higher incidence of HIT, skin reactions or osteoporosis with prolonged use, increased risk of bleeding. / Kratko poluvrijeme eliminacije u plazmi, potreba za kontinuiranom primjenom infuzije, potreba za čestim praćenjem aktivnosti kroz laboratorijske parametre, veća učestalost trombocitopenije izazvane heparinom (HIT), kožnih reakcija ili osteoporoze kod produljene primjene, povećan rizik od krvarenja.
LMWH / Niskomolekularni heparin (NMH)	Greater bioavailability, easy administration, longer effect compared to the unfractionated, possibility of faster dose adjustment, lower risk of HIT, lower incidence of osteoporosis. / Bolja bioraspoloživost, laka primjena, dulji učinak u odnosu na nefrakcionirani heparin, mogućnost bržeg prilagođavanja doze, manji rizik od trombocitopenije izazvane heparinom (HIT), manja pojavnost osteoporoze.	The effect appears after 20–30 minutes, slower ability to stop bleeding due to the longer action, protamine sulfate has less effect on LMWH, prolonged plasma half-life in renal insufficiency (especially enoxaparin) / Učinak se javlja nakon 20 do 30 minuta, sporija sposobnost zaustavljanja krvarenja zbog duljeg djelovanja, slabiji učinak protamin sulfata na NMH, produljeno poluvrijeme eliminacije u plazmi kod bubrežne insuficijencije (osobito pri primjeni enoksaparina).

aPTT / APTV – *activated Partial Thromboplastin Time* / aktivirano parcijalno tromboplastinsko vrijeme; HIT – *heparin-induced thrombocytopenia* / trombocitopenija izazvana heparinom; LMWH / NMH – *Low Molecular Weight Heparin* / niskomolekularni heparin

lant therapy is indicated in the prophylaxis of venous thromboembolism (VTE), in the treatment and prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE), in the treatment of acute coronary syndrome, for the prevention of ischemic stroke or transient ischaemic attack (TIA), in the pediatric population (VTE, DVT, PE, cerebral venous thrombosis), during pregnancy, under neuraxial anesthesia, and perioperatively, postoperatively and during hospitalization in the form of thromboprophylaxis (10,11).

The choice of the appropriate pharmacological agent should be in accordance with the indication and the characteristics of the patient himself, taking into account the pharmacodynamic and pharmacokinetic properties of the drug.

Table 1 shows the characteristics of parenteral anti-coagulant therapy. Heparin, used in clinical practice, has been isolated from the intestines of pigs or cows (11,12). Low molecular weight heparin (LMWH; enoxaparin, dalteparin, nadroparin, bemiparin, certoparin, tinzaparin) is obtained by enzymatic or chemical depolymerization of unfractionated heparin (15 segments in the form of polysaccharides) (11). The mechanism of action of heparin is binding to anti-thrombin and thus inactivating factor Xa (10). The difference between unfractionated heparin and LMWH is that, in theory, it is a much more effective thrombin inhibitor (direct intravenous thrombin inhibitors such as argatroban and bivalirudin are also used in practice) (10). Unfractionated heparin is metabolized through

tromboembolije (VTE), u liječenju i prevenciji duboke venske tromboze (DVT) i plućne embolije (PE), u liječenju akutnog koronarnog sindroma, u prevenciji ishemijskog moždanog udara ili tranzitorne ishemijske atake (TIA), u pedijatrijskoj populaciji (VTE, DVT, PE, cerebralna venska tromboza), tijekom trudnoće, u neuraksijalnoj anesteziji, te perioperativno, postoperativno i tijekom hospitalizacije u obliku tromboprolakse (10,11).

Odabir odgovarajućeg farmakološkog sredstva treba biti u skladu s indikacijom i karakteristikama samog bolesnika, uzimajući u obzir farmakodinamička i farmakokinetička svojstva lijeka.

U tablici 1 prikazane su karakteristike parenteralne antikoagulantne terapije. Heparin, koji se primjenjuje u kliničkoj praksi, izoliran je iz crijeva svinja ili krava (11,12). Niskomolekularni heparin (NMH; enoksaparin, dalteparin, nadroparin, bemiparin, certoparin, tinzaparin) dobiva se enzimskom ili kemijskom depolimerizacijom nefrakcioniranog heparina (15 segmenata u obliku polisaharida) (11). Mehanizam djelovanja heparina vezanje je na antitrombin, čime se postiže inaktivacija faktora Xa (10). Razlika između nefrakcioniranog heparina i niskomolekularnog heparina (NMH) u tome je što je prvi navedeni, u teoriji, učinkovitiji inhibitor trombina (u praksi se također primjenjuju i direktni intravenski inhibitori trombina kao što su argatroban i bivalirudin) (10). Nefrakcionirani heparin metabolizira se kroz retikuloendotelni sustav i jetru, a izlučuje se urinom (10). Što se tiče terapijskih

the reticuloendothelial system and liver, and it is excreted through urine (10). In terms of therapeutic doses, renal function does not affect elimination (13,14). The maximum effect of heparin, whether administered intravenously or subcutaneously, is two to four hours, and the plasma half-life is 45 minutes to one hour. Heparin cannot be administered intramuscularly or orally (10,13,14). LMWH is metabolized in the liver, and the excretion itself is through the kidneys. Renal clearance is between 10 to 40%. Peak plasma values are reached three to five hours after subcutaneous administration and two hours after intravenous administration (10,13,14). The plasma half-life is three to seven hours. The therapeutic effect can be monitored by activated partial thromboplastin time (aPTT) and anti-factor Xa activity, and it is recommended to use any available test (10). APTT values greater than 1.5 to 2.5 times the upper reference limit are accepted in clinical practice (10).

WARFARIN DERIVATIVES (VITAMIN K ANTAGONISTS)

Vitamin K antagonists (warfarin, acenocoumarol, phenprocoumon, fluindione) are anticoagulant drugs for oral use (10,15). The indications for using vitamin K antagonists are atrial fibrillation (for stroke prevention), acute coronary syndrome, heart failure, mechanical valve implantation, DVT treatment, PTE prevention, PE treatment, and antiphospholipid syndrome. Their mechanism of action is blocking the vitamin K epoxide reductase complex subunit 1 (encoded by vitamin K epoxide reductase complex subunit 1 – VKORC1 gene) (10,16). They block proteins C and S and inhibit coagulation factors II, VII, IX, and X (17).

Warfarin is rapidly and completely absorbed from the intestine after oral administration. It has a small volume of distribution and is strongly bound to plasma albumin. The peak plasma concentration of warfarin is achieved after one hour, while acenocoumarol reaches it after one to three hours. It is metabolized by the CYP2C9 enzyme. The bioavailability of warfarin and acenocoumarol is 99.4% and 60%, respectively (Table 2) (10).

Their advantages are that they still represent the first and only option after mechanical valve implantation, in case of left ventricular apex aneurysm and thrombotic mass, low cost, the possibility of reversibility of effect (vitamin K, fresh frozen plasma, prothrombin concentrated complex (PCC)) (10). Its disadvantages are that the metabolism of the drug is individually dependent, the level of the drug depends on comorbidities, and frequent controls of PV and INR are required, which are dependent even on the type of diet. Foods rich in vitamin K will impair the values, and the value of INR is also affected by the use of alcohol, smoking,

doza, bubrežna funkcija ne utječe na njegovu eliminaciju (13,14). Maksimalni je učinak heparina, bilo da se primjenjuje intravenski ili supkutano, dva do četiri sata, a poluvrijeme eliminacije u plazmi iznosi 45 minuta do jedan sat. Heparin se ne može primijeniti intramuskularno ili oralno (10,13,14). NMH se metabolizira u jetri, a izlučuje se putem bubrega. Bubrežni klirens iznosi između 10% i 40%. Vršne vrijednosti u plazmi postižu se tri do pet sati nakon supkutane primjene i dva sata nakon intravenske primjene (10,13,14). Poluvrijeme eliminacije u plazmi iznosi tri do sedam sati. Terapijski učinak može se pratiti pomoću aktiviranoga parcijalnog tromboplastinskog vremena (APTV) i antifaktora Xa aktivnosti, a preporučuje se upotreba bilo kojeg dostupnog testa (10). U kliničkoj praksi prihvaćene su vrijednosti APTV-a koje su od 1,5 do 2,5 puta veće od gornje referentne granice (10).

DERIVATI VARFARINA (ANTAGONISTI VITAMINA K)

Antagonisti vitamina K (warfarin, acenokumarol, fenprocumon, fluindion) predstavljaju antikoagulanse za oralnu primjenu (10,15). Indikacije za primjenu antagonista vitamina K su sljedeće: atrijska fibrilacija (za prevenciju moždanog udara), akutni koronarni sindrom, zatajenje srca, implantacija mehaničke valvule, liječenje duboke venske tromboze (DVT), prevencija plućne tromboembolije (PTE), liječenje plućne embolije (PE) i antifosfolipidni sindrom. Njihov mehanizam djelovanja uključuje blokiranje podjedinice 1 vitamin K epoksid reduktaza kompleksa (kodirane podjedinicom 1 kompleksa vitamin K epoksid reduktaze – VKORC1 gen) (10,16). Oni blokiraju proteine C i S i inhibiraju faktore koagulacije II, VII, IX i X (17).

Warfarin se nakon oralne primjene brzo i potpuno apsorbira iz crijeva. Ima mali volumen distribucije i snažno se veže za albumin, protein krvne plazme. Vršna koncentracija varfarina u plazmi postiže se nakon jednog sata, a acenokumarola nakon jednog do tri sata. Metabolizira ga enzim CYP2C9. Bioraspoloživost varfarina iznosi 99,4%, a acenokumarola 60% (tablica 2) (10).

Prednosti su im što još uvijek predstavljaju prvu i jedinu opciju nakon implantacije mehaničke valvule, u slučaju aneurizme vrha lijeve klijetke i tromba, niska cijena, mogućnost reverzibilnosti učinka (vitamin K, svježe smrznuta plazma, koncentrat protrombinskog kompleksa [PCC]) (10). Njihovi su nedostaci što je metabolizam lijeka individualno ovisan, razina lijeka ovisi o komorbiditetima, a potrebne su i česte kontrole u obliku protrombinskog vremena (PV) i internacionalnog normaliziranog omjera (INR), koje ovise čak i o načinu prehrane. Hrana bogata vitaminom K narušit će vrijednosti, a na vrijednost INR-a utječe i konzumacija alkohola, pušenje, pa čak i upotreba vitaminskih

TABLE 2. Pharmacokinetic differences between warfarin and acenocoumarol (10)

TABLICA 2. Farmakokinetičke razlike između varfarina i acenokumarola (10)

	Warfarin / Varfarin	Acenocoumarol / Acenokumarol
Route of administration / Način primjene	oral / oralno	oral / oralno
Monitoring / Praćenje	PT / PV (INR)	PT / PV (INR)
Peak plasma concentration / Vršna koncentracija u plazmi	4 hours / sata	1–3 hours / 1 do 3 sata
Plasma half-time / Poluvrijeme eliminacije u plazmi	30–80 hours / 30 do 80 sati	10.9 hours / 10,9 sati
Duration of action / Trajanje djelovanja	2–5 days / 2 do 5 dana	2 days / 2 dana
Elimination / Eliminacija	renal 92% / renalna 92%	renal 60% / renalna 60%
Dependency on the CYP2C9 metabolism / Ovisnost o enzimu CYP2C9 u metabolizmu lijekova	++	+
Antidote / Antidot	vitamin K1, prothrombin complex concentrate, fresh or frozen plasma / vitamin K1, koncentrat protrombinskog kompleksa, svježa ili smrznuta plazma	vitamin K1
Preganancy / Trudnoća	contraindicated / kontraindiciran	contraindicated / kontraindiciran

PT / PV – prothrombin time / protrombinsko vrijeme; INR – international normalized ratio / internacionalni normalizirani omjer

and even the use of vitamin supplements. Warfarin is a less compelling option than new oral anticoagulants (NOACs) for the prevention of ischemic stroke, as well as the prophylaxis and treatment of PTE itself (10). However, due to its low cost, it is still the most commonly used option for anticoagulant therapy in Bosnia and Herzegovina. The development of pharmacogenetics, especially the understanding of CYP2C9 and VKORC1 gene polymorphisms, has developed different schemes of therapy initiation but also made it known that control of therapeutic modality by warfarin derivatives is challenging.

Therapeutic values of INR are usually in the range of 2.0 to 3.0, and after implantation of the mechanical valve, that range is between 3.0 and 4.0 (18). The plasma half-life of warfarin is 36 to 42 hours, acenocoumarol 8 to 11 hours, phenprocoumon 3 to 5 days, and flu-

suplemenata. Varfarin predstavlja manje uvjerljivu opciju od novih oralnih antikoagulanasa (NOAK) za prevenciju ishemijskog moždanog udara, kao i za profilaksu i liječenje same plućne tromboembolije (PTE) (10). Međutim, zbog svoje niske cijene i dalje je najčešće upotrebljavana opcija antikoagulantne terapije u Bosni i Hercegovini. Razvoj farmakogenetike, posebice razumijevanje polimorfizama gena CYP2C9 i VKORC1, potaknuo je razvoj različitih shema inicijacije terapije, ali i potvrdio činjenicu da je kontrola terapijskog modaliteta derivatima varfarina izazovan proces.

Terapijske vrijednosti INR-a obično su u rasponu od 2,0 do 3,0, a nakon implantacije mehaničke valvule taj se raspon kreće između 3,0 i 4,0 (18). Poluvrijeme eliminacije varfarina u plazmi iznosi 36 do 42 sata, acenokumarola 8 do 11 sati, fenprocumona 3 do 5 dana, a fluindiona 69 sati, što dodatno otežava donošenje odluke o hitnim kirurškim zahvatima te donosi probleme u pogledu farmakokinetičkih interakcija (10). Na vrijednosti INR-a mogu utjecati lijekovi uključujući kotrimoksazol, metronidazol, makrolide, fluorokinolone i lijekove koji se metaboliziraju s pomoću enzima CYP2C9 (flukonazol, amiodaron, sulfametoksazol), acetaminofen, kao i lijekove koji se vežu na albumin. Primjena nesteroidnih antireumatika (i acetilsalicilne kiseline) ili određenih alkaloida može povećati rizik od krvarenja, dok svi lijekovi koji induciraju enzim CYP2C9 mogu smanjiti antikoagulantni učinak (10).

U slučaju krvarenja opasnog po život potrebno je prekinuti primjenu varfarina, uvesti ampularnu terapiju vitaminom K1 i liječiti bolesnika svježe smrznutom plazmom ili koncentratom protrombinskog kompleksa (PCC) (25 do 50 jedinica po kilogramu tjelesne težine) (10).

Novi oralni antikoagulansi (NOAK)

Novi oralni antikoagulansi (NOAK) uključuju pet predstavnika, od kojih su četiri izravni inhibitori faktora Xa (rivaroksaban, apiksaban, edoksaban i betriksaban), a peti je izravni inhibitor trombina (dabigatran). Betriksaban nije odobren za uporabu u Europi, ali ga je odobrila Agencija za hranu i lijekove Sjedinjenih Američkih Država (FDA) (10).

U kliničkim studijama, u kojima se predstavila upotreba NOAK-a, navodi se da su novi oralni antikoagulansi (NOAK) jednako učinkoviti kao varfarin i njegovi derivati u prevenciji moždanog udara kod pacijenata s nevalvularnom atrijskom fibrilacijom i za liječenje VTE, te da su sigurniji za upotrebu zbog nižih stopa intrakranijalnog krvarenja (10). Odabir određene primjene NOAK-a trebao bi se temeljiti na individualnim karakteristikama pacijenata, kao i na farmakološkim svojstvima same tvari.

indione 69 hours, which additionally complicates decisions about urgent surgical procedures, as well as complicates the story of pharmacokinetic interactions (10). INR values may be affected by drugs including cotrimoxazole, metronidazole, macrolides, fluoroquinolones, and drugs that metabolize CYP2C9 (fluconazole, amiodarone, sulfamethoxazole), acetaminophen, as well as drugs that bind to albumin. The use of nonsteroidal antirheumatic drugs (and acetylsalicylic acid) or certain alkaloids may increase the risk of bleeding, whereas all drugs that induce CYP2C9 may reduce the anticoagulant effect (10).

In case of life-threatening bleeding, it is necessary to discontinue warfarin use, administer ampullary vitamin K1, and treat the patient with fresh frozen plasma or PCC (25–50 units per kilogram of body weight) (10).

New oral anticoagulants (NOAC)

New oral anticoagulants (NOACs) include five representatives, four of which are direct inhibitors of factor Xa (rivaroxaban, apixaban, edoxaban, and betrixaban), and the fifth is a direct thrombin inhibitor (dabigatran). Betrixaban is not approved for use in Europe, while it is approved by U.S. Food and Drug Administration (FDA) (10).

Clinical studies that have established the use of NOAC state that NOACs are as effective as warfarin and its derivatives in stroke prevention in patients with non-valvular atrial fibrillation and for the treatment of VTE, and are safer to use due to lower rates of intracranial hemorrhage (10). The choice of particular NOAC use should be based on the individual characteristics of the patients, as well as the pharmacological properties of the substance itself.

The first representative of this group to emerge was dabigatran, with the initial study “Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY)” (19). Dabigatran achieves peak plasma values within two hours after administration. It inhibits free thrombin, fibrin-bound thrombin, and thrombin-induced platelet aggregation. Its bioavailability is about 6.5%, and the elimination half-life is between 12 and 14 hours (19). It is eliminated by the kidneys, and about 80% of the drug is excreted as unchanged (19).

Rivaroxaban has been established in clinical practice with two studies, “Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF)” and “Xarelto on Prevention of Stroke and Non-Central Nervous System Embolism in Patients with Non-Valvular and Atrial Fibrillation (XANTUS)” (20,21). Rivaroxaban is the most frequently prescribed NOAC in Bosnia and Herzegovina. Peak plasma value is reached between 2 to 4 hours after ingestion. It is a selective, direct, and re-

Prvi predstavnik ove skupine koji se pojavio bio je dabigatran, čije je djelovanje opisano u početnoj studiji Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) (19). Primjenom dabigatrana postižu se vršne vrijednosti u plazmi unutar dva sata nakon primjene lijeka. On inhibira slobodni trombin, trombin vezan na fibrin i agregaciju trombocita induciranu trombinom. Bioraspoloživost mu je oko 6,5%, a poluvrijeme eliminacije između 12 i 14 sati (19). Eliminacija se vrši putem bubrega, a oko 80% lijeka izlučuje se nepromijenjeno (19).

Rivaroksaban je u kliničkoj praksi predstavljen u dvije studije: Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) i Xarelto on Prevention of Stroke and Non-Central Nervous System Embolism in Patients with Non-Valvular and Atrial Fibrillation (XANTUS) (20,21). Rivaroksaban je NOAK koji se najčešće propisuje u Bosni i Hercegovini. Njegova vršna vrijednost u plazmi postiže se između 2 i 4 sata nakon ingestije. On je selektivni, izravni i reverzibilni inhibitor faktora Xa, koji sprječava i unutarnje i vanjske putove koagulacije, čime inhibira stvaranje trombina i sam razvoj tromba (10). Poluvrijeme eliminacije iz plazme je oko 9 sati u mlađih osoba i između 11 i 13 sati u starijih osoba. Dvije trećine lijeka metabolički se razgrađuje, jedna polovica se eliminira putem bubrega, a druga putem crijeva. Preostala jedna trećina lijeka izlučuje se izravno putem bubrega u mokraću kao nepromijenjena djelatna tvar. Tjelesna težina, dob i spol ne utječu na farmakodinamička svojstva lijeka (10). Rivaroksaban je klinički ispitan u dozi od 2,5 mg za primarnu i sekundarnu prevenciju kardiovaskularnih događaja, kao i za liječenje bolesti perifernih arterija (22).

U kliničkim studijama Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) i Apixaban for Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First Line Therapy (AMPLIFY) predstavljena je primjena apiksabana u kliničkoj praksi (23,24). Nakon 3 do 4 sata od ingestije, lijek će postići maksimalnu vrijednost u plazmi, s dominantnim hepatičkim klirensom. Studije navode da je apiksaban najsigurniji NOAK u smislu rizika od krvarenja, iako je teško donijeti takav zaključak s obzirom na neujednačenost uzorka u početnim studijama. On je selektivni, reverzibilni inhibitor faktora Xa koji sprječava stvaranje trombina (10). Oko 87% apiksabana veže se na proteine plazme. Njegovo poluvrijeme eliminacije iznosi otprilike 12 sati, dok se 27% lijeka eliminira putem bubrega, a 63% putem fecesa (10).

Primjena edoksabana u kliničkoj praksi predstavljena je u kliničkoj studiji Effective Anticoagulation with

versible factor Xa inhibitor, interrupting both intrinsic and extrinsic coagulation pathways, thus inhibiting thrombin formation and thrombus development itself (10). The plasma elimination half-life is about 9 hours in younger individuals and between 11 and 13 hours in the elderly. Two-thirds of the drug is degraded metabolically, with one-half eliminated by the kidneys and the other by the gut. The remaining one-third is excreted directly by the kidneys into the urine as an unchanged active substance. Bodyweight, age, and sex do not affect the pharmacodynamic properties of the drug (10). Rivaroxaban has been tested in clinical studies at a dose of 2.5 mg for both primary and secondary prevention of cardiovascular events, as well as in the treatment of peripheral arterial disease (22).

The clinical studies "Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE)" and "Apixaban for Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy (AMPLIFY)" established apixaban in clinical practice (23,24). After 3 to 4 hours of ingestion, it will achieve a maximum value in plasma, with a dominant hepatic clearance. Studies state that apixaban is the safest NOAC in terms of bleeding risk, although it is difficult to draw this type of conclusion given the non-uniformity of the sample in initiation studies. It is a selective, reversible factor Xa inhibitor that prevents thrombin formation (10). About 87% of apixaban binds to plasma proteins. Its elimination half-life is approximately 12 hours, whereas 27% of it is eliminated through the kidneys and 63% through the feces (10).

The clinical study "Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48)" established edoxaban in clinical practice. It reaches peak plasma concentration in 1–2 hours after the ingestion (25). Edoxaban is a selective inhibitor of factor Xa. Its bioavailability is about 62%, and the plasma half-life is about 10 to 14 hours (25).

The only NOAC to receive an indication for use in an acute endangered patient is betrixaban, with the study "Acute Medical Ill VTE (Venous Thromboembolism) Prevention with Extended Duration Betrixaban (APEX)". Its bioavailability is approximately 34%, and the plasma half-life is between 19 to 27 hours, with the lowest renal clearance (26).

Regarding antidotes, idarucizumab is used to reverse the effect of dabigatran, while andexanet alfa is used for rivaroxaban and apixaban (10). Aripazine is under ongoing investigation for use as a factor Xa inhibitor. In the absence of options, the use of PCC or activated PCC is meaningful (10). Dosage and pharmacological properties of NOAC are listed in Table 3, effects on

Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48). Vršna koncentracija lijeka u plazmi postiže se 1 do 2 sata nakon ingestije (25). Edoxaban je selektivni inhibitor faktora Xa. Bioraspoloživost mu je oko 62%, a poluvrijeme eliminacije u plazmi između 10 i 14 sati (25).

Jedini NOAK koji je indiciran za primjenu kod akutno ugroženih pacijenata je betriksaban, čija je primjena predstavljena u studiji Acute Medical Ill VTE (venous Thromboembolism) Prevention with Extended Duration Betrixaban (APEX). Bioraspoloživost mu je oko 34%, a poluvrijeme eliminacije u plazmi između 19 i 27 sati, s najnižim bubrežnim klirensom (26).

Što se tiče antidota, idarucizumab se upotrebljava za poništavanje učinka dabigatrana, dok se andeksanet alfa upotrebljava za rivaroksaban i apiksaban (10). U tijeku je ispitivanje aripazina za upotrebu kao inhibitora faktora Xa. U nedostatku drugih opcija, smislenom se smatra upotreba koncentrata protrombinskog kompleksa (PCC) ili aktiviranog PCC-a (10). Doziranje i farmakološka svojstva NOAK-a navedeni su u tablici 3, učinci na laboratorijske parametre navedeni su u tablici 4, dok je doziranje u različitim indikacijama objašnjeno u tablici 5. Ne savjetuje se uporaba NOAK-a u slučaju implantiranih mehaničkih ventila ili umjerenih i teških mitralnih stenoz. Nadalje, nema dovoljno podataka za primjenu NOAK-a u bolesnika s teškom aortnom stenozom, perkutanom transluminalnom aortnom valvuloplastikom ili transkateterskom implantacijom aortnog zalistka. Za bolesnike kod kojih je antikoagulantna terapija kontraindicirana treba razmotriti postavljanje filtera u donju šuplju venu. Indicirana je u bolesnika s rekurentnom plućnom embolijom (PE) unatoč primjeni antikoagulantne terapije, te u bolesnika s plućnom hipertenzijom i zatajenjem srca. Njihova se primjena može razmotriti u bolesnika s trombima u području zdjelice ili donje šuplje vene s pokretnim dijelovima, u rekurentnoj DVT prije planiranog kirurškog zahvata, prije plućne tromboektomije i u bolesnika s rekurentnim embolijama kojima je dijagnosticiran rak.

Odluka o tome koje sredstvo upotrebljavati ovisi o riziku od krvarenja. U literaturi su primijećene veće stope gastrointestinalnog krvarenja u bolesnika koji su uzimali rivaroksaban (3,2 na 100 pacijent-godina liječenja) nego s drugim lijekovima (2,5 za apiksaban i 1,9 za dabigatran, možda zbog primjene doze lijeka jednom dnevno) (27). U budućnosti će se vjerojatno pojaviti sredstva koja će inhibirati faktor XI. Milveksian (milvexian) je ispitivani NOAK koji cilja faktor XI, a pri ispitivanju lijeka za određivanje doze, stope postoperativne VTE bile su niže pri primjeni milveksiana u usporedbi sa standardnom profilaktičkom dozom

TABLE 3. The NOACs in clinical practice (according to reference No.10)
 TABLICA 3. Novi oralni antikoagulansi u kliničkoj praksi (u skladu s literaturom br. 10)

New oral anticoagulant / Novi oralni koagulansi	Dabigatran	Rivaroxaban / Rivaroksaban	Apixaban / Apiksaban	Edoxaban / Edoksaban	Betrixaban / Betriksaban
Initial clinical study / Početna klinička studija	RE-LY	ROCKET-AF	ARISTOTLE	ENGAGE-AF	APEX
Pharmacological mechanism of action / Farmakološki mehanizam djelovanja	Direct thrombin inhibitor / Izravni inhibitor trombina	Factor Xa inhibitor / Inhibitor faktora Xa	Factor Xa inhibitor / Inhibitor faktora Xa	Factor Xa inhibitor / Inhibitor faktora Xa	Factor Xa inhibitor / Inhibitor faktora Xa
Bioavailability (%) / Bioraspoloživost (%)	6,5	80 – 100	50	62	34
Half-life (hours) / Poluvrijeme eliminacije (u satima)	12 – 14	5 – 13	8 – 15	9 – 11	19 – 27
Dose (mg) / Doza (mg)	110; 150	2,5; 10; 15; 20	2,5; 5	30; 60	40; 20
Dosing regimen / Doziranje	BID	OD	BID	OD	BID
CYP450 metabolism / CYP450 u metabolizmu lijevkova	No / Ne	Yes / Da	Yes / Da	Yes / Da (<10 %)	No / Ne (<1 %)
CYP3A4/5	–	Yes / Da	Yes / Da	Yes / Da (<10 %)	–
CYP2J2	–	Yes / Da	Yes / Da	–	–
Renal clearance (%) / Bubrežni klirens (%)	85	66	27	50	17,8
CrCl 30 – 50 ml/min	2 x 110 mg once a day / 2 x 110 mg jedanput na dan	15 mg once a day / 15 mg jedanput na dan	2.5 mg twice a day or 5 mg twice a day / 2,5 mg dvaput na dan ili 5 mg dvaput na dan	30 mg once a day / 30 mg jedanput na dan	40 mg once a day / 40 mg jedanput na dan
CrCl 15 – 29 ml/min	Contraindicated / Kontraindiciran	15 mg once a day / 15 mg jedanput na dan	2.5 mg twice a day / 2,5 mg dvaput na dan	30 mg once a day / 30 mg jedanput na dan	40 mg once a day / 40 mg jedanput na dan
CrCl < 15 ml/min	Contraindicated / Kontraindiciran	Contraindicated / Kontraindiciran	Contraindicated / Kontraindiciran	Contraindicated / Kontraindiciran	Contraindicated / Kontraindiciran

CrCl – creatine clearance / kreatininski klirens; OD: once a day / jedanput na dan; BID: twice a day / dvaput na dan

laboratory parameters are mentioned in Table 4, while dosage in different indications is explained in Table 5. NOACs are not advised to be used in case of implanted mechanical valves or moderate and severe mitral stenosis. Moreover, insufficient data is available for the use of NOACs in patients with severe aortic stenosis, percutaneous transluminal aortic valvuloplasty, or transcatheter aortic valve implantation. For patients in whom anticoagulant therapy is contraindicated, the use of inferior vena cava filters should be considered. It is indicated in patients with recurrent PE attacks, despite anticoagulant therapy, in patients with pulmonary hypertension and heart failure. Their use may be considered in patients with pelvic or inferior vena cava thrombi with mobile parts, in recurrent DVT before planned surgery, prior to pulmonary thrombendarterectomy, and in patients with recurrent emboli who are diagnosed with cancer.

enoksaparina (28). Uz to, abelacimab, monoklonsko antitijelo koje sprječava aktivaciju faktora XI, smanjilo je stopu postoperativne VTE na učinkovitiji način od NMH (29).

ANTIKOAGULANSI U REUMATSKIM BOLESTIMA

Bolesnici s reumatoidnim artritisom (RA) imaju povećan rizik od VTE koji je vjerojatno povezan s osnovnom upalom, dok kliničari često gledaju na reumatske bolesti kao na stanja hiperkoagulacije (30–36). Rizik od pojave VTE kod sistemskih autoimunih bolesti prikazan je u tablici 6. Indikacije za primjenu antagonista vitamina K prikazane su u tablici 7. Indikacije u kojima bi se novi oralni antikoagulansi (NOAK) trebali upotrebljavati kao prva opcija prikazane su u tablici 8. Stanja u kojima antikoagulantna terapija nije korisna prikazana su u tablici 9. Interakcije lijek – lijek između

TABLE 4. Laboratory monitoring of NOACs and their effect on certain parameters (according to reference No.10)

TABLICA 4. Laboratorijsko praćenje NOAK-a i njihov učinak na određene parametre (u skladu s literaturom br. 10)

	Dabigatran	Apixaban / Apiksaban	Edoxaban / Edoksaban	Rivaroxaban / Rivaroksaban
Prothrombin time (PT) / Protrombinsko vrijeme (PV)	+	(+)	+ (+)	++ (+)
Activated partial thromboplastin time (aPTT) / Aktivirano parcijalno tromboplastinsko vrijeme (APTV)	++ (+)	(+)	+	+
Activated clotting time (ACT) / Aktivirano vrijeme zgrušavanja (AVZ)	+ (+)	+	+	+
Thrombin time (TT) / Trombinsko vrijeme (TV)	+++	–	–	–

TABLE 5. Dosing of NOACs according to indications (according to reference No.10)

TABLICA 5. Doziranje NOAK-a prema indikacijama (u skladu s literaturom br. 10)

Dabigatran
1. Stroke prevention in atrial fibrillation – 150 mg BID (after PCI in dual therapy with clopidogrel without dose reduction) / Prevencija moždanog udara kod atrijske fibrilacije – 150 mg BID (nakon perkutane koronarne intervencije (PCI) u dvojnoj terapiji klopidogetrelom bez smanjenja doze) 2. VTE prophylaxis – 220 mg OD / Profilaksa venske tromboembolije (VTE) – 220 mg OD 3. VTE treatment – after initial parenteral therapy / Liječenje VTE – nakon inicijalne parenteralne terapije 4. Patients aged ≥ 80 years or having eGFR of 30–50 mL/min – 110 mg BID / Bolesnici u dobi od ≥ 80 godina ili s procijenjenom brzinom glomerularne filtracije (eGFR) u rasponu od 30 – 50 ml/min – 110 mg BID
Rivaroxaban / Rivaroksaban
1. Stroke prevention in atrial fibrillation – 20 mg OD (after PCI in triple therapy 15 mg OD) / Prevencija moždanog udara kod atrijske fibrilacije – 20 mg OD (nakon perkutane koronarne intervencije (PCI) u trojnoj terapiji u dozi od 15 mg OD) 2. VTE treatment – 15 mg BID for 3 weeks, then 20 mg OD up to 6 months, after that, consider 10 mg OD / VTE prophylaxis – 10 mg OD / Profilaksa venske tromboembolije (VTE) – 10 mg OD 3. Liječenje VTE – 15 mg BID tijekom 3 tjedna, zatim 20 mg OD u trajanju do 6 mjeseci, nakon toga razmotriti dozu od 10 mg OD 4. Reduction of risk of MACE (CV death, MI, and stroke) in chronic CAD or PAD – 2.5 mg BID (with an antiaggregant drug) / Smanjenje rizika od velikih kardiovaskularnih događaja (MACE) (KV smrt, MI i moždani udar) kod kronične koronarne bolesti srca (KBS) ili bolesti perifernih arterija (BPA) – 2,5 mg BID (s antiagregacijskim lijekom) 5. Patients aged ≥ 80 years or eGFR 15–49 mL/min – 15 mg OD / Bolesnici u dobi od ≥ 80 godina ili s procijenjenom brzinom glomerularne filtracije (eGFR) u rasponu od 15 – 49 ml/min – 15 mg OD
Apixaban / Apiksaban
1. Stroke prevention in atrial fibrillation – 5 mg BID / Prevencija moždanog udara kod atrijske fibrilacije – 5 mg BID 2. VTE prophylaxis – 2.5 mg BID / Profilaksa venske tromboembolije (VTE) – 2,5 mg BID 3. VTE treatment – 10 mg BID for 7 days, then 5 mg BID for at least 6 months / Liječenje VTE – 10 mg BID tijekom razdoblja od 7 dana, zatim 5 mg BID tijekom razdoblja od najmanje 6 mjeseci 4. Two of three criteria present in a patient: age ≥ 80 years, weight ≤ 60 kg, and Cr ≥ 1.5 mg/dL – 2.5 mg BID / U bolesnika su prisutna dva od tri kriterija: dob ≥ 80 godina, težina ≤ 60 kg i koncentracija kreatinina (Cr) ≥ 1,5 mg/dl – 2,5 mg BID
Edoxaban / Edoksaban
1. Stroke prevention in atrial fibrillation – 60 mg OD / Prevencija moždanog udara kod atrijske fibrilacije – 60 mg OD 2. VTE prophylaxis – 60 mg OD (only proven in Asia) / Profilaksa venske tromboembolije (VTE) – 60 mg OD (dokazano samo u Aziji) 3. VTE treatment – after initial parenteral therapy / Liječenje VTE – nakon inicijalne parenteralne terapije 4. ≥ 1 of 3 criteria – concomitant use of potent P-gp inhibitors, body weight ≤ 60 kg, CrCl 30–50 mL/min – 30 mg OD / Ako je prisutno ≥ 1 od 3 kriterija – istodobna primjena snažnih inhibitora P-glikoproteina (P-gp), tjelesna težina ≤ 60 kg, kreatininski klirens (CrCl) 30 – 50 ml/min – 30 mg OD
Betrixaban / Betriksaban
1. VTE prophylaxis – 80 mg OD for 35–42 days / Profilaksa venske tromboembolije (VTE) – 80 mg OD tijekom razdoblja od 35 do 42 dana 2. VTE treatment – 160 mg OD / Liječenje venske tromboembolije (VTE) – 160 mg OD

Legend / Legenda: AF: atrial fibrillation / atrijska fibrilacija; OD: once a day / jedanput dnevno; BID: twice a day / dva puta dnevno; VTE: venous thromboembolism / venska tromboembolija; eGFR: estimated glomerular filtration rate / procijenjena brzina glomerularne filtracije; PCI: percutaneous coronary intervention / perkutana koronarna intervencija; MACE: major adverse cardiac events / veliki kardiovaskularni događaji; CV: cerebrovascular / kardiovaskularni; MI: myocardial infarction / infarkt miokarda; CAD / KBS: coronary artery disease / koronarna bolest srca; PAD / BPA: peripheral artery disease / bolest perifernih arterija; P-gp: P-glycoprotein / P-glikoprotein

TABLE 6. Risk of VTE in rheumatological diseases (according to references No. 30, 36)

TABLICA 6. Rizik od venskog tromboembolizma (VTE) u reumatskim bolestima (u skladu s literaturom br. 30 i 36)

Disease / Bolest	Risk of VTE (%) / Rizik od venskog tromboembolizma (VTE) (%)
Rheumatoid arthritis / Reumatoidni artritis	1,17 – 1,91
Ankylosing spondylitis / Ankilozantni spondilitis	1,16 – 1,93
Systemic lupus erythematosus / Sistemska eritemski lupus	1,23 – 3,71
Systemic sclerosis / Sistemska skleroza	1,61 – 1,97
Polymyositis/dermatomyositis / Polimiozitis/dermatomiozitis	3,04 – 3,36
Sjögren syndrome / Sjögrenov sindrom	2,02 – 2,19
Polymyalgia / Polimialgija	1,91
Polyarteritis nodosa / Nodozni poliarteritis	2,57 – 3,53
Behçet disease / Behçetov sindrom	1,68

VTE – venous thromboembolism / venski tromboembolizam

Deciding on which agent to use depends on the risk of bleeding. In literature, higher rates of gastrointestinal bleeding were observed in patients taking rivaroxaban (3.2 per 100 patient-years) than with the other agents (2.5 for apixaban and 1.9 for dabigatran, perhaps due to once-daily dosing) (27). The future is likely to bring agents that will inhibit factor XI. Milvexian is an investigational NOAC that targets factor XI, and in a dose-finding trial, rates of postoperative VTE were lower with milvexian compared to standard prophylactic enoxaparin (28). Also, abelacimab, a monoclonal antibody that prevents activation of factor XI, reduced the rate of post-operative VTE more effectively than LMWH (29).

ANTICOAGULANTS IN RHEUMATOLOGICAL DISEASES

Patients with rheumatoid arthritis (RA) have an increased risk of VTE likely related to underlying inflammation, while clinicians often view rheumatic diseases as a hypercoagulable condition (30–36). The risk of VTE in systemic autoimmune diseases is presented in Table 6. Indications for using vitamin K antagonists are presented in Table 7. Indications in which NOACs should be used as the first option are presented in Table 8. Conditions where anticoagulant therapy is without benefit, are shown in Table 9. Drug interactions between anticoagulant therapy and drugs that are used in the treatment of rheumatological diseases are shown in Table 10.

TABLE 7. Indications for using vitamin K antagonists

TABLICA 7. Indikacije za primjenu antagonista vitamina K

Antiphospholipid syndrome (acetylsalicylic acid is not enough) / Antifosfolipidni sindrom (acetilsalicilna kiselina nije dovoljna)	First VTE (INR 2–3, recurrent 3–4) / Prva pojava VTE (INR 2–3, rekurentna 3–4)
Pulmonary artery hypertension resulting from Systemic sclerosis / Plućna arterijska hipertenzija koja je posljedica sistemske skleroze	For treatment of pulmonary arterial hypertension / Za liječenje plućne arterijske hipertenzije
Kawasaki disease / Kawasakijska bolest	Indicated / Indicirana
Polyarteritis nodosa / Nodozni poliarteritis	Indicated (along with antiphospholipid syndrome) / Indiciran (uz antifosfolipidni sindrom)

VTE – venous thromboembolism / venski tromboembolizam, INR – international ratio / internacionalni normalizirani omjer

antikoagulansa i lijekova koji se upotrebljavaju u liječenju reumatskih bolesti prikazane su u tablici 10.

Dvojbena je primjena inhibitora Janus kinaze (JAK) i rizik od VTE. Značajno veća incidencija PE zabilježena je u liječenju tofacitinibom (10 mg dva puta dnevno) u usporedbi s tofacitinibom u dozi od 5 mg ili inhibitorima faktora nekroze tumora (31). Dokazana je neravnoteža u incidenciji VTE za dnevnu dozu od 4 mg baricitiniba u odnosu na placebo, dok nema povezanosti s velikim kardiovaskularnim događajima (MACE), arterijskim trombotičkim događajima ili kongestivnim zatajenjem srca (31).

O mjerama profilakse VTE treba odlučiti unutar 24 sata od prijema u bolnicu, uz procjenu rizika (zajedno s kontraindikacijama za profilaksu). Ako se upotrebljava profilaksa VTE, enoksaparin je indiciran za primjenu u liječenju (nema indikacija za NOAK). Kontraindikacije za primjenu NOAK-a uključuju mehaničku protetičku valvulu, umjerenu do tešku mitralnu stenozu (obično reumatskog podrijetla), dok je dvojbena primjena NOAK-a u blagim do umjerenim drugim valvularnim bolestima (ograničeni podatci), teškoj aortalnoj stenozu (ograničeni podatci), hipertrofičnoj kardiomiopatiji (nema prospektivnih podataka) i perkutanoj aortalnoj valvuloplastici i transkateterskoj implantaciji aortnog zalistka (ali nema prospektivnih podataka; može zahtijevati kombinaciju s jednostrukom ili dvostrukom antitrombotskom terapijom; razmotriti rizik od krvarenja) (10). Nakon popravka mitralnog zalistka i bioprostetičkog zalistka prihvatljiva je primjena NOAK-a, osim u razdoblju od prva tri mjeseca nakon operacijskog zahvata.

Čimbenici koji povećavaju hiperkoagulabilnost kod reumatskih poremećaja uključuju povećanu ekspresiju tkivnog faktora, povećane mikročestice (povišene su

TABLE 8. Indications in which NOACs can be used (should be the first option if we have indications for it)

TABLICA 8. Indikacije u kojima se mogu upotrebljavati novi oralni antikoagulansi (NOAK) (trebali bi biti prva opcija ako za to postoje indikacije)

Rheumatoid arthritis (psoriatic) / Reumatoidni artritis (psorijatični)
Ankylosing spondylitis / Ankilozantni spondilitis
Polymyositis / Polimiozitis
Dermatomyositis / Dermatomiozitis
Polymyalgia rheumatica / Reumatska polimialgija
Sjögren syndrome / Sjögrenov sindrom
Sarcoidosis / Sarkoidoza
Systemic sclerosis / Sistemska skleroza
Systemic lupus erythematosus / Sistemski eritemski lupus
Retroperitoneal fibrosis with venous thrombosis / Retroperitonealna fibroza s venskom trombozom

Janus kinase (JAK) inhibitors and the risk of VTE are questionable. A significantly higher incidence of PE was reported in treatment with tofacitinib (10 mg twice daily) compared with tofacitinib 5 mg or tumor necrosis factor inhibitors (31). Imbalance in the incidence of VTE for a 4-mg daily dose of baricitinib versus placebo was proved, while there is no link with major adverse cardiovascular events, arterial thrombotic events, or congestive heart failure (31).

VTE prophylaxis measures should be decided within 24 hours of hospital admission, with a risk assessment (along with contraindications for prophylaxis). If VTE prophylaxis is used, enoxaparin is indicated (there is no indication for NOACs). Contraindications for NOACs include mechanical prosthetic valve, moderate to severe mitral stenosis (usually of rheumatic origin), while dubious use is in mild to moderate other valvular diseases (limited data), severe aortic stenosis (limited data), hypertrophic cardiomyopathy (no prospective data) and percutaneous aortic valvuloplasty and transcatheter aortic valve implantation (but no prospective data; may require combination with single or double antiplatelets; consider bleeding risk) (10). After mitral valve repair and bioprosthetic valve, NOACs are eligible, except for the first three months post-operatively.

Factors increasing hypercoagulability in rheumatic disorders encompass increased tissue factor expression, increased microparticles (levels of platelet-derived microparticles are elevated), platelet activation, increased fibrinogen level through inflammation, hypercoagulability via complement activation and interaction with coagulation factors, reduced thrombomodulin, as well as increased plasminogen activator inhibitor-1 (PAI-1) (33–35).

TABLE 9. Conditions where we do not have indications for anticoagulant treatment

TABLICA 9. Bolesti u kojima ne postoje indikacije za antikoagulantnu terapiju

ANCA-associated vasculitis – non-beneficial anticoagulant treatment / Vaskulitis povezan s ANCA protutijelima – beskorisno liječenje antikoagulansima
Behcet syndrome – non-beneficial anticoagulant treatment (corticosteroids and azathioprine (venous thromboembolism), cyclophosphamide or cyclosporin A (arterial involvement)) / Behçetov sindrom – beskorisno liječenje antikoagulansima (kortikosteroidi i azatioprin [venska tromboembolija], ciklofosamid ili ciklosporin A [zahvaćenost arterija])
Giant Cell Arteritis (GCA) and Takayasu arteritis (TA) – marginal benefit of using anticoagulation together with corticosteroids in the treatment of venous thromboembolism; in TA there is a benefit of acetylsalicylic acid in the ischemia stroke prevention) / Arteritis velikih stanica (GCA) i Takayasuov arteritis (TA) – marginalna korist primjene antikoagulacijske terapije zajedno s kortikosteroidima u liječenju venske tromboembolije; u TA korisna je primjena acetilsalicilne kiseline u prevenciji ishemijskog moždanog udara
Henoch-Schönlein purpura – no indication (extremely rare incidence of venous thromboembolism) / Henoch-Schönleinova purpura – nema indikacija (izuzetno rijetka incidencija venske tromboembolije)

razine mikročestica izvedenih iz trombocita), aktivaciju trombocita, povećanu razinu fibrinogena koja nastaje kao odgovor na upalu, hiperkoagulabilnost putem aktivacije komplementa i interakcije s faktorima koagulacije, smanjene razine trombomodulina, kao i povećani inhibitor aktivatora plazminogena-1 (PAI-1) (33–35).

Zanimljiva je činjenica da se u Behçetovom sindromu uzrokom DVT-a smatra vaskulitis, a ne hiperkoagulabilnost. Cerebralna venska tromboza koja se javlja u ovih bolesnika treba se liječiti visokim dozama kortikosteroida, nakon čega slijedi smanjenje doze (metilprednizolon treba davati na dnevnoj bazi u obliku parenteralnih pulseva od 1000 mg tijekom 3 do 5 dana, nakon čega slijedi oralna primjena prednizona, počevši s dozom od 1 mg/kg dnevno, dok se doza kortikosteroida za održavanje [koji se daju oralnom primjenom] treba smanjivati tijekom 2 do 3 mjeseca, a antikoagulansi se mogu uvesti kratkotrajno) (36). Zbog toga je primjena antikoagulansa (iako je u različitim studijama utvrđeno da je njihova uloga u Behçetovom sindromu diskutabilna) dopuštena tijekom prijelaznog razdoblja, ali tek nakon što se isključi aneurizma plućne arterije i procijeni rizik od krvarenja. Primjena antikoagulantne terapije preporučuje se i u slučajevima Budd-Chiarijevog sindroma, u slučajevima odgovarajuće imunosupresivne terapije za liječenje rekurentne tromboze, kada su u pitanju drugi uzroci trombofilije: faktor V Leiden ili mutacija gena za protrombin, nedo-

TABLE 10. Interactions of anticoagulants drugs with drugs that are used in rheumatology (according to references No. 31,32)
 TABLICA 10. Interakcije antikoagulanasa s lijekovima koji se upotrebljavaju u reumatologiji (u skladu s literaturom br. 31, 32)

Warfarin / Varfarin	Dabigatran	Rivaroxaban / Rivaroksaban	Apixaban / Apiksaban	Edoxaban / Edoksaban
Methotrexate / Metotrexat	P-gp competition; no relevant interaction anticipated / P-gp kompeticija; bez očekivane relevantne interakcije	No clinical significance / Bez klinički značajnih promjena	No clinical significance / Bez klinički značajnih promjena	No clinical significance / Bez klinički značajnih promjena
Rituximab / Rituksimab	No relevant interaction assumed / Bez pretpostavke relevantne interakcije	No clinical significance / Bez klinički značajnih promjena	No clinical significance / Bez klinički značajnih promjena	No clinical significance / Bez klinički značajnih promjena
Cyclosporine / Ciklosporin	Strong-to-moderate P-gp inhibition, moderate CYP3A4 inhibition; CYP3A4/P-gp competition / Snažna do umjerena inhibicija P-gp-a, umjerena inhibicija CYP3A4; CYP3A4/P-gp kompeticija	Caution required, especially in case of polypharmacy or in the presence of > 2 bleeding risk factors / Potreban oprez, osobito u slučaju polifarmacije ili u prisutnosti > 2 čimbenika rizika od krvarenja	Caution required, especially in case of polypharmacy or in the presence of > 2 bleeding risk factors / Potreban oprez, osobito u slučaju polifarmacije ili u prisutnosti > 2 čimbenika rizika od krvarenja	+73% AUC (dose reduction to 30 mg once daily by label) / +73% u područjima ispod krivulje (AUC) (smanjenje doze na 30 mg jednom dnevno prema uputama)
Dexamethasone / Deksametazon	Moderate CYP3A4 induction; CYP3A4 competition / Umjerena indukcija CYP3A4; CYP3A4 kompeticija	Caution required, especially in case of polypharmacy or in the presence of > 2 bleeding risk factors / Potreban oprez, osobito u slučaju polifarmacije ili u prisutnosti > 2 čimbenika rizika od krvarenja	Caution required, especially in case of polypharmacy or in the presence of > 2 bleeding risk factors / Potreban oprez, osobito u slučaju polifarmacije ili u prisutnosti > 2 čimbenika rizika od krvarenja	No clinical significance / Bez klinički značajnih promjena
Prednisone / Prednizon	Moderate CYP3A4 induction; CYP3A4 competition / Umjerena indukcija CYP3A4; CYP3A4 kompeticija	Caution required, especially in case of polypharmacy or in the presence of > 2 factors that can reduced NOAC plasma levels. / Potreban oprez, osobito u slučaju polifarmacije ili u prisutnosti > 2 čimbenika koji mogu smanjiti razinu NOAK-a u plazmi	Caution required, especially in case of polypharmacy or in the presence of > 2 factors that can reduced NOAC plasma levels. / Potreban oprez, osobito u slučaju polifarmacije ili u prisutnosti > 2 čimbenika koji mogu smanjiti razinu NOAK-a u plazmi	No clinical significance / Bez klinički značajnih promjena
Tofacitinib / Tofacitinib	Risk or severity of bleeding can be increased / Rizik ili jačina krvarenja mogu se povećati	Risk or severity of bleeding can be increased / Rizik ili jačina krvarenja mogu se povećati	Risk or severity of bleeding can be increased / Rizik ili jačina krvarenja mogu se povećati	Risk or severity of bleeding can be increased / Rizik ili jačina krvarenja mogu se povećati
Baricitinib	The metabolism of baricitinib can be increased when combined with warfarin. / Metabolizam baricitiniba može se povećati kada se upotrebljava u kombinaciji s varfarinom	may decrease the excretion rate, which could result in a higher serum level / Može smanjiti brzinu izlučivanja, što može rezultirati višom serumskom koncentracijom	may decrease the excretion rate, which could result in a higher serum level / Može smanjiti brzinu izlučivanja, što može rezultirati višom serumskom koncentracijom	The serum concentration of Baricitinib can be increased when it is combined with Edoxaban. / Serumska koncentracija baricitiniba može se povećati kada se upotrebljava u kombinaciji s edoksabanom
Lefunomide / Lefunomid	Concentration can be decreased. / Koncentracija se može smanjiti	No clinical significance / Bez klinički značajnih promjena	No clinical significance / Bez klinički značajnih promjena	No clinical significance / Bez klinički značajnih promjena
Sulfasalazine / Sulfasalazin	Increased risk of bleeding. / Povećan rizik od krvarenja	Increased risk of bleeding. / Povećan rizik od krvarenja	Increased risk of bleeding. / Povećan rizik od krvarenja	Increased risk of bleeding. / Povećan rizik od krvarenja

Interestingly, in Behçet's disease, vasculitis, and not hypercoagulability, is thought to be the cause of DVT. Cerebral venous thrombosis occurring in these patients should be treated with high doses of corticosteroids followed by tapering (methylprednisolone should be given as daily parenteral pulses of 1000 mg for 3–5 days followed by oral prednisone starting at 1 mg/kg daily, oral maintenance corticosteroids should be tapered over 2–3 months, while anticoagulants may be added for a short duration) (36). On that account, even though the role of anticoagulation in Behçet's disease is debatable among different studies, their use is allowed transiently, but only after a pulmonary artery aneurysm has been ruled out and the risk of bleeding has been assessed; they are also recommended in Budd-Chiari syndrome, in cases of recurrent thrombosis appropriate immunosuppressive therapy, when other causes of thrombophilia are involved – Factor V Leiden or prothrombin gene mutation, protein C, proteins S, and antithrombin III deficiencies, as well as the presence of antiphospholipid (APL) antibodies (41,42,43).

Systemic lupus erythematosus is an independent risk factor for both arterial and venous thrombotic events and is particularly associated with the presence of aPL antibodies; such patients may also use anticoagulation during high-risk periods such as pregnancy and puerperium, postoperatively or if immobilized (42,43,44). One of the manifestations of systemic lupus erythematosus is acute pericarditis, primarily related to high disease activity as well as high D-dimer, and for which NSAIDs are the mainstay of the therapy. Additionally, concurrent use of heparin with another anticoagulant is frequently regarded as a risk factor for hemorrhagic pericardial effusion, leading to cardiac tamponade in SLE patients manifesting pericarditis.

Systemic sclerosis is yet another rheumatic disease characterized by pulmonary hypertension, peripheral arterial disease, positive anti-Scl-70, and aPL antibodies, which all represent risk factors for VTE. However, anticoagulation is not indicated in scleroderma-associated pulmonary hypertension because of the unfavorable risk-to-benefit ratio due to an increased gastrointestinal bleeding rate (45). Anticoagulation, on the other hand, is beneficial in SSc patients with positive aPL antibodies. In other autoimmune rheumatic diseases, namely rheumatoid arthritis, ankylosing spondylitis, polymyositis/dermatomyositis, Sjögren syndrome, and sarcoidosis, which also lead to an increased incidence of DVT and VTE, prophylactic anticoagulation is recommended in cases with a high risk of thrombosis (45). Risk assessment of such patients is based on the Padua Prediction Score, whereby patients with a score ≥ 4 are identified as candidates who would benefit from thromboprophylaxis.

statak proteina C, proteina S i antitrombina III, kao i prisutnost antifosfolipidnih (aPL) protutijela (41,42,43).

Sistemska eritemski lupus neovisni je čimbenik rizika i za arterijske i za venske tromboze i posebno je povezan s prisutnošću aPL protutijela. U tih pacijenata također je moguća primjena antikoagulantne terapije tijekom visokorizičnih razdoblja kao što su trudnoća i puerperij, postoperativno ili ako su imobilizirani (42,43,44). Jedna od manifestacija sistemskog eritemskog lupusa jest akutni perikarditis, prvenstveno povezan s visokom aktivnošću bolesti kao i visokim D-dimerom, a za koji su nesteroidni protuupalni lijekovi glavni oslonac terapije. Osim toga, istodobna primjena heparina s drugim antikoagulantom često se smatra čimbenikom rizika za hemoragični perikardijalni izljev, što uzrokuje tamponadu srca u pacijenata sa sistemskim eritemskim lupusom u kojih se javljaju manifestacije perikarditisa.

Sistemska skleroza još je jedna reumatska bolest koju karakteriziraju plućna hipertenzija, bolest perifernih arterija, pozitivna anti-Scl-70 i aPL protutijela, a sve prethodno navedene karakteristike predstavljaju čimbenike rizika za VTE. Međutim, antikoagulacija nije indicirana kod plućne hipertenzije povezane sa sklerodermijom zbog nepovoljnog omjera rizika i koristi zbog povećane stope gastrointestinalnog krvarenja (45). Antikoagulacija je, s druge strane, korisna u bolesnika sa sistemskom sklerozom s pozitivnim aPL protutijelima. Kod drugih autoimunih reumatskih bolesti, poput reumatoidnog artritisa, ankilozantnog spondilitisa, polimiozitisa/dermatomiozitisa, Sjögrenovog sindroma i sarkoidoze, koje također dovode do povećane incidencije DVT i VTE, preporučuje se profilaktička antikoagulantna terapija u bolesnika s visokim rizikom od tromboze (45). Procjena rizika takvih bolesnika temelji se na bodovnom sustavu Padua (Padua Prediction Score), pri čemu se bolesnici s rezultatom ≥ 4 identificiraju kao kandidati koji bi imali koristi od trombopofilakse.

Bolesnici s vaskulitisom povezanim s aktivnim anti-neutrofilnim citoplazmatskim protutijelima (ANCA) u stanju su hiperkoagulacije i imaju vrlo visok rizik od razvoja VTE. Ovaj rizik vjerojatno ostaje povišen, iako u puno manjim razmjerima, tijekom remisije (38). Ne postoje dostupne određene smjernice za liječenje VTE i/ili plućne embolije u bolesnika s vaskulitisom povezanim s ANCA protutijelima (AAV) (38). U bolesnika s apsolutnim kontraindikacijama za antikoagulantnu terapiju preporučuje se postavljanje filtera u donju šuplju venu (36). Antitrombotska / antikoagulantna terapija prije dijagnoze arteritisa velikih stanica (GCA) nije bila povezana sa smanjenjem teških ishemijskih komplikacija (36). U Takayasuovom arteritisu (TA) čini se da primjena antitrombotske terapije ima zaštitni učinak protiv ishemijskih događaja, dok izgleda da niti

Patients with active antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis are in hypercoagulable states and have a very high risk of VTE. This risk probably remains elevated, although to a much lower degree, during remission (38). No specific guidelines are available for VTEs and/or pulmonary embolism treatment in ANCA-Associated Vasculitis (AAV) patients (38). Insertion of vena cava filter is recommended in patients with absolute contraindications for anticoagulation therapy (36). Antiplatelet/anticoagulant therapy prior to the diagnosis of Giant cell arteritis (GCA) was not associated with a reduction in severe ischemic complications (36). In Takayasu's Arteritis (TA), the use of antiplatelet treatment appears to have a protective effect against ischemic events, while neither anticoagulants nor corticosteroids/immunosuppressive drugs seem to be able to prevent cardiovascular events (36).

Rheumatic heart disease (RHD), specifically rheumatic mitral stenosis, is often complicated by AF, and in these patients, oral anticoagulant therapy is imperative regardless of the stenosis severity and the CHA₂DS₂-VASc score (37). In rheumatic mitral stenosis patients, permanent or paroxysmal AF is a Class I indication for anticoagulation using vitamin K antagonists. Conversely, non-vitamin K antagonist oral anticoagulants (NOACs) are not recommended in patients with moderate-to-severe mitral stenosis (IIIC) owing to the scarcity of data but are now considered in guidelines for patients who develop AF on aortic valve diseases or mitral regurgitation due to rheumatic disease (37,38,39). Individuals with RHD who have a history of stroke or another cardioembolic complication are at increased risk for experiencing recurrent episodes and should be anticoagulated (37).

Indications for rheumatic heart disease anticoagulation include a history of cardioembolic complications such as ischemic stroke, AF, left atrial spontaneous contrast or thrombus in left appendage on echocardiography, mechanical valve implantation, as well as transiently following postoperative valve repair or bioprosthetic implantation (37,38,39).

Efficacy, risk of bleeding, safety, reversibility, and pregnancy suitability are all essential factors to be accounted for when choosing an anticoagulant agent and managing RHD patients. Essentially, warfarin remains the cornerstone of anticoagulation in RHD, owing to the limited evidence of other drugs' efficacy. Warfarin is the treatment of choice for preventing valve thrombosis and thromboembolic complications following mechanical valve implantation.

Anticoagulation requisite in pregnancy due to mechanical valve replacement or AF can be attained with warfarin or heparin (40). Unfractionated or LMWH is mainly reserved for individuals who need anticoagula-

antikoagulansi niti kortikosteroidi / imunosupresivni lijekovi ne mogu spriječiti kardiovaskularne događaje (36).

Reumatska bolest srca, točnije reumatska mitralna stenoza, često se javlja uz komplikacije zbog atrijske fibrilacije (AF), te je u ovih bolesnika oralna antikoagulantna terapija obvezna bez obzira na težinu stenoze i CHA₂DS₂-VASc bodovanje (37). U bolesnika s reumatskom mitralnom stenozom, trajna ili paroksizmalna AF indikacija je klase I za antikoagulaciju uz upotrebu antagonista vitamina K. Suprotno tomu, oralni antikoagulansi (NOAK) koji nisu antagonisti vitamina K ne preporučuju se u bolesnika s umjerenom do teškom mitralnom stenozom (stadij IIIC) zbog nedostatka podataka, ali se sada razmatraju u smjernicama za bolesnike koji razviju AF zbog bolesti aortnog zalistka ili mitralnu regurgitaciju zbog reumatske bolesti (37,38,39). Bolesnici s reumatskim bolestima srca koji u anamnezi imaju moždani udar ili neku drugu kardioembolijsku komplikaciju izloženi su povećanom riziku od rekurentnih epizoda bolesti i trebaju uzimati antikoagulantnu terapiju (37).

Indikacije za primjenu antikoagulantne terapije u bolesnika s reumatskim bolestima srca uključuju anamnezu kardioembolijskih komplikacija kao što su ishemijski moždani udar, AF, spontani kontrast lijevog atrija ili trombu u artikuli lijevog atrija na ehokardiografiji, implantacija mehaničke valvule, kao i prijelazno razdoblje nakon postoperativnog popravka zalistka ili implantacije bioprotetskog zalistka (37,38,39).

Učinkovitost, rizik od krvarenja, sigurnost, reverzibilnost i prikladnost za primjenu u trudnoći ključni su čimbenici koje treba uzeti u obzir pri odabiru antikoagulansa i liječenju bolesnika s reumatskim bolestima srca. Zbog ograničenih dokaza o učinkovitosti drugih lijekova, varfarin ostaje temeljni antikoagulans za primjenu u liječenju reumatskih bolesti srca. Varfarin je lijek koji je prvi odabir u prevenciji tromboze zalistaka i tromboembolijskih komplikacija nakon implantacije mehaničke valvule.

Antikoagulacijska terapija potrebna u trudnoći zbog zamjene valvule mehaničkom valvulom ili AF može se postići primjenom varfarina ili heparina (40). Nefrakcionirani heparin ili NMH uglavnom je rezerviran za bolesnike kojima je potrebna antikoagulacijska terapija tijekom trudnoće ili kada je potrebna brza reverzibilnost u perioperativnom razdoblju ili u slučaju krvarenja. Međutim, iznimka se odnosi na bolesnice s mehaničkim srčanim valvulama, kod kojih se antagonisti vitamina K (VKA) mogu razmatrati kao opcija za primjenu tijekom trudnoće jer, za razliku od heparina, imaju manju vjerojatnost za razvoj tromboze zalistka i manju vjerojatnost da će doći do smrti majke (40). Paralelno, prema preporuci klase I, pacijentice s mehaničkim srčanim valvulama trebaju uzimati male doze

tion during pregnancy or when quick reversibility is required in the perioperative period or the case of bleeding. However, an exception applies to patients with mechanical heart valves, in whom VKAs may be considered an option during pregnancy because, as opposed to heparins, they carry a lesser likelihood of valve thrombosis and maternal death (40). In parallel, by Class I recommendation, patients with MHV should take low-dose aspirin (75–100 mg per day) during the second and third trimesters of pregnancy, in addition to VKAs. LMWH should therefore not be used in pregnant women with rheumatic heart disease and ensuing mechanical heart valves unless weekly monitoring of anti-Xa levels and dose adjustments of LMWH are made, as renal clearance is increased during pregnancy.

In antiphospholipid syndrome (APS) patients presenting with VTE, unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) is the standard first-line therapy, followed by VKA with INR target range 2.0–3.0. Anticoagulation for APS patients with unprovoked VTE ought to be long-term because of the high risk of thrombosis recurrence after discontinuation (41,42,43,44). Recurrent thrombosis with VKA treatment at therapeutic INR is a noted complication of APS, but it can be controlled by increasing the INR target range, switching to LMWH, or adding low-dose aspirin. To prevent pregnancy complications in women with obstetrical APS, a combination of prophylactic dose of LMWH (or prophylactic dose of UFH) and low-dose aspirin is commonly indicated (41,42,43,44). It is noteworthy to mention that, for isolated microhemorrhages, anticoagulant therapy could be a confounding factor because of microvascular damage in APS patients and aPL carriers.

Furthermore, Coronavirus disease (COVID-19) has affected a wide range of rheumatological patients, including those diagnosed with systemic lupus erythematosus, juvenile idiopathic arthritis, Still's disease, as well as catastrophic antiphospholipid syndrome (CAPS), mainly through mechanisms related to the cytokine release syndrome. Thereupon, anticoagulation is invaluable in the management of complicated and severely ill patients due to the uncontrolled release of pro-inflammatory mediators, and in particular, COVID-19 patients with catastrophic antiphospholipid syndrome (CAPS) should be handled with thromboprophylaxis or full-dose therapeutic anticoagulation. Moreover, if COVID-19 patients were on antithrombotic medications for a previously diagnosed thrombotic disease, their treatment should continue as prescribed. If there are no contraindications, patients on vitamin K antagonists who have not had recent stable INRs, and are unable to undergo INR testing, should be transitioned to NOACs; if NOACs are neither ap-

aspirina (75 – 100 mg dnevno) tijekom drugog i trećeg tromjesečja trudnoće, uz primjenu antagonista vitamina K (VKA). NMH se stoga ne smije primjenjivati u trudnica s reumatskom bolešću srca i posljedičnim mehaničkim srčanim valvulama osim ako se ne vrši tjedno praćenje razine anti-Xa aktivnosti i prilagodba doze NMH, budući da je bubrežni klirens povećan tijekom trudnoće.

U bolesnika s antifosfolipidnim sindromom (APS) koji imaju VTE, nefrakcionirani heparin (UFH) ili niskomolekularni heparin (NMH) predstavlja standardnu prvu liniju terapije, nakon čega slijedi primjena antagonista vitamina K (VKA) s ciljnim rasponom INR 2,0 – 3,0. Antikoagulantna terapija za bolesnike s antifosfolipidnim sindromom (APS) i neprovociranim venskim tromboembolizmom (VTE) trebala bi biti dugotrajna zbog visokog rizika od recidiva tromboze nakon prekida terapije (41,42,43,44). Rekurentna tromboza s liječenjem antagonistima vitamina K (VKA) pri terapijskom INR-u poznata je komplikacija APS-a, ali se može kontrolirati povećanjem ciljnog raspona INR-a, prelaskom na terapiju NMH ili uvođenjem niske doze aspirina. Kako bi se spriječile komplikacije u trudnoći kod žena s opstetričkim APS-om, obično je indicirana kombinacija profilaktičke doze NMH (ili profilaktičke doze UFH) i niske doze aspirina (41,42,43,44). Bitno je spomenuti da za izolirana mikrokrvarenja antikoagulantna terapija može biti zbunjujući čimbenik zbog mikrovaskularnih oštećenja u bolesnika s APS-om i nositelja aPL protutijela.

Nadalje, koronavirus (COVID-19) je utjecao na bolesnike koji pate od raznih reumatskih bolesti, uključujući one kojima je dijagnosticiran sistemski eritemski lupus, juvenilni idiopatski artritis, Stillova bolest, kao i katastrofalni antifosfolipidni sindrom (CAPS), uglavnom putem mehanizama povezanih sa sindromom otpuštanja citokina. Stoga je antikoagulantna terapija od neprocjenjive važnosti u liječenju kompliciranih i teško bolesnih pacijenata zbog nekontroliranog otpuštanja proupalnih medijatora, a posebice u slučaju bolesnika oboljelih od COVID-19 s katastrofalnim antifosfolipidnim sindromom (CAPS) koje treba liječiti tromboprolifaksom ili terapijom uz primjenu pune doze antikoagulansa. Nadalje, ako su pacijenti oboljeli od COVID-19 uzimali antitrombotike za prethodno dijagnosticiranu trombotičku bolest, njihovo liječenje treba nastaviti na propisani način. Ako ne postoje kontraindikacije, pacijente koji se liječe primjenom antagonista vitamina K, koji nedavno nisu imali stabilne INR-ove i ne mogu se podvrgnuti INR testiranju, treba prebaciti na liječenje novim oralnim antikoagulansima (NOAK). Ako NOAK nisu niti odobreni niti dostupni, kao alternativna opcija može se primijeniti NMH (enoksaparin 40 mg/dan) (10,11,46).

proved nor available, LMWH (enoxaparin 40 mg/day) can be used as an alternativ (10,11,46).

CONCLUSION

Decision-making on the choice of anticoagulation relies heavily on risk assessment of patients as well as the type of disease, its activity and severity, and comorbidities, with special consideration given to possible drug-drug interactions. The use of NOAC should be based on an individual approach to the patient. Occasionally, circumstances require the use of NOAC in different spheres where there was no primary indication. There are recommendations for treating rheumatological patients, owing to the occurrence of thromboembolic events, which could be attributed to inadequate dosing, monitoring, and poor patient adherence resulting in subtherapeutic anticoagulation. The inclusion of anticoagulants in the treatment of rheumatology patients represents a challenging issue but with considerable space for scientific research.

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ZAKLJUČAK

Donošenje odluke o izboru antikoagulansa uvelike ovisi o procjeni rizika bolesnika kao i o vrsti bolesti, njezinoj aktivnosti i težini te komorbiditetima, s posebnim osvrtom na moguće interakcije lijek – lijek. Primjena novih oralnih antikoagulansa (NOAK) treba se temeljiti na individualnom pristupu svakom bolesniku. Povremeno okolnosti zahtijevaju primjenu NOAK-a u različitim sferama u kojima nije bilo primarne indikacije. Postoje preporuke za liječenje reumatoloških bolesnika, zbog pojave tromboembolijskih incidenata koji se mogu pripisati neadekvatnom doziranju, praćenju i slaboj adherenciji bolesnika, što rezultira subterapijskom primjenom antikoagulansa. Uvođenje antikoagulansa u liječenje reumatoloških bolesnika predstavlja velik izazov, ali to je i tema koja ima velik potencijal u znanstvenom istraživanju.

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INDOLENT EXTRANODAL B-NHL CD20 POSITIVE MALT LYMPHOMA IN A PATIENT WITH PRIMARY SJÖGREN'S SYNDROME WITH A GOOD RESPONSE TO RITUXIMAB TREATMENT

INDOLENTNI EKSTRANODALNI B-NHL CD20 POZITIVNI LIMFOM TIPA MALT U BOLESNICE S PRIMARNIM SJÖGREN OVIM SINDROMOM UZ DOBAR ODGOVOR NA LIJEČENJE RITUKSIMABOM

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ABSTRACT

Sjögren's syndrome (SS) is a chronic autoimmune disease in which chronic lymphocytic infiltration leads to progressive destruction of the exocrine glands and consequently causes the dry syndrome. The most commonly affected are the lacrimal and salivary glands. Less often, SS presents with the symptoms of exocrine glands of other localisation, arthritis, myositis, vasculitis involving the skin and the nervous system, interstitial lung disease, and kidney disease. The most serious complication is the development of lymphoproliferative disease, primarily non-Hodgkin's lymphoma (NHL). We present the case of a patient who developed indolent extranodal B-NHL CD20-positive MALT-type lymphoma after 23 years of primary SS duration, with a good response to rituximab treatment.

KEYWORDS: Sjögren's Syndrome, Lymphoproliferative Disorders, B-Cell Marginal Zone Lymphoma, Rituximab

SAŽETAK

Sjögrenov sindrom (SS) kronična je autoimuna bolest u kojoj limfocitna infiltracija dovodi do progresivnog oštećenja egzokrinih žlijezda i sljedstvenoga suhog sindroma. Najčešće zahvaća suzne i slinovne žlijezde, a manje često se javljaju simptomi egzokrinih žlijezda druge lokalizacije, artritis, miozitis, vaskulitis sa zahvaćanjem kože i živčanog sustava, intersticijska bolest pluća i bubrežna bolest. Najteža komplikacija je razvoj limfoproliferativne bolesti, u prvom redu ne-Hodgkinovog limfoma (NHL-a). U radu prikazujemo bolesnicu koja je nakon 23 godine trajanja primarnog SS-a razvila indolentni ektranodalni B-NHL CD20 pozitivni limfom tipa MALT uz dobar odgovor na liječenje rituksimabom.

KLJUČNE RIJEČI: Sjögrenov sindrom, limfoproliferativne bolesti, B-stanični limfom marginalne zone, rituksimab

INTRODUCTION

Sjögren's syndrome (SS) is a chronic autoimmune disease in which chronic lymphocytic infiltration leads to the destruction of the exocrine glands, thus causing the dry syndrome. SS may be classified into primary

UVOD

Sjögrenov sindrom (SS) kronična je autoimuna bolest u kojoj limfocitna infiltracija dovodi do oštećenja egzokrinih žlijezda uzrokujući suhi sindrom. SS se dijeli na primarni (pSS) koji nije udružen s drugim

(pSS), which is not associated with other diseases, and secondary (sSS), which occurs in association with other autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), polymyositis (PM), granulomatosis with polyangiitis (GPA) or progressive systemic sclerosis (PSS) (1). The prevalence of SS ranges from 0.1 to 4.8%, the incidence is nine times higher in women, and it commonly occurs in middle-aged patients (2).

The occurrence of the disease is associated with the HLA-B8 and HLA-DR3 genes and with viral infections (cytomegalovirus and Epstein-Barr virus). SS should be suspected with the occurrence of symptoms of dry eyes and mouth, and the diagnosis is confirmed by objective evidence of reduced secretion of tears and saliva with the presence of autoantibodies (antinuclear antibodies [ANA], anti-SSA/Ro and anti-SSB/La antigens are present in up to 70% of patients, and the rheumatoid factor [RF] may be positive as well), but the diagnosis can also be made when there is an absence of the typical autoantibodies. Sometimes, to confirm the diagnosis, it is necessary to perform minor salivary gland biopsy (most often in the area of the lower lip mucosa) in order to confirm the diagnosis with a typical histopathology finding of lymphocytic infiltration with the formation of lymphocytic foci. It is important to note that dry eyes and mouth can be caused by numerous diseases, conditions, or medications, so before making a diagnosis of pSS, it is necessary to rule out the aforementioned diseases or conditions and take a medical history. There is a clearly defined set of tests that can be used to objectify the reduction of tear or saliva secretion (3–5).

The typical clinical presentation of the disease includes symptoms of dry eyes and dry mouth. Decreased function of the glands in the nose, pharynx and larynx can cause a feeling of dryness in the nose, cough, and hoarseness, while decreased function of the glands in the vagina causes dyspareunia (1). Dryness of the respiratory mucosa can also be the cause of recurrent infections. Since pSS is a systemic disease, extraglandular symptoms also occur in a large number of patients. The most common symptoms include chronic fatigue, Raynaud's syndrome, skin changes such as erythema multiforme (target-shaped lesions or oedematous papules on the edges, i.e., acral), subacute cutaneous lupus erythematosus (papulosquamous lesions with annular lesions in places exposed to the sun, excluding the face) and cutaneous vasculitis (palpable purpura, maculopapular rash or urticaria) (6).

Joints and muscles can also be affected in the form of arthralgia with morning stiffness, joint swelling, and muscle weakness as a result of synovitis and myositis. Involvement of the central and peripheral nervous system is manifested by peripheral polyneuropathy, cra-

olestima i sekundarni (sSS) koji se javlja uz druge autoimune bolesti poput sistemskog eritemskog lupusa (SLE), reumatoidnog artritisa (RA), polimiozitisa (PM), granulomatoze s poliangiitizom (GPA) ili progresivne sistemske skleroze (PSS) (1). Prevalencija SS-a iznosi od 0,1 do 4,8%, pojavnost je devet puta veća u žena, a većinom se pojavljuje u srednjoj životnoj dobi (2).

Pojavnost bolesti povezuje se uz gene HLA-B8 i HLA-DR3 te uz virusne infekcije (citomegalovirus i Epstein-Barrov virus). Na SS treba posumnjati pri simptomima suhoće očiju i usta, a dijagnoza se potvrđuje objektivnim dokazom smanjene sekrecije suza i sline uz prisutnost autoantitijela (antinuklearna antitijela [ANA], antitijela protiv antigena SSA/Ro i SSB/La prisutna su u do 70% bolesnika, može biti pozitivan i reumatoidni faktor [RF]), no dijagnoza se može postaviti i kada su tipična autoantitijela odsutna. Ponekad je za potvrdu dijagnoze potrebno učiniti i biopsiju male slinovne žlijezde (najčešće u području sluznice donje usnice) kako bi se dijagnoza potvrdila tipičnim patohistološkim nalazom (PHD) limfocitne infiltracije uz formiranje limfocitnih fokusa. Važno je napomenuti da suhoća očiju i usta može biti uzrokovana brojnim bolestima, stanjima ili lijekovima pa je prije postavljanja dijagnoze pSS-a potrebno isključiti navedene bolesti ili stanja i uzeti anamnezu o uzimanju lijekova. Jasno je definiran sklop testova kojima se može objektivizirati smanjenje proizvodnje suza ili sline (3–5).

Tipična klinička prezentacija bolesti uključuje simptome suhih očiju i suhih usta. Smanjena funkcija žlijezda u nosu, ždrijelu i grkljanu može uzrokovati osjećaj suhoće nosa, kašalj, promuklost, dok smanjena funkcija žlijezda u rodnicama uzrokuje dispareuniju (1). Suhoća respiratorne sluznice može biti i uzrokom ponavljajućih infekcija. Budući da je pSS sistemska bolest, u velikog broja bolesnika javljaju se i ekstraglandularni simptomi. Među njima su najčešći kronični umor, Raynaudov sindrom, kožne promjene poput multifornog eritema (lezije oblika mete ili edematozne papule na okrajinama, tj. akralno), subakutnoga kožnog eritematoznog lupusa (papulo-skvamozne lezije s prstenastim lezijama na mjestima izloženim suncu, isključujući lice) i vaskulitičnih kožnih promjena (palpabilna purpura, makulopapulozni osip ili urtikarija) (6).

Također mogu biti zahvaćeni zglobovi i mišići u vidu artralgijskog jutarnjeg zastoja, otekline zglobova i mišićne slabosti posljedično sinovitisu i miozitisu. Zahvaćanje središnjeg i perifernog živčanog sustava očituje se perifernom polineuropatijom, neuropatijom kranijalnih živaca, vaskulitisom perifernih živaca, cerebralnim vaskulitisom, transverzalnim mijelitisom ili limfocitnim meningitisom. Zahvaćenost pluća uključuje široki spektar manifestacija, od kašlja do intersticijske bolesti pluća. Zahvaćenost bubrega može se očitovati proteinurijom, leukociturijom, hematurijom,

TABLE 1. ACR/EULAR Classification Criteria for Primary Sjögren's Syndrome (pSS)

TABLICA 1. ACR/EULAR klasifikacijski kriteriji za primarni Sjögrenov sindrom (pSS)

Classification criteria for pSS applies to any individual who meets the inclusion criteria, does not have any of the conditions listed as exclusion criteria, and has a score of ≥ 4 when the weights from the five criteria items in the table are summed. / Klasifikacija pSS-a primjenjuje se na svakog pojedinca koji ispunjava kriterije uključivanja, nema niti jedan isključni kriterij i ima ocjenu ≥ 4 kada se zbroje težinske vrijednosti iz pet kriterija prikazanih u tablici.	
Criterion / Kriterij	Weights / Težinski bodovi
Labial salivary gland biopsy finding of focal lymphocytic sialadenitis with a focus score of ≥ 1 foci/4 mm* / Nalaz biopsije labijalnih žlijezda slinovnica s fokalnim limfocitnim sijaloadenitisom uz ≥ 1 limfocitni fokus u 4 mm ² tkiva*	3
Anti-SSA/Ro antibody positivity / Pozitivna anti-SSA/Ro protutijela	3
Objective assessment of dry eyes using Ocular staining score** ≥ 5 or van Bijsterveld score*** ≥ 4 on at least one eye / Objektivna procjena suhoće očiju pomoću „Ocular staining score“** ≥ 5 ili pomoću „van Bijsterveld score“*** ≥ 4 zadovoljena barem na jednom oku	1
Schirmer ≤ 5 mm / 5 min on at least one eye / Schirmerov test ≤ 5 mm/5 min na barem na jednom oku	1
Unstimulated whole saliva flow rate**** ≤ 0.1 ml/min / Nestimulirano lučenje sline**** $\leq 0,1$ ml/min	1

Adapted from: Shiboski CH, Shiboski SC, Seror R, Criswell LA, Labetoulle M, Lietman TM et al. 2016 ACR-EULAR Classification Criteria for primary Sjögren's Syndrome: A Consensus and Data-Driven Methodology Involving Three International Patient Cohorts. *Arthritis Rheumatol Hoboken NJ*. 2017;69(1):35–45. (9) / Prilagođeno prema: Shiboski CH, Shiboski SC, Seror R, Criswell LA, Labetoulle M, Lietman TM i sur. 2016 ACR-EULAR Classification Criteria for primary Sjögren's Syndrome: A Consensus and Data-Driven Methodology Involving Three International Patient Cohorts. *Arthritis Rheumatol Hoboken NJ*. 2017;69(1):35–45. (9)

* * Numerical assessment of lymphocyte infiltration (focus score) refers to the number of focal aggregations of lymphocytes in 4 mm² of tissue (aggregation ≥ 50 lymphocytes is considered as the focus), and biopsy should be done according to the protocol of the study conducted by Daniels et al. which was published in 2011 (12). / Numerička procjena limfocitne infiltracije (engl. focus score) odnosi se na broj fokalnih agregacija limfocita u 4 mm² tkiva (agregacija ≥ 50 limfocita smatra se fokusom), a biopsiju treba učiniti prema protokolu studije Danielsa i suradnika iz 2011. godine (12).

** The Ocular Staining Score based on the method described by Whitcher et al., which was published in 2010 (3). / Ocular staining score prema protokolu Whitchera i suradnika iz 2010. godine (3).

*** Van Bijsterveld score, based on the van Bijsterveld protocol, which was published in 1969 (4). / Van Bijsterveld score prema protokolu istomenog autora iz 1969. godine (4).

**** The unstimulated salivary flow rate should be assessed based on the method described by Navazesh and Kumar, which was published in 2008 (5). / Nestimulirano lučenje sline prema protokolu Navazesh i Kumara iz 2008. (5).

Sensitivity and specificity of the criteria is 96% (95% CI 92% to 98%) and 95% (95% CI 92% to 97%), respectively, thus they are appropriate for use as criteria for enrolment in clinical trials. / Senzitivnost i specifičnost kriterija iznosi 96% (95% CI 92% do 98%) i 95% (95% CI 92% do 97%), kako slijedi, a pogodni su za uključivanje ispitanika u klinička istraživanja.

nial neuropathy, vasculitis of peripheral nerves, cerebral vasculitis, transverse myelitis, or lymphocytic meningitis. Pulmonary involvement includes a wide spectrum of manifestations, from cough to interstitial lung disease. Renal involvement can be manifested by proteinuria, leukocyturia, haematuria, interstitial nephritis, renal tubular acidosis, and glomerulonephritis. Haematological manifestations of the disease include autoimmune anaemia, neutropenia, lymphopenia, and thrombocytopenia, followed by hypergammaglobulinemia and hypogammaglobulinemia, reduced complement production and cryoglobulinemia (7,8).

By using a methodology in accordance with the new SS classification criteria adopted by the umbrella organisations for rheumatology of the United States of America and the European Union (2017 ACR/EULAR classification criteria), a unique set of consensus classification criteria was developed based on data for pSS, which proved to be useful in evaluation and are suitable as entry criteria for clinical trials (Table 1) (9). In order to apply the above classification criteria to an individual patient, it is necessary to first meet the inclu-

intersticijskim nefritisom, renalnom tubularnom acidozom i glomerulonefritisom. Od hematoloških očitovanja bolesti moguće su autoimuna anemija, neutropenija, limfopenija i trombocitopenija, zatim hipergamaglobulinemija i hipogamaglobulinemija, smanjena produkcija komplementa i krioglobulinemija (7,8).

Koristeći metodologiju u skladu s novim kriterijima klasifikacije SS-a donesenim od krovnih reumatoloških organizacija Sjedinjenih Američkih Država i Europske unije (klasifikacijski kriteriji ACR/EULAR iz 2017. godine), razvijen je jedinstveni skup konsenzusnih klasifikacijskih kriterija na temelju podataka za pSS, koji su se dobro pokazali u validaciji i koji su prikladni kao ulazni kriteriji za klinička ispitivanja (tablica 1) (9). Za primjenu navedenih klasifikacijskih kriterija u individualnog bolesnika potrebno je prvo zadovoljiti kriterije uključivanja i isključivanja koje prikazuje tablica 2. Ulazni kriterij za primjenu klasifikacijskih kriterija jest postojanje simptoma suhog oka ili simptoma suhih usta ili pozitivne barem jedne domene u indeksu aktivnosti bolesti ESSDAI (10), uz odsutnost isključujućih kriterija (tablica 2) (9).

TABLE 2. The exclusion and inclusion criteria for identification of patients applicable for ACR/EULAR Classification Criteria for Primary Sjögren's Syndrome

TABLICA 2. Kriteriji uključivanja i isključivanja bolesnika pri primjeni ACR/EULAR klasiifikacijskih kriterija za primarni Sjögrenov sindrom

Inclusion criteria are applicable to any patient with at least one symptom of ocular or oral dryness, defined as a positive response to at least one of the following 5 questions or in whom there is suspicion of Sjögren's syndrome (SS) from the EULAR SS Disease Activity Index questionnaire (at least one domain with a positive item at ESSDAI). / Kriteriji uključivanja označuju prisutnost barem jednog simptoma suhoće očiju ili usta, tj. pozitivan odgovor na barem jedno od 5 pitanja niže navedenih u tablici ili postojanje sumnje na Sjögrenov sindrom (SS) prema EULAR upitniku za procjenu aktivnosti bolesti SS (pozitivna barem jedna domena upitnika ESSDAI).
1. Have you had daily, persistent, troublesome dry eyes for more than 3 months? / Jeste li imali svakodnevne, uporne, poteškoće vezane uz suhoću očiju dulje od 3 mjeseca?
2. Do you have a recurrent sensation of sand or gravel in the eyes? / Imate li ponavljajući osjećaj pijeska ili šljunka u očima?
3. Do you use tear substitutes more than three times a day? / Koristite li umjetne suze više od tri puta dnevno?
4. Have you had a daily feeling of dry mouth for more than 3 months? / Jeste li imali svakodnevni osjećaj suhih usta dulje od 3 mjeseca?
5. Do you frequently drink liquids to aid in swallowing dry food? / Pijete li često tekućinu kako biste lakše progutali suhu hranu?
Exclusion criteria: prior diagnosis of any of the following conditions would exclude diagnosis of SS / Kriterij isključivanja: poznata dijagnoza bolesti ili stanja niže navedenih u tablici isključuje dijagnozu SS-a
1. History of head and neck radiation treatment / Anamneza liječenja zračenjem glave i vrata
2. Active Hepatitis C infection (with positive PCR) / Aktivna infekcija hepatitisom C (potvrđena PCR testom)
3. Acquired immunodeficiency syndrome / AIDS
4. Sarcoidosis / Sarkoidoza
5. Amyloidosis / Amiloidoza
6. Graft-versus-host disease / Bolest odbacivanja presatka
7. IgG4-related disease / Bolest povezana s IgG4

Adapted from: Shiboski CH, Shiboski SC, Seror R, Criswell LA, Labetoulle M, Lietman TM et al. 2016 ACR-EULAR Classification Criteria for primary Sjögren's Syndrome: A Consensus and Data-Driven Methodology Involving Three International Patient Cohorts. *Arthritis Rheumatol* Hoboken NJ. 2017;69(1):35–45. (9) / Prilagođeno prema: Shiboski CH, Shiboski SC, Seror R, Criswell LA, Labetoulle M, Lietman TM i sur. 2016 ACR-EULAR Classification Criteria for primary Sjögren's Syndrome: A Consensus and Data-Driven Methodology Involving Three International Patient Cohorts. *Arthritis Rheumatol* Hoboken NJ. 2017;69(1):35–45. (9)

sion and exclusion criteria shown in Table 2. The entry criterion for the application of the classification criteria is the occurrence of symptoms such as dry eyes and dry mouth or at least one domain with a positive item at the EULAR Sjögren's syndrome (SS) disease activity index (ESSDAI) (10), with the absence of the exclusion criteria (Table 2) (9).

Indeks aktivnosti bolesti ESSDAI razvijen je za bolesnike s pSS-om. Riječ je o indeksu koji mjeri sustavnu aktivnost bolesti, a koji je generiran 2009. godine. Njegova je primjena prvenstveno u kliničkim istraživanjima. Uključuje 12 domena, tj. organskih sustava (*kožni* – vaskulitis; *respiratorni* – intersticijska bolest pluća; *bubrežni* – renalna tubularna acidoza, glomerulonefritis; *zglobni* – artralgijske, sinovitis; *mišićni* – miozitis; *periferni živčani sustav* – aksonalna motorna i/ili senzorna neuropatija i/ili polineuropatija, upalna demijelinizirajuća polineuropatija, gangliopatija, vaskulitis sa slikom multiplog mononeuritisa; *središnji živčani sustav* – neuropatija kranijalnih živaca, sindrom sličan multiploj sklerozi, vaskulitis sa slikom tranzitorne ishemijske atake ili cerebrovaskularnog inzulta ili transverzalnog mijelitisa, limfocitni meningitis; *žljezdani* – uvećanje suznih ili slinovnih žlijezda; *hematološki* – autoimune citopenije; *konstitucijski* – vrućica; noćno znojenje; nevoljni gubitak na tjelesnoj težini; limfadenopatski – limfadenopatija ili limfom; *biološki* – hipokomplementemija, hipergamaglobulinemija, hipogamaglobulinemija, krioglobulinemija), a svaka domena podijeljena je na tri do četiri razine aktivnosti (10).

Liječenje u prvom redu uključuje simptomatsko liječenje suhoće sluznica. Kod bolesnika koji imaju aktivnu bolest barem jednog organa ili organskog sustava (posebice kod ekstrapulmonarnih prezentacija bolesti) potrebno je primijeniti sistemsku imunosupresivnu i/ili imunomodulacijsku terapiju, koja uključuje glukokortikoidne, antimalariske, klasične imunosupresive, intravenske imunoglobuline i biološke lijekove (u prvom redu rituksimab). Primjena antimalarika (klorokina/hidroklorokina) ima pozitivan učinak na opće simptome i artritis te veličinu slinovnih žlijezda (11).

PRIKAZ BOLESNICE

Autoimuna bolest započela je 1997. godine (u dobi od 30 godina) recidivirajućim simetričnim artritisom šaka praćenim ubrzanom sedimentacijom eritrocita (SE). Bolesnica je do 2004. godine povremeno liječena malom dozom prednizolona (do 10 mg dnevno) i nesteroidnim antireumaticima. Dijagnoza pSS-a postavljena je 2008. godine na osnovi simetričnoga neerozivnog artritisa malih zglobova šaka (slika 1), umjereno ubrzane SE, subjektivnog i objektivnog nalaza suhoće očiju i usta, tipičnog PHD nalaza male slinovne žlijezde (fokalni limfocitni infiltrati), pozitivnog ANF-a (točkasta indirektna imunofluorescencija) i RF-a uz negativan nalaz anti-dsDNA, Sm, SSA/Ro, SSA/La, a u kasnijim kontrolama i negativnog nalaza anti-CCP-a. Tada su ultrazvučnim pregledom utvrđene tipične difuzne promjene slinovnica (heterogena ehofrukturna, hipoehogena područja, linearni hiperehogeni odjeci uz brojne cistične formacije i kalcifikacije). Od 2008. godine u nalazima se bilježi višekratna odsutnost hi-

The ESSDAI disease activity index was developed for patients with pSS. It is an index that measures the systemic activity of the disease, and which was generated in 2009. It is primarily applied in clinical research. It includes 12 domains, i.e. organ systems (*cutaneous* – vasculitis; *respiratory* – interstitial lung disease; *renal* – renal tubular acidosis, glomerulonephritis; *articular* – arthralgias, synovitis; *muscular* – myositis; *peripheral nervous system (PNS)* – axonal motor and/or sensory neuropathy and/ or polyneuropathy, inflammatory demyelinating polyneuropathy, gangliopathy, vasculitis with a pattern of mononeuritis multiplex; *central nervous system (CNS)* – neuropathy of the cranial nerves, a syndrome similar to multiple sclerosis, vasculitis with a pattern of transient ischemic attack or cerebrovascular insult or transverse myelitis, lymphocytic meningitis; *glandular* – enlargement of lacrimal or salivary glands; *haematological* – autoimmune cytopenias; *constitutional* – fever; night sweats; unintentional weight loss; *lymphadenopathic* – lymphadenopathy or lymphoma; *biological* – hypocomplementemia, hypergammaglobulinemia, hypogammaglobulinemia, cryoglobulinemia), and each domain is divided into three to four levels of activity (10).

The first-line treatment includes the symptomatic treatment of dry mucous membranes. In patients who have an active disease of at least one organ or organ system (especially with extraglandular presentations of the disease), it is necessary to apply systemic immunosuppressive and/or immunomodulating therapy, which includes glucocorticoids, antimalarials, classical immunosuppressants, intravenous immunoglobulins and biological drugs (primarily rituximab). The use of antimalarials (chloroquine/hydroxychloroquine) has a positive effect on general symptoms and arthritis and the size of the salivary glands (11).

CASE REPORT

The autoimmune disease started in 1997 (when the patient was 30 years old) with recurrent symmetric arthritis of the hands followed by accelerated erythrocyte sedimentation rate (ESR). Until 2004, the patient was occasionally treated with a small dose of prednisolone (up to 10 mg per day) and non-steroidal anti-inflammatory drugs (NSAIDs). The diagnosis of pSS was established in 2008 on the basis of symmetric non-erosive arthritis of the small joints of the hands (Figure 1), moderately accelerated ESR, subjective and objective findings of dry eyes and mouth, standard histopathological findings of a small salivary gland (focal lymphocytic infiltrates), positive ANF (dotted staining pattern in indirect immunofluorescence) and RF with a negative anti-dsDNA, Sm, SSA/Ro and SSA/La result, and, at later follow-ups, a negative anti-CCP result. Then, typical diffuse changes of the salivary glands

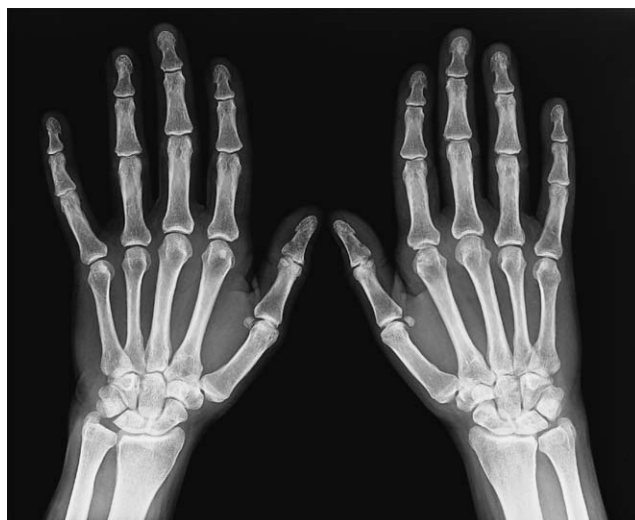


FIGURE 1. Symmetric non-erosive arthritis of the small joints of the hands on a plain radiograph

SLIKA 1. Simetrični neerozivni artritis malih zglobova šaka na standardnom radiogramu šaka

pergamaglobulinemije i citopenije. Bolesnica je od 2008. godine kontinuirano liječena antimalarikom (klorokin), a od 2008. do 2016. godine i prednizolonom u dnevnoj dozi do 10 mg, kada se lijek postupno ukida radi razvoja intolerancije glukoze, a bez posljedice aktivacije artritisa. Od prosinca 2013. godine prati se klinički, ultrazvučno i citološki bezbolna nodozna otekline desne parotide uz odsustvo B-simptoma, limfadenopatije i splenomegalije (slika 2A). Nodozna otekline desne parotide u početku je shvaćena kao limfni čvor unutar žlijezde. U listopadu 2017. godine prvi put citološki nalaz ukazuje na mogući razvoj NHL-a tipa MALT (ekstranodalni B-stanični limfom marginalne zone podrijetlom limfatičnog tkiva sluznice). Krajem 2020. godine nastupa nagli porast čvora desne parotide. Početkom 2021. godine po hematologu je potvrđena dijagnoza indolentnoga ekstranodalnog B-staničnog NHL-a, CD20 pozitivnog, tipa MALT, bez zahvaćanja limfnih čvorova i koštane srži i bez splenomegalije (utvrđen stadij II AE desne parotide; II – lokalizacija samo s jedne strane dijafragme, A – odsutnost B-simptoma u vidu vrućice i gubitka na tjelesnoj težini te noćnih znojenja, E – ekstranodalno podrijetlo, tj. iz tkiva izvan limfnog sustava). Bolesnica je u travnju 2021. godine primila prvi ciklus rituksimaba s dobrim učinkom u kombinaciji s bendamustinom. Klinički i ultrazvučno nastupilo je smanjenje desne parotidne žlijezde za 30% već tri tjedna nakon početka liječenja uz poboljšanje salivacije (slika 2B).

RASPRAVA

Dosadašnja istraživanja opisala su povećani rizik od razvoja limfoma u bolesnika sa SS-om u odnosu na opću populaciju, a također i u odnosu na bolesnike s

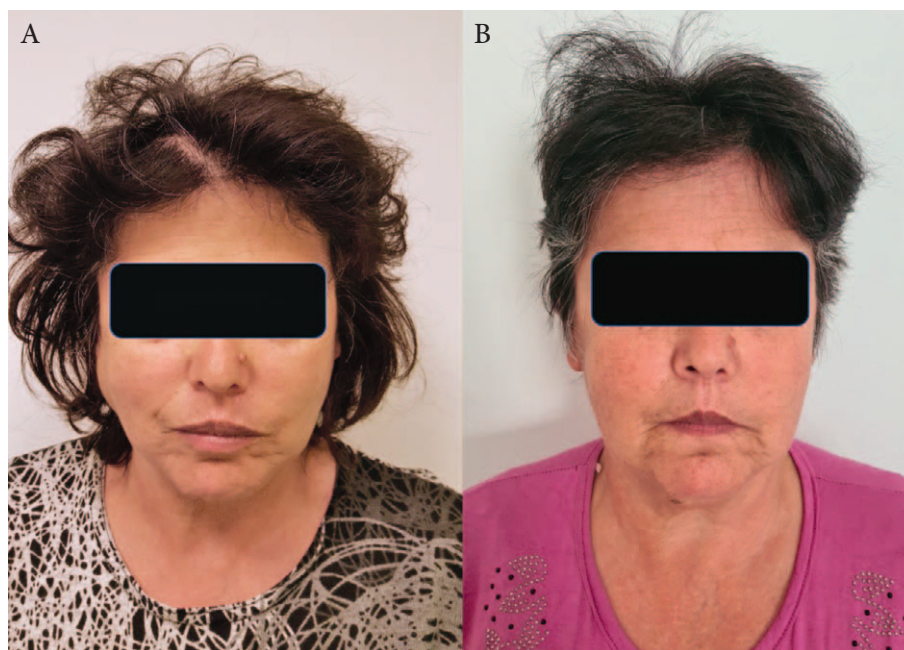


FIGURE 2. Nodular swelling of the right parotid gland before (A) and after (B) rituximab treatment
SLIKA 2. Nodozna oteklina desne parotidne žlijezde prije (A) i poslije (B) liječenja rituksimabom

were observed through an ultrasound (heterogeneous echogenicity, hypoechoic areas, linear hyperechoic masses with numerous cystic formations and calcifications). Since 2008, the findings have shown repeated absence of hypergammaglobulinemia and cytopenia. Since 2008, the patient has been continuously treated with an antimalarial (chloroquine), and from 2008 to 2016 with prednisolone at a daily dose of up to 10 mg. Then, the drug was gradually discontinued due to the development of glucose intolerance, without the consequent activation of arthritis. Since December 2013, the follow-up of the painless nodular swelling of the right parotid gland, with the absence of B-symptoms, lymphadenopathy, and splenomegaly, was carried out through clinical, ultrasound and cytological findings (Figure 2A). The nodular swelling of the right parotid gland was initially understood as a lymph node within the gland. In October 2017, for the first time, a cytological finding indicated the possible development of NHL of the MALT type (extranodal B-cell marginal zone lymphoma arising in the lymphatic tissue of the mucous membrane). At the end of 2020, there was a rapid growth in the right parotid node. At the beginning of 2021, the haematologist confirmed the diagnosis of indolent extranodal B-cell NHL of the CD20 positive MALT lymphoma, without the involvement of the lymph nodes and bone marrow and without splenomegaly (stage II AE of the right parotid gland; II – localisation only on one side of the diaphragm, A – absence of B-symptoms in the form of fever, weight loss and night sweats, E – extranodal origin, i.e. from tissues outside the lymphatic system). In April 2021, the

drugim autoimunim bolestima (12–15). Najčešći oblik limfoma u bolesnika sa SS-om jest B-stanični NHL niskog do srednjeg stupnja malignosti, histološki podijeljen na limfom marginalne zone koji obuhvaća limfoidne tumore povezane sa sluznicom, takozvani MALT limfom (engl. *mucosa associated lymphoid tissue*) i nodalni B-stanični limfom marginalne zone (NMZL; engl. *nodal marginal zone lymphoma*). Mogući drugi oblici NHL-a u bolesnika sa SS-om jesu difuzni B-velikostanični limfom (DLBCL; engl. *diffuse large B-cell lymphoma*) koji pripada u skupinu visokog stupnja malignosti. Rjeđe se mogu razviti leukemije, Waldenstromova makroglobulinemija i multipli mijelom (16–22). MALT i NMZL smatraju se limfomima niskog do srednjeg stupnja malignosti.

Ne-Hodgkinovi limfomi koji kompliciraju tijek pSS-a karakterizirani su bezbolnim oteklinama žlijezda slinovnica (najčešće parotida), indolentnim tijekom, normalnim razinama laktat dehidrogenaze (LDH) i beta2 mikroglobulina, dobrim općim stanjem, odsutnošću B-simptoma, a zahvaćenost koštane srži je rijetka. U pristupu takvim bolesnicima i odabiru modaliteta liječenja koristi se klasifikacija Lugano (23) koja je trenutno najnovija klasifikacija proširenosti primarnih nodalnih limfoma i dopunjuje dosadašnje klasifikacije naglašavajući važnost PET/CT-a s FDG-om (PET, engl. *positron emission tomography*; CT, engl. *computed tomography*; FDG, engl. *fluorodeoxyglucose*), za određivanje proširenosti bolesti (tablica 3).

Važnost klasifikacije osim odabira modaliteta liječenja jest i u individualnom pristupu i praćenju bolesnika jer je poznato da se u desetak posto bolesnika limfo-

patient received the first cycle of rituximab which yielded good results in combination with bendamustine. The clinical and ultrasound findings revealed a reduction of the right parotid gland by 30%, as early as three weeks after the start of treatment, with an improvement in salivation (Figure 2B).

DISCUSSION

Previous research has described an increased risk of developing lymphoma in patients with SS compared to the general population, and also compared to patients with other autoimmune diseases (12–15). The most common form of lymphoma in patients with SS is B-cell NHL of low to intermediate grade of malignancy, which is histologically divided into marginal zone lymphoma that includes lymphoid tumours associated with the mucosa, the so-called MALT lymphoma (mucosa-associated lymphoid tissue) and nodal B-cell marginal zone lymphoma (NMZL). Possible other forms of NHL in patients with SS include diffuse large B-cell lymphoma (DLBCL) which belongs to high-grade malignancy group. Leukemias, Waldenstrom macroglobulinemia and multiple myeloma usually develop less frequently (16–22). MALT and NMZL are considered low- to intermediate-grade lymphomas.

Non-Hodgkin's lymphomas that complicate the course of pSS are characterised by painless swelling of the salivary glands (most often the parotid gland), indolent disease course, normal levels of lactate dehydrogenase (LDH) and beta-2 microglobulin (B2M), good general condition and absence of B-symptoms, while bone marrow involvement rarely occurs as a characteristic of this disease. In the approach to such patients and the selection of treatment modality, the Lugano classification (23) is used, which is currently the most recent classification of the extent of spread of primary nodal lymphomas which serves as an addition to the previous classifications by emphasising the importance of (FDG) PET/CT (positron emission tomography (PET), computed tomography (CT), fluorodeoxyglucose (FDG)), in order to determine the extent of spread of the disease (Table 3).

The importance of classification, in addition to the choice of treatment modality, is also in the individual approach to each patient and patient follow-up, because it is known that in ten percent of patients, low-grade lymphomas can transform into high-grade lymphomas, mostly in the case of diffuse large B-cell lymphoma (DLBCL), which we know originates from the same clone as low-grade lymphomas (22–24).

As a result of new insights about the potential malignant transformation in pSS, which, after RA, is the second most frequent systemic autoimmune disease, predictive risk factors for the development of lymphoma in patients with SS have been identified over time,

TABLE 3. The Lugano classification for primary nodal lymphomas

TABLICA 3. Klasifikacija Lugano za primarne nodalne limfome

Stage / Stadij	Involvement / Proširenost	Extranodal (E) / Ekstranodalno (E)
I	One node or a group of adjacent nodes / Jedan limfni čvor ili grupa susjednih čvorova	Single extranodal lesions without nodal involvement / Pojedinačne ekstranodalne lezije bez uključenosti limfnih čvorova
II	Two or more nodal groups on the same side of the diaphragm / Dvije ili više grupa čvorova na istoj strani dijafragme	Stage I or II by nodal extent with limited contiguous extranodal involvement / Stadij I ili II po nodalnoj proširenosti s ograničenom kontinuiranom proširenosti ekstranodalno
II bulky / glomazni	As stage II with single large tumour mass (bulky); ≥ 10 cm in diameter or $>1/3$ transthoracic diameter on CT / Kao stadij II bolesti, no prisutna je pojedinačna velika tumorska masa (engl. <i>bulky</i>); ≥ 10 cm u promjeru ili $>1/3$ transtorakalnog dijametara na CT-u	Not applicable / Nije primjenjivo
III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement / Čvorovi s obje strane dijafragme; čvorovi iznad dijafragme sa zahvaćanjem slezene	Not applicable / Nije primjenjivo
IV	Additional noncontiguous extralymphatic involvement / Dodatna nekontinuirana ekstralimfatička proširenost bolesti	Not applicable / Nije primjenjivo

Adapted from: Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol.* 2014;32(27):3062. (23) / Prilagođeno prema: Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E i sur. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol.* 2014;32(27):3062. (23)

mi niskog stupnja mogu transformirati u limfom visokog stupnja, uglavnom u tip DLBCL, a za koji znamo da proizlazi iz istog klona kao i limfomi niskog stupnja (22–24).

which can be classified into clinical and laboratory factors (24,25). Clinical predictive factors include persistent parotid swelling, splenomegaly, lymphadenopathy, palpable purpura, and peripheral neuropathy. Laboratory risk factors include lymphopenia (especially CD4-positive T lymphocytes), cryoglobulinemia, the presence of monoclonal protein in serum and urine, and reduced values of the complement C4. Histopathological predictive factors in the salivary gland biopsy include the presence of structures similar to germinal centres (GC) and a high focus score (23,24). In addition to that, high disease activity with the ESSDAI index was shown to be a predictor of lymphoma development (10).

Although the cause of pSS is not known, various research studies that were conducted so far have revealed a lot about its etiopathogenesis, which explains the increased frequency of the development of lymphoproliferative diseases in these patients.

Reactive lymphocytic infiltration and changes in epithelial cells in SS can cause lymphoepithelial lesions, i.e., lymphoepithelial sialadenitis (LESA), which is a histological feature of the disease, and which has a high risk of transformation into lymphoproliferative diseases (26,27). This process is generally long-lasting and is made up of various histopathological mechanisms. Chronic inflammation, enhanced activation of T and B lymphocytes, secretion of cytokines, oncogenes and chromosomal anomalies can cause the transition from B-polyclonal proliferation to monoclonal proliferation and the development of lymphoma. The prevailing opinion is that the driving role in the transformation of SS into NHL is played by a chronic inflammatory process in which exogenous and endogenous antigens stimulate the swelling of lymphocytes and cause changes in the epithelial cells of the salivary glands, which increases the risk of malignant transformation (2,26–28).

Since the salivary glands are the target organ of pSS, epithelial cells play an active role in the pathogenesis of this disease. They express costimulatory molecules and can present autoantigen to immune cells, and also participate in B-cell activation by secreting B-cell activating factor (BAFF; also known as tumour necrosis factor ligand superfamily member 13B), and after stimulation with viruses or interferon alpha (IFN- α). BAFF levels in plasma and salivary glands have been shown to be significantly elevated in patients with pSS, which is associated with greater disease activity, but also with a greater risk of developing B-cell lymphoma (29–33). Surface RF-expressing B-cells are frequently detected in salivary glands in pSS, suggesting that clonal expansion may result from antigenic selection of RF-expressing B-cells (25). This continuous stimulation of B-cells is the main driver of lymphoproliferation. The identi-

Posljedično spoznajama o potencijalnoj malignoj transformaciji u sklopu pSS-a koji je, nakon RA, druga po učestalosti sistemska autoimuna bolest, s vremenom su identificirani prediktivni rizični čimbenici razvoja limfoma u bolesnika sa SS-om, koje možemo podijeliti na kliničke i laboratorijske (24,25). U kliničke prediktivne čimbenike ubrajaju se trajno povećanje parotida, splenomegalija, limfadenopatija, palpabilna purpura i periferna neuropatija. Laboratorijski čimbenici rizika jesu limfopenija (posebice CD4-pozitivnih limfocita T), krioglobulinemija, prisutnost monoklonskog proteina u serumu i urinu te snižene vrijednosti C4 komponente komplementa. U PHD prediktivne čimbenike u biopatu slinovne žlijezde ubraja se prisutnost struktura sličnih germinativnim centrima (GC) i veći broj limfocitnih fokusa (engl. *high focus score*) (23,24). Također, pokazalo se da je visoka aktivnost bolesti s indeksom ESSDAI prediktor razvoja limfoma (10).

Iako nije poznat uzrok pSS-a, dosadašnjim istraživanjima mnogo se saznalo o njegovoj etiopatogenezi, koja nam objašnjava povećanu učestalost razvoja limfoproliferativnih bolesti u tih bolesnika.

Reaktivna limfocitna infiltracija i promjene na epitelnim stanicama u SS-u mogu uzrokovati limfoepitelijsko oštećenje, odnosno limfoepitelijski sialoadenitis (LESA), što je histološko obilježje bolesti i koji ima visok rizik za transformaciju u limfoproliferativne bolesti (26,27). Taj proces u pravilu je dugotrajan i čine ga različiti patohistološki mehanizmi. Kronična upala, pojačana aktivacija limfocita T i B, lučenje citokina, onkogeni i kromosomske anomalije mogu uzrokovati prijelaz iz B-poliklonske proliferacije u monoklonsku proliferaciju i razvoj limfoma. Prevladavajući je stav da pokretačku ulogu u transformaciji SS-a u NHL ima kronični upalni proces u kojem egzogeni i endogeni antigeni potiču bujanje limfocita i uzrokuju promjene na epitelnim stanicama žlijezda slinovnica, što povećava rizik maligne transformacije (2,26–28).

Budući da su žlijezde slinovnice ciljani organ pSS-a, epitelne stanice imaju aktivnu ulogu u patogenezi ove bolesti. One izražavaju kostimulacijske molekule i mogu prezentirati autoantigen imunološkim stanicama, a također sudjeluju u aktivaciji B-stanica izlučivanjem faktora aktivacije B-stanica (BAFF, engl. *B-cell activating factor B*, također poznat kao član superobitelji TNF liganda 13B), a nakon stimulacije virusima ili interferonom alfa (IFN α). Pokazalo se da su razine BAFF-a u plazmi i žlijezdama slinovnicama značajno povišene u bolesnika s pSS-om, što je povezano s većom aktivnošću bolesti, ali i s većim rizikom od razvoja limfoma B-stanica (29–33). B-stanice koje ekspiriraju površinski RF često se otkrivaju u žlijezdama slinovnicama kod pSS-a, što sugerira da bi klonska ekspanzija mogla proizaći iz antigenske selekcije B-sta-

cation of multiple steps that support B-cell activation has led to the development of promising targeted therapies that will hopefully lead to the development of an effective therapeutic strategy for pSS.

CONCLUSION

In this paper, we presented the case of a patient with long-term pSS who later developed indolent extranodal B-NHL CD20 positive MALT lymphoma with a good response to treatment with rituximab in combination with bendamustine. The development of malignant lymphoma from benign lymphocytic infiltration, or lymphoepithelial sialadenitis in patients with pSS is usually a long-term process, which is also the case with the patient in this case report. MALT lymphoma is the most common histological type, has a good prognosis and is most often treated with rituximab in combination with an alkylating agent. The development of NHL in patients with SS is considered one of the most serious complications of the disease. The aforementioned is important in the clinical follow-up of patients for the purpose of early diagnosis and timely and adequate treatment, given that lymphoproliferative disorders are the main cause of mortality in SS. Considering the above, it is important to determine the set of clinical, laboratory and imaging tests and their frequency in patient follow-up. For example, in patients with permanently enlarged parotid glands, cutaneous changes and neuropathy, it is necessary to perform a clinical examination and ultrasound every six months in order to detect the possible signs of lymphadenopathy and splenomegaly, closely monitor the lymphocyte values in the laboratory markers, determine the presence of monoclonal protein in serum and urine, cryoglobulin, LDH and beta-2 microglobulin values, and, if necessary, perform a cytological puncture and biopsy of the salivary gland or lymph node with the aim of early detection of the development of lymphoma. Also, it is necessary to continue research in order to get a better understanding of the pathogenetic mechanisms of the disease itself and its lymphoproliferation in order to find targeted therapeutic options and develop an effective therapeutic strategy for pSS.

CONFLICT OF INTEREST STATEMENT: The authors declare no conflict of interest.

nica koje eksprimiraju RF (25). Ova kontinuirana stimulacija B-stanica glavni je pokretač limfoproliferacije. Identifikacija višestrukih koraka koji podržavaju aktivaciju B-stanica dovela je do razvoja obećavajućih ciljanih terapija koje će, nadamo se, dovesti do razvoja učinkovite terapijske strategije za pSS.

ZAKLJUČAK

U ovom smo radu prikazali bolesnicu s dugogodišnjim pSS-om i kasnije razvijenim indolentnim ekstranodalnim B-NHL CD20 pozitivnim limfomom tipa MALT uz dobar odgovor na liječenje rituksimabom u kombinaciji s bendamustinom. Razvoj malignog limfoma iz benigne limfocitne infiltracije, odnosno limfoepitelijalnog sijaloadenitisa u bolesnika s pSS-om u pravilu je dugotrajan proces, što je slučaj i u prikazane bolesnice. MALT limfom je najčešći histološki tip, ima dobru životnu prognozu i najčešće se liječi rituksimabom u kombinaciji s alkilirajućim lijekom. Razvoj NHL-a u bolesnika sa SS-om smatra se jednom od najtežih komplikacija bolesti. Navedeno je važno u kliničkom praćenju bolesnika radi rane dijagnoze i pravovremenog i adekvatnog liječenja s obzirom na to da su limfoproliferativne bolesti glavni uzrok mortaliteta u SS-u. S obzirom na navedeno, važno je odrediti set kliničkih, laboratorijskih i slikovnih pretraga i njihovu učestalost u praćenju bolesnika. Primjerice u bolesnika s trajno uvećanim parotidama, kožnim promjenama i neuropatijom potrebno je svakih šest mjeseci kliničkim pregledom i ultrazvučno tražiti limfadenopatiju i splenomegaliju, laboratorijski pratiti vrijednosti limfocita, utvrditi prisutnost monoklonskog proteina u serumu i urinu, krioglobuline, vrijednosti LDH i beta2 mikroglobulina te po potrebi učiniti citološku punkciju i biopsiju slinovne žlijezde ili limfnog čvora s ciljem ranog otkrivanja razvoja limfoma. Također, potrebno je nastaviti s istraživanjima u svrhu boljeg razumijevanja patogenetskih mehanizama same bolesti i njezine limfoproliferacije u cilju pronalaska ciljanih terapijskih opcija te razvoja učinkovite terapijske strategije za pSS.

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TUBERCULOSIS SPONDYLODISCITIS IN A PATIENT WITH PSORIATIC ARTHRITIS ON TARGETED SYNTHETIC DISEASE-MODIFYING ANTIRHEUMATIC DRUGS – CASE REPORT

TUBERKULOZNI SPONDILODISCITIS U BOLESNIKA S PSORIJATIČNIM ARTRITISOM LIJEČENOG CILJANIM SINTETSKIM ANTIREUMATSKIM LIJEKOVIMA KOJI MODIFICIRAJU BOLEST – PRIKAZ BOLESNIKA

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ABSTRACT

Tuberculosis (TB) has been recognised as an important opportunistic infection that occurs in patients with inflammatory rheumatic diseases. The results of global registries show that the risk of reactivation of latent TB or the development of new TB infection increases in patients treated with tumour necrosis factor inhibitors (TNFis). However, the results of randomised clinical studies and few data from everyday practice show that targeted synthetic disease-modifying anti-rheumatic drugs (tsDMARDs) such as apremilast and janus kinase inhibitors (JAKi), have a lower risk of TB activation compared to TNFis.

In this article, we shall present a male patient in whose case skin psoriasis preceded the development of articular involvement, and the definite diagnosis of psoriatic arthritis (PsA). He was treated with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) methotrexate and sulfasalazine, and, following that, with tsDMARDs apremilast and tofacitinib, with previously obtained negative results of hepatitis markers and QuantiFERON-TB Gold (QFT) test for latent tuberculosis. Considering the intense pain in the lumbosacral segment of the spine along with the occurrence of fever and alteration of serological inflammatory laboratory markers, the diagnostic evaluation was performed in order to determine the presence of TB spondylodiscitis L5-S1 with epidural abscess and abscess in the right psoas muscle. Specific therapy was discontinued, and, following that, surgical abscess drainage, and microdiscectomy and vertebrosynthesis of the L5-S1 lumbosacral joint were performed. In addition to that, the anti-TB therapy was induced for a total duration of 12 months.

In conclusion, this is the first case report in literature which discusses the case of tuberculous spondylodiscitis in patients with PsA treated with tofacitinib. The patient had been treated with apremilast for 3 months a year earlier, but the connection between the use of the aforementioned drug and the development of extrapulmonary tuberculosis was not established. Results from national registries need to be collected due to the fact that phase III randomised controlled trials did not register any cases of TB in PsA patients treated with tofacitinib. In the event of symptoms that do not fit into the clinical features of PsA, the possibility of developing pulmonary or extrapulmonary TB manifestations should be considered even though the patient is being treated with tsDMARDs.

KEY WORDS: apremilast, psoriatic arthritis, tofacitinib, tuberculosis

SAŽETAK

Tuberkuloza (TBC) je prepoznata kao važna oportunistička infekcija koja se javlja u bolesnika s upalnim reumatskim bolestima. Rezultati svjetskih registara pokazuju da se rizik od reaktivacije latentne TBC ili nastanka nove TBC-infekcije povećava u bolesnika liječenih inhibitorima faktora tumorske nekroze (TNFi). Dok rezultati randomiziranih kliničkih studija i malobrojni podatci iz svakodnevne prakse pokazuju da ciljani sintetski antireumatski lijekovi koji modificiraju bolest (*eng. targeted synthetic disease-modifying anti-rheumatic drugs*; tsDMARD), kao što su apremilast te inhibitori janus-kinaza (JAK-i), imaju niži rizik za aktivaciju TBC-a u usporedbi s TNFi.

U ovom članku prikazati ćemo bolesnika u kojega je dugi niz godina psorijaza kože prethodila razvoju zglobnih tegoba i postavljanju dijagnoze psorijatičnog artritisa (PsA). Liječen je konvencionalnim sintetskim antireumatskim lijekovima koji modificiraju bolest (*eng. conventional synthetic disease-modifying anti-rheumatic drugs*; csDMARD) metotreksatom i sulfasalazinom, te potom i tsDMARD-ovima apremilastom i tofacitinibom, uz prethodno utvrđene negativne nalaze hepatitis markera i kvantiferonskog testa na latentnu tuberkulozu. S obzirom na intenzivnu bolnost lumbosakralnog segmenta kralježnice uz febrilitet i alteraciju upalnih laboratorijskih parametara, učini se dijagnostička obrada kojom se utvrdi postojanje tuberkuloznog spondilodiscitisa L5-S1, epiduralnog apscesa i apscesa desnog mišića psoasa. Ukinu se specifična terapija te se učini kirurška evakuacija apscesa, mikrodiscektomija i vertebrosinteza L5-S1 te započne antituberkulotska terapija u ukupnom trajanju od 12 mjeseci.

Zaključno, ovo je prvi prikaz u literaturi tuberkuloznog spondilodiscitisa u bolesnika sa PsA liječenog tofacitinibom. Pacijent je godinu dana ranije bio liječen apremilastom tri mjeseca, ali ga ne možemo povezati s razvojem ekstrapulmonalne tuberkuloze. Potrebno je prikupiti rezultate iz nacionalnih registara s obzirom na to da randomizirane kontrolirane studije faze III nisu registrirale niti jedan slučaj TBC-a u pacijenata s PsA liječenih tofacitinibom. Kod pojave simptoma koji se ne uklapaju u kliničku sliku PsA, treba razmišljati o mogućnosti razvoja pulmonalne ili ekstrapulmonalne manifestacije tuberkuloze iako se bolesnik liječi tsDMARD-om.

KLJUČNE RIJEČI: apremilast, psorijatični artritis, tofacitinib, tuberkuloza

INTRODUCTION

Patients with autoimmune rheumatic diseases have an increased risk of developing tuberculosis (TB) as an opportunistic infection. Results from global registries show that the risk of reactivation of TB or the development of *de novo* TB is higher in patients treated with tumour necrosis factor inhibitors (TNFis) (1). It is also a well-known fact that in rheumatoid arthritis (RA), long-term use of glucocorticoids and methotrexate represent a slightly increased risk of TB infection (2), while TNFis increase this risk by 4–8 times (3). Over the last few years, new therapeutic options have been introduced for the treatment of inflammatory rheumatic diseases, both for RA and psoriatic arthritis (PsA). The treatment of PsA includes targeted synthetic disease-modifying anti-rheumatic drugs (tsDMARDs), such as apremilast and Janus-kinase inhibitors (JAKi). The results of randomised clinical trials and data from clinical practice show that these drugs have a lower risk of TB activation in patients with PsA compared to TNFis (1). In the following text, we shall present the case of a patient with PsA who developed TB, spondylodiscitis and psoas muscle abscess during treatment with tsDMARDs.

CASE REPORT

A male patient, born in 1952, has been suffering from psoriasis for many years with involvement of the

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Bolesnici s autoimunim reumatskim bolestima imaju povišeni rizik za razvoj tuberkuloze (TBC) kao oportunističke infekcije. Podatci iz svjetskih registara pokazuju da je rizik za reaktivaciju TBC-a ili nastanak TBC-a *de novo* viši u bolesnika koji su liječeni inhibitorima faktora tumorske nekroze (engl. skr. TNFi) (1). Također se zna da kod reumatoidnog artritisa (RA) trajno uzimanje glukokortikoida i metotreksata predstavljaju blago povećan rizik za nastanak TBC infekcije (2) dok TNFi povišuju taj rizik za 4–8 puta (3). Tijekom zadnjih nekoliko godina uvedene su nove terapijske opcije za liječenje upalnih reumatskih bolesti, kako za RA tako i za psorijatični artritis (PsA). U liječenje PsA uključeni su ciljani sintetski antireumatski lijekovi koji modificiraju bolest (*eng. targeted synthetic disease-modifying anti-rheumatic drugs*; tsDMARD-ovi) kao što su apremilast i inhibitori janus-kinaza (engl. skr. JAK-i). Rezultati randomiziranih kliničkih studija i podatci iz kliničke prakse pokazuju da navedeni lijekovi imaju niži rizik za aktivaciju TBC-a u bolesnika s PsA u usporedbi s TNFi (1). U daljnjem tekstu prikazat ćemo bolesnika s PsA koji je razvio TBC spondilodiscitis i apsces mišića psoasa tijekom liječenja tsDMARD-ovima.

PRIKAZ BOLESNIKA

Muškarac, rođen 1952. godine, dugi niz godina boluje od psorijaze uz zahvaćenost vlasišta, kože eksten-

scalp, skin of the extensor surfaces of the knees and nails. The patient was treated with local therapy as recommended by a dermatologist. In 2017, the patient was diagnosed with PsA on the basis of the clinical findings of asymmetric polyarthritis of the small joints in the hands and feet, along with dactylitis of the second toe of the right foot, without any signs of enthesitis. The inflammatory markers are mildly raised, anaemia of chronic disease with uric diathesis is observed. In addition to that, the disease activity score, measured by the Disease Activity Score 28 (ESR) (DAS28/ESR), was 4.31 and measured by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) it was evaluated as 3.8, which indicates moderate disease activity. In addition to non-steroidal anti-inflammatory drugs (NSAIDs), conventional synthetic disease-modifying anti-rheumatic drug (csDMARDs), methotrexate, was also included in the therapy, at a dose of up to 20 mg once a week. Furthermore, due to the exacerbation of joint symptoms with the occurrence of inflammatory back pain and the raised inflammatory laboratory markers (ESR 61, C-reactive protein (CRP) 12 mg/L), in November 2018 sulfasalazine was introduced in a daily dose of 2 grams. Smaller areas of bone marrow oedema in the ventral and caudal part of the vertebral body of T12 and L1 vertebrae were detected through MRI, while no signs of sacroiliitis were observed on the sacroiliac joints. Therapy with csDMARDs was difficult for the patient to tolerate due to pronounced gastrointestinal complications. In May 2019, exacerbation of the joint disease had occurred, DAS28(CRP) was 4.88, and a diagnostic evaluation was performed before the application of a biological drug or tsDMARDs. The results of markers for hepatitis B and C were negative, as well as the results of the QuantiFERON-TB Gold (QFT) test for latent tuberculosis. Since the patient was not inclined to intravenous and subcutaneous administration of the biological drug, treatment with orally administered tsDMARD apremilast was initiated in August 2019. At the evaluation after three months of treatment, the clinical features continued to show pronounced signs of asymmetric polyarthritis of the small joints in the hands and feet, with enthesitis of the right Achilles tendon, while the DAS28(ESR) score was 3.91. In December 2019, apremilast was replaced, due to the ineffectiveness of the drug, by another tsDMARD, tofacitinib. After its application, remission of the disease activity occurred at the evaluation after three months of treatment (March 2020), with a DAS28(SE) score of 2.62. In August 2020, the patient had a fever up to 38 °C with a negative result of the PCR *Polymerase Chain Reaction*) test for SARS-CoV-2 (*severe acute respiratory syndrome coronavirus 2*), raised inflammatory laboratory markers (ERS 61

zornih strana koljena te noktiju. Liječen je lokalnom terapijom po preporuci dermatologa. Godine 2017. postavljena je dijagnoza PsA temeljem kliničkog nalaza asimetričnog poliartritisa malih zglobova šaka i stopala, uz daktilitis II. prsta desnog stopala, a bez znakova entezitisa. Upalni parametri su blago povišeni, registrira se anemija kronične bolesti uz uričnu dijatezu, a indeks aktivnosti bolesti mjeren indeksom *Disease activity score* 28 (SE) (DAS28/SE) bila je 4,31 te indeksom *The Bath Ankylosing Spondylitis Disease Activity Index* (BASDAI) bila je 3,8, što pokazuje umjereno aktivnu bolest. U terapiju je tada uz nesteroidni antireumatski lijek (skr. NSAR) uključen i konvencionalni sintetski antireumatski lijek koji modificira bolest (engl. *conventional synthetic disease-modifying anti-rheumatic drugs*; skr. csDMARD) metotreksat u dozi do 20 mg 1 x tjedno, a zbog pogoršanja zglobovni simptoma uz pojavu upalne križobolje te povišenja laboratorijskih upalnih parametara (SE 61, C-reaktivni protein (CRP) 12 mg/L) od studenog 2018. dodaje se sulfasalazin u dnevnoj dozi od 2 grama. Na snimkama magnetske rezonancije utvrđene su manje zone koštano edema ventrokaudalnog dijela trupa Th12 i L1 kralješka, dok je prikaz sakroilijakalnih zglobova bio bez znakova sakroileitisa. Terapiju csDMARD-ovima bolesnik je teško podnosio zbog izraženih gastričnih tegoba. U svibnju 2019. nastupilo je pogoršanje zglobne bolesti, DAS28(CRP) je bio 4,88 te je učinjena dijagnostička obrada prije primjene biološkog lijeka ili ciljane sintetske molekule. Nalazi markera na hepatitis B i C bili su negativni, kao i nalaz kvantiferonskog testa na latentnu tuberkulozu. Budući da bolesnik nije bio sklon intravenskoj i supkutanoj aplikaciji biološkog lijeka, u kolovozu 2019. započne se liječenje peroralnim tsDMARD-om apremilastom. Na evaluaciji nakon tri mjeseca liječenja i dalje je bila izražena klinička slika asimetričnog poliartritisa malih zglobova šaka i stopala, uz entezitis desne Ahilove tetive, dok je vrijednost DAS28(SE) bila 3,91. U prosincu 2019. apremilast je zbog neučinkovitosti lijeka zamijenjen drugim tsDMARD-om, tofacitinibom. Po njegovoj primjeni nastupila je remisija aktivnosti bolesti na evaluaciji nakon tri mjeseca (ožujak 2020.), uz vrijednost DAS28(SE) 2,62. U kolovozu 2020. bolesnik je postao febrilan do 38°C uz negativan nalaz PCR (engl. *Polymerase Chain Reaction*) testa na SARS-CoV-2 (engl. *severe acute respiratory syndrome coronavirus 2*), povišenih vrijednosti upalnih laboratorijskih parametara (SE 61 mm/h, CRP 72 mg/L), uz jaku križobolju i bolnost u području zdjelice mjerenu vizualnom skalom boli (skr. VAS) 10/10. Iz kliničkog statusa ističe se hod uz pomoć dviju podlaktanih štaka, bolni i ograničeni pokretni lumbosakralnog segmenta kralježnice, a bez radikularne simptomatologije, te palpatorna bolnost sakroilijakalnih zglobova, bez aktivne upale u perifernim zglo-

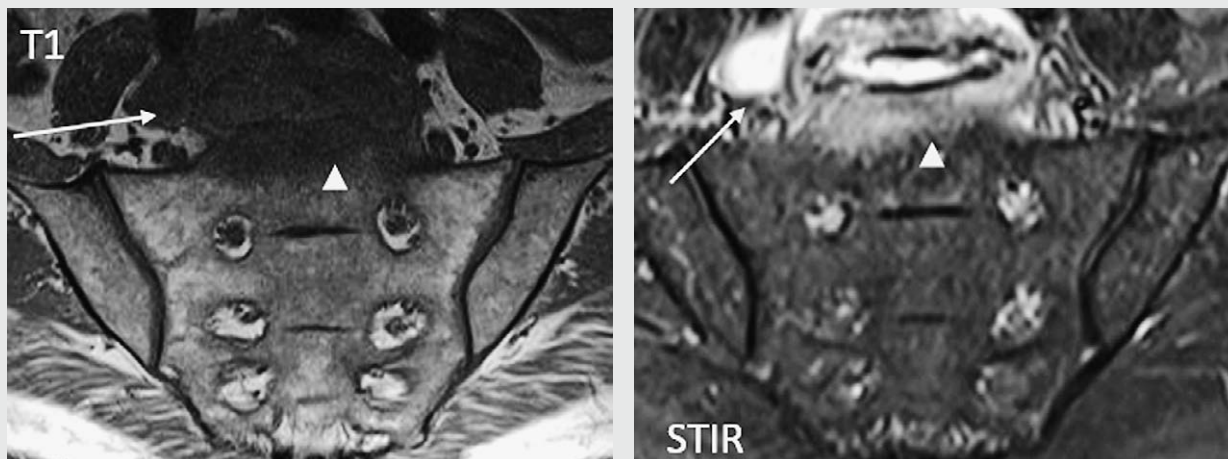


FIGURE 1. MRI of coronal cross-section of the lumbosacral L5-S1 spine in STIR (short TI inversion recovery) and T1 images which show inflammatory changes. Arrowhead: bone oedema – high signal in STIR and low signal in T1; long arrows: epidural abscess – low signal in T1, high signal in STIR.

SLIKA 1. Koronalni presjek na magnetskoj rezonanciji (MR) lumbosakralnog L5-S1 segmenta kralježnice u STIR (engl. short TI inversion recovery) i T1 slikama u smislu upalnih promjena. Glava strelice: edem kosti – visok signal u STIR, nizak signal u T1. Duge strelice: epiduralni apsces (u T1 je nizak signal, u STIR je visok).

mm/h, CRP 72 mg/L), and severe back pain and pelvic pain measured by the visual analogue scale (VAS) with his pain intensity score evaluated as 10/10. The patient's clinical status indicates that the patient is walking with the help of two forearm crutches, with painful and limited movement of the lumbosacral segment of the spine, without any symptoms of radiculopathy, and the presence of tenderness on palpation in the sacroiliac joints, with no signs of active inflammation in the peripheral joints, with DAS28(CRP) score of 3.9, while the score of disease activity index (BASDAI) of spinal affection was 6.6. Following that, the drug tofacitinib was discontinued from therapy. In diagnostic evaluation, the radiograph of the thorax organs, thoracic and lumbar segment of the spine, sacroiliac joints and pelvis with hips did not show any significant deviation. On the bone scan (Tc-99), intense remodelling was observed in the area of the lumbosacral transitional vertebrae with a well-vascularised process in the early phase of the imaging, indicating a possible inflammatory component, but the finding was of unknown aetiology. On the magnetic resonance cross-sections, spondylodiscitis at the L5-S1 level, epidural abscess and abscess of the right psoas muscle were confirmed (Figure 1, Figure 2). A positive result of the QuantiFERON-TB Gold (QFT) test for tuberculosis was also obtained. In October 2020, drainage of the epidural abscess as well as microdiscectomy, transpedicular fixation and intercorporeal vertebrosynthesis of the L5-S1 lumbosacral joint were performed. Microbiological analysis of the sample taken intraoperatively revealed a positive finding for *Mycobacterium tuberculosis*. Fur-

bovima uz DAS28(CRP) 3,9, dok je vrijednost indeksa aktivnosti bolesti afekcije kralježnice BASDAI bila 6,6. Tada je iz terapije isključen lijek tofacitinib. U dijagnostičkoj obradi radiogram grudnih organa, torako-lumbalnog segmenta kralježnice, sakroilijakalnih zglobova i zdjelice s kukovima nije pokazao značajnije odstupanje. Na scintigramu skeleta (Tc-99) uočena je intenzivna pregradnja u području lumbosakralnog prijelaza kralježnice uz dobro vaskulariziran proces u ranoj fazi snimanja, moguće upalne komponente, no nalaz je bio otvorene etiologije. Na presjecima magnetske rezonancije verificiran je spondilodiscitis u razini L5-S1, epiduralni apsces i apsces desnog mišića psoasa (slika 1, slika 2). Utvrđen je i pozitivan nalaz kvantiferonskog testa na tuberkulozu. U listopadu 2020. operativno je učinjena evakuacija epiduralnog apscesa te mikrodiscektomija, transpedikularna fiksacija i interkorporealna vertebrosinteza L5-S1. Mikrobiološkom analizom intraoperativno uzetog materijala utvrđen je pozitivan nalaz na mikobakterijum tuberkuloze. Daljnjom obradom nije dokazano postojanje plućne tuberkuloze te je postavljena dijagnoza ekstrapulmonalne tuberkuloze s razvojem tuberkuloznog spondilodiscitisa s apscesom desnog mišića psoasa. Započeto je liječenje antituberkulotskom terapijom (rifampicin, etambutol, pirazinamid, izonijazid) u trajanju od dva mjeseca, a potom izonijazid i rifampicin u trajanju do ukupno 12 mjeseci. Provedeno je i preporučeno liječenje hiperbaričnom oksigenoterapijom (50 terapija). U rujnu 2021. bolesnik je dobrog općeg stanja, afebrilan, pokretan pomoću štapa na duže relacije ili bez ortopedskog pomaga na kraće relacije, minimalnog opsega kretnji lumbosakralnog segmenta kralježnice te bolnih više zglo-

ther processing did not prove the occurrence of pulmonary tuberculosis, and extrapulmonary tuberculosis with the development of tuberculous spondylodiscitis with the abscess of the right psoas muscle was diagnosed. Treatment with antituberculosis therapy (rifampicin, ethambutol, pyrazinamide, isoniazid) was initiated and it lasted for two months, followed by the treatment with the use of isoniazid and rifampicin for a total duration of 12 months. Hyperbaric oxygen therapy (50 treatments) was also recommended and carried out. In September 2021, the patient was in a good general condition, afebrile, using a cane for long distances or walking without an orthopaedic aid for short distances, with a minimal range of motion of the lumbosacral segment of the spine, with painful multiple joints (both hips, both knees) and painful and swollen second metacarpophalangeal joints of both hands, and with improved inflammatory laboratory parameters (ESR 62 mm/h, CRP 11 mg/L), with a DAS28(CRP) score of 4.07, and with a BASDAI score of 1.6. The patient was referred for a control computed tomography (CT) of the lumbosacral segment of the spine (on 8 June 2021), which showed an extensive bone destruction of the vertebral body of the L5 vertebra and the superior surface of the S1 vertebra as part of the progression of changes from the previously known spondylodiscitis, while the previously noted soft tissue substrate of the L5/S1 level in the ventral part of the spinal canal and in the prevertebral space is in regression. By performing the follow-up of the patient's clinical status and laboratory markers, we have decided against reintroducing csDMARDs or tsDMARDs for the time being.

DISCUSSION

The results of global registries show that the risk of reactivation of latent TB or the development of new TB infection increases in patients treated with TNFis, especially if these patients reside in countries in which TB is an endemic disease (1,4). In recent years, new drugs were introduced in the treatment of inflammatory rheumatic diseases, tsDMARDs, such as apremilast and JAKi. The results of randomised clinical trials and few data from clinical practice show that these drugs have a lower risk of TB activation compared to TNFis (1.4). Randomised clinical trials that included the follow-up of patients with PsA that were treated with apremilast during one year of follow-up (5,6) and later in a four-year extension of the studies, did not detect the occurrence of a TB infection, and the authors concluded that the long-term risk for opportunistic infection is similar to a one-year period of using apremilast and that it is comparable to a placebo treatment (6,7). In national registries there is no data regarding

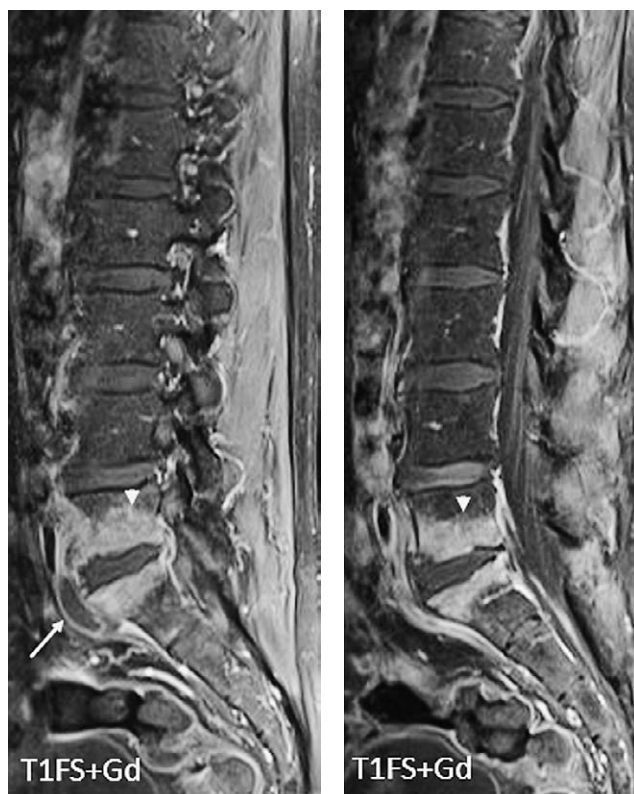


FIGURE 2. Sagittal T1 fat saturated post contrast cross-sectional MR images of the lumbosacral segment of the spine demonstrate extensive enhancement of L5 and S1 vertebral endplates, enhancement of paravertebral soft tissues and epidural abscess in keeping with spondylodiscitis of the L5/S1 segment. Arrowhead: bone oedema/osteitis – high signal in T1FSGd; long arrow: epidural abscess – low signal in T1, low signal in the centre (necrotic content) and post contrast peripheral enhancement.

SLIKA 2. Sagitalni postkontrastrni presjeci na MR lumbosakralne kralježnice prikazuju širu zonu patološkog povišenja signala u području subdiskalne kosti trupova kralježaka L5 i S1, povišenje signala okolnog mekog tkiva i epiduralni apsces u sklopu spondilodiscitisa segmenta L5/S1. Glava strelice: upalno promijenjena kost – visok signal u T1FSGd. Duga strelica: epiduralni apsces – u T1 je nizak signal, postkontrastrno se rubno boji, a centar je niskog signala (nekrotični sadržaj).

bova (oba kuka, oba koljena) i bolnih i otečenih II. metakarpofalangealnih zglobova obje šake, poboljšanih upalnih laboratorijskih parametara (SE 62 mm/h, CRP 11 mg/L), DAS28(CRP) 4,07; BASDAI 1,6. Upućen je na kontrolnu kompjuteriziranu tomografiju (CT) lumbosakralnog segmenta kralježnice (8. 6. 2021.), koja je pokazala opsežniju koštanu destrukciju korpusa kralješka L5 i gornje pokrovne plohe kralješka S1 u sklopu progresije promjena od prethodno poznatog spondilodiscitisa, dok je prethodno notirani mekotkivni supstrat razine L5/S1 u ventralnom dijelu spinalnog kanala te prevertebralno u regresiji. Praćenjem bolesnikova kliničkog statusa i laboratorijskih parametara za sada se nismo odlučili na ponovno uključivanje csDMARD-ova ni tsDMARD-ova.

the detection and recording of latent or active TB in patients during treatment with apremilast (1,6,8). In addition to that, two observational studies that included 202 patients with PsA and their follow-up during 6 months of apremilast administration did not detect or record the occurrence of a TB infection (8,9). Furthermore, tofacitinib is one of the drugs in the JAKi group. Numerous studies have been conducted on its effectiveness and safety in patients with RA, and it was concluded that the risk of developing TB during treatment is the same as with treatment with TNFi. It is also important to note that in half of the patients who developed TB, it was a case of extrapulmonary manifestation (10). However, phase III randomised controlled trials on the efficacy and safety of tofacitinib in patients with PsA did not record a single case of TB (11,12). There is currently no data available from extension studies and from national registers.

In this case report which describes the case of a patient with predominantly peripheral manifestations of PsA with the activation of axial symptoms, the possibility of progression of the underlying inflammatory rheumatic disease, i.e., the development of spondylitis and/or sacroiliitis as part of PsA, should be taken into account. Given the patient's age, which in this case is over 65, the differential diagnosis should consider the development of osteodegenerative changes, i.e., the occurrence of mechanical low back pain in patients with established inflammatory rheumatic disease, and the possibility of oncological disease should also be ruled out in accordance with the patient's age. Due to the presence of general symptoms, i.e., fever and raised inflammatory laboratory markers that are relatively higher than normal values found in the case of reactivation of PsA disease activity, further processing is carried out with the aim of detecting a possible infection. Regardless of the previous negative result of the QuantiFERON-TB Gold (QFT) obtained during the introduction of tsDMARD in therapy, there was enough reasons to suspect the *de novo* TB infection, and this suspicion was later confirmed by further processing.

Therefore, it is important to note that, in the event of symptoms that do not fit into the clinical features of PsA, the possibility of developing pulmonary or extrapulmonary TB manifestations should be considered even though the patient is being treated with tsDMARDs, in order to apply the appropriate treatment as soon as possible.

CONCLUSION

In this case report, based on the clinical features and diagnostic evaluation, we did not find the connection between the use of apremilast and the development of extrapulmonary TB, so the aforementioned drug could

RASPRAVA

Rezultati svjetskih registara pokazuju da se rizik od reaktivacije latentne TBC ili nastanka nove TBC infekcije povećava u bolesnika liječenih TNFi-ma, pogotovo ako žive u zemljama u kojima je TBC endemska bolest (1,4). Zadnjih godina u liječenje upalnih reumatskih bolesti uključeni su novi lijekovi, tsDMARD kao što su apremilast te JAK-i. Rezultati randomiziranih kliničkih studija i malobrojnih podataka iz svakodnevne prakse pokazuju da navedeni lijekovi imaju niži rizik za aktivaciju TBC-a u usporedbi s TNFi-ma (1,4). Randomizirane kliničke studije koje su pratile bolesnike s PsA na apremilastu tijekom jedne godine praćenja (5,6) te kasnije u četverogodišnjem produžetku studija nisu registrirale TBC infekciju, te su autori zaključili da je dugoročni rizik za oportunističku infekciju sličan jednogodišnjem uzimanju apremilasta te je usporediv s placebom (6,7). Nema podataka glede evidentiranja latentne ili aktivne TBC iz nacionalnih registara u bolesnika tijekom liječenja apremilastom (1,6,8). Također, dvije opservacijske studije koje su uključile 202 bolesnika s PsA i pratile ih tijekom 6 mjeseci primjene apremilasta nisu registrirale TBC infekciju (8,9). Nadalje, tofacitinib je jedan od lijekova skupine JAK-i te su provedene brojne studije o njegovoj učinkovitosti i sigurnosti u bolesnika s RA, sa zaključkom da je rizik od razvoja TBC-a tijekom liječenja jednak kao i kod liječenja TNFi, a važno je napomenuti da je u polovici bolesnika koji su razvili TBC ona bila ekstrapulmonalna manifestacija (10). No, randomizirane kontrolirane studije faze III o učinkovitosti i sigurnosti tofacitiniba u bolesnika s PsA nisu registrirale niti jedan slučaj TBC-a (11,12). Trenutno nema dostupnih podataka iz produžetaka studija i iz nacionalnih registara.

U ovom prikazu bolesnika dominantno periferne manifestacije PsA, kod koje dolazi do aktivacije aksijalne simptomatologije, treba uzeti u obzir u prvom redu mogućnost progresije osnovne upalne reumatske bolesti, odnosno razvoj spondilitisa i/ili sakroileitisa u sklopu PsA. S obzirom na dob bolesnika, koja je u ovom slučaju veća od 65 godina, diferencijalno-dijagnostički valja razmišljati o razvoju osteodegenerativnih promjena, odnosno pojave mehaničke križbolje u bolesnika s etabliranom upalnom reumatskom bolesti, a sukladno dobi valja otkloniti i mogućnost nastanka onkološke bolesti. S obzirom na prisutnost općih simptoma, odnosno visokog febriliteta i povišenja upalnih laboratorijskih parametara koji su razmjerno viših vrijednosti od uobičajenih nego kod reaktivacije aktivnosti bolesti PsA, provede se daljnja obrada s ciljem otkrivanja mogućega infektivnog zbivanja. Bez obzira na prethodno negativan nalaz kvantiferonskog testa kod uključivanja tsDMARD-a postavljena je sumnja na *de novo* TBC infekciju koja se obradom i potvrdi.

Stoga je važno napomenuti da kod pojave simptoma koji se ne uklapaju u kliničku sliku PsA treba razmi-

have been a safer treatment option if its effectiveness had been confirmed, which was not the case with our patient. In patients treated with tsDMARDs, when symptoms do not fit the clinical features of PsA, the possibility of developing pulmonary or extrapulmonary tuberculosis should be considered in order to apply the appropriate treatment as soon as possible. This should be done even though phase III randomised controlled trials did not record a single case of TB, and there are no results from national registers which would confirm this occurrence. Finally, the question arises as to when and which drug to choose for patients after treatment with antituberculosis drugs, and in case of increased activity of the PsA disease.

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šljati o mogućnosti razvoja pulmonalne ili ekstrapulmonalne manifestacije TBC-a iako se bolesnik liječi tsDMARD-om, kako bi se što prije primijenilo odgovarajuće liječenje.

ZAKLJUČAK

Kod prikazanog bolesnika temeljem kliničke slike i dijagnostičke obrade nismo povezali apremilast s razvojem ekstrapulmonalne TBC i navedeni lijek bi mogao biti sigurnija opcija liječenja ako postoji njegova učinkovitost, što kod našeg bolesnika nije bio slučaj. U bolesnika koji se liječe tsDMARD-om svakako bi kod pojave simptoma koji se ne uklapaju u kliničku sliku PsA trebalo razmišljati o mogućnosti razvoja pulmonalne ili ekstrapulmonalne tuberkuloze, iako randomizirane kontrolirane studije faze III nisu registri-rale niti jedan slučaj TBC-a, a nema rezultata niti iz nacionalnih registara, kako bi se što prije primijenilo odgovarajuće liječenje. Također se na kraju postavlja pitanje kada i koji lijek izabрати kod bolesnika nakon provedene antituberkulostatske terapije, a u slučaju pojačanja aktivnosti bolesti PsA.

IZJAVA O SUKOBU INTERESA: Autori izjavljuju da nisu u sukobu interesa.

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THERAPEUTIC APPROACH TO A PATIENT WITH ANTISYNTHEASE SYNDROME – A CASE REPORT

TERAPIJSKI PRISTUP BOLESNIKU S ANTISINTETAZNI SINDROMOM – PRIKAZ BOLESNIKA

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ABSTRACT

Introduction: Antisynthetase syndrome (ASS) is a rare autoimmune systemic disease characterised by myositis, arthritis, Raynaud's syndrome, mechanic's hands, and interstitial lung disease. **Materials and methods:** We present the case of a 50-year-old patient with predominant signs of polymyositis, pulmonary interstitium involvement and positive anti-Jo1 antibodies with suspected antisynthetase syndrome. **Results:** He was treated with glucocorticoids and following that the treatment was continued with an additional immunosuppressive therapy drug, azathioprine, which was discontinued due to a liver lesion. The treatment was then continued with cyclophosphamide. In the later course of the disease, radiological regression of pulmonary changes was monitored, and mycophenolate mofetil was introduced as a maintenance therapy. **Conclusion:** If left unrecognised, ASS can lead to the development of irreversible pulmonary fibrosis. However, timely application of immunosuppressive therapy can improve the quality of life and the prognosis of patients with ASS.

KEY WORDS: antisynthetase syndrome, anti-Jo1 antibody, interstitial lung disease

SAŽETAK

Uvod: Antisintetazni sindrom (ASS) je rijetka autoimunosna sustavna bolest koju karakteriziraju miozitis, artritis, Raynaudov sindrom, mehaničarske ruke i intersticijska bolest pluća. **Materijali i metode:** Prikazujemo 50-godišnjeg bolesnika sa znacima polimiozitisa i zahvaćanja plućnog intersticija uz pozitivna anti-Jo1 protutijela kod kojega je postavljena sumnja na antisintetazni sindrom. **Rezultati:** Liječen je glukokortikoidima, a potom je kao dodatna imunosupresivna terapija uveden azatioprin koji je isključen zbog jetrene lezije, a liječenje je nastavljeno ciklofosfamidom. U kasnijem tijeku bolesti pratila se radiološka regresija plućnih promjena te se kao terapija održavanja uvede mikofenolat mofetil. **Zaključak:** Ako ostane neprepoznat ASS dovodi do razvoja ireverzibilne plućne fibroze, međutim pravovremenom primjenom imunosupresivne terapije može se poboljšati kvaliteta života i prognoza bolesnika s ASS-om.

KLJUČNE RIJEČI: antisintetazni sindrom, anti-Jo1 protutijela, intersticijska bolest pluća

INTRODUCTION

Antisynthetase syndrome (ASS) belongs to a group of systemic autoimmune disorders characterised by antibodies against aminoacyl-tRNA synthetase (1). It accounts for 30% of all inflammatory myopathies (2). The most common antisynthetase antibodies are those against histidyl (anti-Jo1). Other aminoacyl-tRNA synthetase antibodies, found in 1%–5% of cases, include anti-PL7, anti-PL12, anti-OJ, anti-EJ, anti-KS, anti-ZO, and anti-tyrosyl antibodies (2, 3, 4, 5, 6). Standard clinical features of ASS include myositis, arthritis, Raynaud's syndrome, mechanic's hands, and interstitial lung disease (ILD) (2). ILD occurs in approximately 70% of patients with ASS and most significantly affects the outcome and prognosis of patients with ASS (2, 7). The treatment of ASS is a demanding process, and it is based on the results of small retrospective studies (8, 9).

CASE REPORT

Our patient was a 50-year-old man with a one-month case history of polymyalgia, polyarthralgia, pain in the inguinal region, and weight loss. He was treated at the Department of Urology under the diagnosis of left-sided epididymitis and nephrolithiasis. During the patient's hospital stay, the diagnosis of bilateral interstitial lung infiltration was confirmed through radiologic testing. Due to the suspected autoimmune disease, further diagnostic processing and treatment were continued at the Division of Rheumatology, Clinical Immunology and Allergology. The leading symptoms included polymyalgia, upper and lower limb muscle weakness, fever, sudden extreme fatigue, and general weakness. A physical examination revealed that the patient had poor grip strength and difficulty standing up from a squatting position (positive Gowers' sign), without signs of limb muscular hypotrophy. The patient's body mass index was 22.5 kg/m², and his anamnesis included information about a 5 kg weight loss in the past month.

The results at diagnosis were the following: leukocyte count 17.1 x 10⁹/L (3.4–9.7 x 10⁹/L), erythrocyte sedimentation rate (ESR) 91 mm/3.6 ks (2–13 mm/3.6 ks), C-reactive protein (CRP) 198.7 mg/L (0–5 mg/L), lactate dehydrogenase (LDH) 150 U/L (< 241), aspartate aminotransferase (AST) 44 U/L (< 38), alanine aminotransferase (ALT) 130 U/L (< 48), ferritin 2580.3 µg/L (30 – 300 µg/L), with normal values of creatine kinase (CK) and myoglobin (Mb). Immunologic testing showed high values of rheumatoid factor (RF) 2350 IU/ml (< 15) with positive antibodies to histidyl (anti-Jo1) 85 AU/ml (< 30). Hepatomegaly was detected through an abdominal ultrasound, while serological testing results for HBV, HCV, HIV, CMV and EBV were negative. Radiograph (X-ray) of the thoracic or-

UVOD

Antisintetazni sindrom (ASS) pripada skupini sustavnih autoimunskih poremećaja koji su karakterizirani protutijelima na aminoacil-tRNA sintetazu (1). Čini 30% svih upalnih miopatija (2). Najčešća antisintetazna protutijela su ona na histidil (anti-Jo1). Ostala protutijela na aminoacil-tRNA sintetazu koja su nađena u 1–5% slučajeva uključuju anti-PL7, anti-PL12, anti-OJ, anti-EJ, anti-KS, anti-ZO i anti-tirozil protutijela (2, 3, 4, 5, 6). Klasična slika ASS-a uključuje miozitis, artritis, Raynaudov sindrom, mehaničarske ruke i intersticijsku bolest pluća (IBP) (2). IBP se pojavljuje u oko 70% bolesnika s ASS-om te najznačajnije utječe na ishod i prognozu bolesnika s ASS-om (2, 7). Liječenje ASS-a je zahtjevno te se temelji na rezultatima malih retrospektivnih studija (8, 9).

PRIKAZ BOLESNIKA

Naš bolesnik je bio 50-godišnji muškarac s jednomjesečnom anamnezom polimijalgija, poliartralgijskih bolova u ingvinalnoj regiji te gubitka na tjelesnoj masi. Liječen je na Odjelu za urologiju pod dijagnozom lijevostranog epididimitisa i nefrolitijaze. Tijekom boravka radiološki je verificirana bilateralna intersticijska infiltracija pluća. Zbog sumnje na autoimunsku bolest daljnja dijagnostička obrada i liječenje su nastavljena na Zavodu za reumatologiju, kliničku imunologiju i alergologiju. Vodeći simptomi bili su polimijalgija, slabost miškulature gornjih i donjih ekstremiteta, febrilitet, brzo umaranje i opća slabost. Fizikalnim pregledom otkriveni su oslabljena snaga stiska šaka te poteškoće prilikom ustajanja iz čučnja (pozitivan Gowersov znak), a bez znakova hipotrofije miškulature ekstremiteta. Indeks tjelesne mase bolesnika je bio 22,5 kg/m², uz anamnestički podatak o gubitku od 5 kg na tjelesnoj masi u proteklom mjesecu.

Nalazi kod postavljanja dijagnoze bili su: leukociti 17,1 x 10⁹/L (3,4 – 9,7 x 10⁹/L), sedimentacija eritrocita (SE) 91 mm/3,6 KS (2 – 13 mm/3,6 KS), C-reaktivni protein (CRP) 198,7 mg/L (0 – 5 mg/L), laktat dehidrogenaza (LDH) 150 U/L (< 241), aspartat aminotransferaza (AST) 44 U/L (< 38), alanin aminotransferaza (ALT) 130 U/L (< 48), feritin 2580,3 µg/L (30 – 300 µg/L), uz normalne vrijednosti kreatin kinaze (CK) i mioglobina (Mgb). Imunološka obrada pokazala je visoke vrijednosti reumatoidnog faktora (RF) 2350 IU/ml (< 15) uz pozitivna protutijela na histidil (anti-Jo1) 85 AU/ml (< 30). Na ultrazvuku abdomena opisana je hepatomegalija, dok je serologija na HBV, HCV, HIV, CMV i EBV bila negativna. Radiogram (RTG) torakalnih organa pokazao je intersticijski crtež retikulonodularnog tipa (slika 1), dok je difuzijski kapacitet za CO (skr. DLCO) bio značajno snižen po tipu restriktivnih promjena za 43%. Nalaz visokorazlučivog

gans showed a reticulonodular interstitial pattern (Figure 1), while the diffusing capacity for carbon monoxide (DLCO) was significantly reduced by 43% according to the type of restrictive changes. The findings of the high-resolution computed tomography (HRCT) indicated diffuse changes according to the ground-glass opacity type with reticulation and traction bronchiectasis (Figure 2). Bronchoscopy findings were in the normal range. Electromyoneurography (EMNG) showed a high percentage of low-voltage polyphasic action potentials.

On the basis of clinical and laboratory markers, along with EMNG of the muscles, polymyositis with ILD was detected, and due to the presence of anti-Jo1 antibodies, ASS was diagnosed. The patient was treated with methylprednisolone at a dose of 1 mg/kg in addition to antibiotic therapy. The applied therapy resulted in the improvement in the clinical status of the patient and a gradual normalisation of laboratory markers. The entire process was monitored closely. As an additional immunosuppressive therapy, azathioprine was introduced at a dose of 100 mg per day. Glucocorticoid treatment was continued on an outpatient basis with a gradual dose reduction.

After three months, azathioprine was discontinued due to the development of a liver lesion, and treatment was continued with cyclophosphamide administered intravenously at a dose of 15 mg/kg (1000 mg) during the course of 6 treatment cycles. The control HRCT scan of the thorax revealed the regressive dynamics of changes according to the type of ground-glass opacity. In the later course of the disease, symptoms of Raynaud's syndrome appeared in the patient, immunological findings have revealed an anti-Jo1 antibody result of 47 AU/ml, unremarkable inflammatory markers, and mycophenolate mofetil administered intravenously was introduced as maintenance therapy, at a dose of 1000 mg per day. Regular outpatient follow-up of the clinical status, laboratory markers and radiological changes was resumed. The clinical status of the patient is stable, but with mild limitations in carrying out difficult physical activities.

DISCUSSION

Antisynthetase syndrome (ASS) was first described as a separate entity in 1990, in patients suffering from polymyositis and ILD, who had antibodies directed against aminoacyl t-RNA synthetase (10). The estimated prevalence of the disease is 1.5 per 100,000 population. The disease more commonly occurs in women (2–3:1) (5). The diagnosis is made on the basis of two major criteria (interstitial lung disease, polymyositis, or dermatomyositis) and one major and two minor criteria (arthritis, Raynaud's syndrome, and mechanic's hands) (11). Myositis occurs in approximately 90% of



FIGURE 1. Radiography of the heart / lungs – interstitial pattern of the reticulonodular type

SLIKA 1. Radiogram srca/pluća – intersticijski crtež retikulonodularnog tipa

CT-a toraksa (skr. HRCT) upućivao je na difuzne promjene po tipu mliječnog stakla uz retikulacijske i trakcijske bronhiektazije (slika 2). Nalaz bronhoskopije je bio uredan. Elektromioneurografija (EMNG) je pokazala visok postotak niskonaponskih polifaznih akcijskih potencijala.

Na temelju kliničkih i laboratorijskih parametara uz EMNG mišića detektiran je poliomiozitis uz IBP, a uz prisutna anti-Jo1 protutijela postavljena je dijagnoza ASS-a. Bolesnik je liječen metilprednizolonom u dozi od 1 mg/kg uz antibiotsku terapiju. Na primijenjenu terapiju pratilo se poboljšanje kliničkog stanja uz postupnu normalizaciju laboratorijskih parametara. Kao dodatna imunosupresivna terapija uveden je azatioprin u dozi od 100 mg na dan. Liječenje glukokortikoidima je nastavljeno ambulantno uz postupno snižavanje doze.

Nakon tri mjeseca azatioprin je isključen zbog razvoja jetrene lezije, a liječenje je nastavljeno intravenoskom primjenom ciklofosfamida u dozi od 15 mg/kg (1000 mg) kroz 6 ciklusa. Na kontrolnom HRCT-u toraksa bila je vidljiva regresivna dinamika promjena po tipu mliječnog stakla. U kasnijem tijeku bolesti kod bolesnika su se pojavili simptomi Raynaudovog sindroma, u imunološkim nalazima anti-Jo1 47 AU/ml, mirni upalni parametri, te se kao terapija održavanja uvede mikofenolat mofetil i.v. u dozi od 1000 mg na dan. Nastavljeno je redovito ambulantno praćenje kliničkog stanja, laboratorijskih parametara i radioloških promjena. Bolesnik je stabilnoga kliničkog stanja, ali uz blažu ograničenost u obavljanju težih fizičkih aktivnosti.

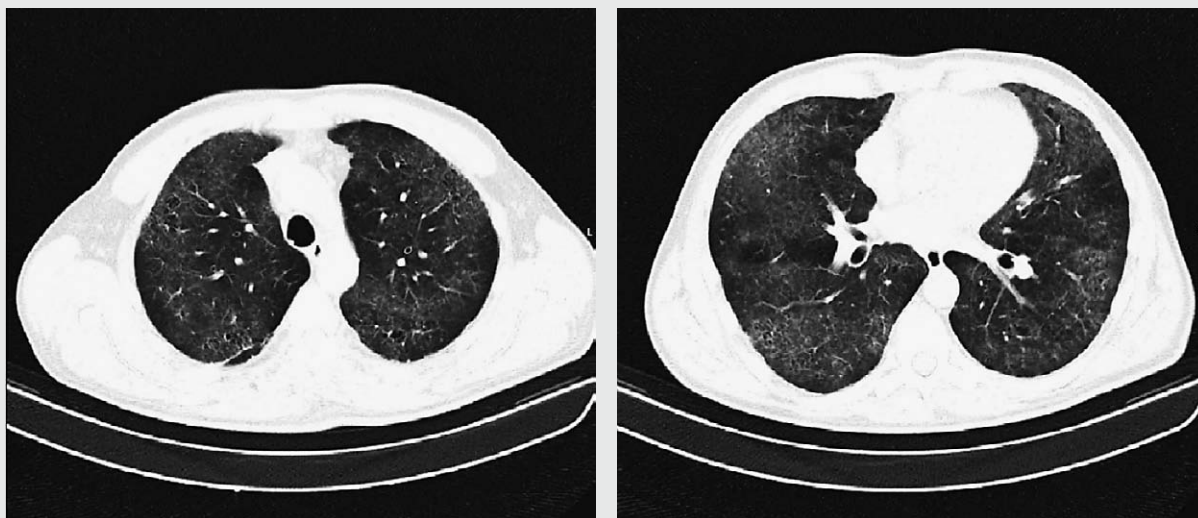


FIGURE 2. High-resolution computed tomography (HRCT) of the chest – axial section: interstitial lung disease
SLIKA 2. Kompjuterska tomografija visoke razlučivosti toraksa – horizontalni presjek: intersticijska bolest pluća

patients. The values of muscle enzymes are usually 5–50 times higher than the normal upper limit. However, CK values may be in the normal range due to significant loss of muscle mass (12). In the case of our patient, the CK values were within the reference interval, while the EMNG showed a myopathic pattern. Therefore, it is important to highlight the fact that normal CK values do not exclude the diagnosis of polymyositis. Arthritis occurs in 50% of patients with ASS, most often at the very onset of the disease. Its characteristics include symmetric polyarthritis of the small joints of the hands and feet and is usually non-erosive. Therefore, ASS should be considered primarily in the differential diagnosis of rheumatoid arthritis (12).

ILD occurs in approximately 70% of patients, it is usually described as non-specific interstitial pneumonia (NSIP) and is the main cause of morbidity. In patients with ASS and ILD, the course of the disease can be complicated by the development of pulmonary hypertension (6). Pulmonary function tests indicate restrictive changes, while CD8 T lymphocytes predominate in the bronchoalveolar lavage (BAL) findings (13). In the case of our patient, the presence of CD8 T lymphocytes was confirmed in BAL findings. Clinical features should take precedence over laboratory markers in establishing the diagnosis of ASS. If anti-Jo1 antibodies are negative, and there is a clinical suspicion of ASS, diagnostic tests for other antibodies associated with ASS should be performed (14).

In the case of our patient, antinuclear antibodies were negative. In a cohort study conducted by Noguchi et al., which included 51 patients with ASS, the presence of ANA antibodies was confirmed in only 12% of subjects (15).

RASPRAVA

Antisintetazni sindrom (ASS) je kao zaseban entitet opisan 1990. godine u bolesnika koji su bolovali od polimiozitisa i IBP-a, a imali su antitijela usmjerena na aminoacil t-RNA sintetazu (10). Procijenjena prevalencija je 1,5 na 100.000 stanovnika. Bolest se češće javlja u žena (2–3:1) (5). Dijagnoza se postavlja na temelju dvaju velikih kriterija (intersticijska bolest pluća, polimiozitis ili dermatomiozitis) te jednog velikog i dvaju malih kriterija (artritis, Raynaudov sindrom i „mehaničarske“ ruke) (11). Miozitis se javlja u 90% bolesnika. Vrijednosti mišićnih enzima uobičajeno su povišene i do 5–50 puta iznad gornje granice. Međutim, vrijednosti CK mogu biti uredne uslijed značajnog gubitka mišićne mase (12). Kod našeg bolesnika vrijednosti CK su bile unutar referentnog intervala, dok je na EMNG-u dokazan miopatski uzorak. Stoga, važno je naglasiti da uredne vrijednosti CK ne isključuju dijagnozu polimiozitisa. Artritis se javlja u 50% bolesnika s ASS-om, najčešće u samom početku bolesti. Karakterizan je simetričnim poliartritisom malih zglobova šaka i stopala te je najčešće neerozivan. Stoga, ASS treba razmotriti u diferencijalnoj dijagnozi prvenstveno reumatoidnog artritisa (12).

IBP se javlja u oko 70% bolesnika, uobičajeno se opisuje kao nespecifična intersticijska pneumonija (NSIP) te je glavni uzrok morbiditeta. Kod bolesnika s ASS-om i IBP-om tijekom bolesti se može komplicirati razvojem plućne hipertenzije (6). Testovi plućne funkcije ukazuju na restriktivne promjene, dok u nalazu bronhoalveolarnog lavata (BAL) prevladavaju CD8 T limfociti (13). Kod našeg bolesnika potvrđen je nalaz CD8 T limfocita u BAL-u. Klinička obilježja trebaju imati prednost nad laboratorijskim parametrima u po-

There is still no standardised treatment for ASS with ILD. The first-line therapy includes the use of glucocorticoids. The second-line therapy consists of drugs that reduce the need for glucocorticoids, such as azathioprine, methotrexate, cyclophosphamide, and mycophenolate mofetil (16). Multiple randomised trials have confirmed the better effectiveness of the combination of prednisone and azathioprine compared to prednisone monotherapy (5). In ASS with significant pulmonary involvement that does not respond to the use of glucocorticoids and azathioprine, the use of cyclophosphamide administered intravenously should be considered (5, 17). In the case of our patient, the first-line therapy included the use of glucocorticoids, and azathioprine was introduced as a drug that reduces the need for glucocorticoids. However, due to the development of a liver lesion as a consequence of azathioprine use, and due to the extent of pulmonary involvement, we decided to use cyclophosphamide administered intravenously. In a study conducted by Qureshi et al., the case of a patient with ASS and ILD of the NSIP type was presented. The applied cyclophosphamide therapy resulted in the improvement in the clinical status and the laboratory markers of the patient. The entire process was monitored closely. (18). In a study conducted by Kumar et al., a significant improvement was described in the case of a patient with ASS and ILD of the NSIP type who was using cyclophosphamide during the course of seven treatment cycles (19). A similar case report was published in a study conducted by Cleetus et al. A patient from their study initially presented with respiratory problems, there were no signs of myositis, a HRCT chest scan confirmed that this was a case of ILD according to the type of NSIP pattern. However, immunological findings revealed a positive anti-PL12 antibody result (20). ASS patients who are anti-Jo1 negative have a worse survival rate than the patients who are anti Jo-1 positive (13). In a study conducted by Brulhart et al., a case of a 57-year-old patient with ASS was presented, who initially responded well to the use of methotrexate and prednisone, but three months later the patient had a relapse and rituximab was administered with a good response (21). Langlois et al. published the results of an observational study that included 62 patients with ASS and ILD. Out of the total number of patients, 34 of them were treated with cyclophosphamide administered in cycles, while 28 of them received rituximab. The results showed an equal efficacy on pulmonary progression-free survival at six months of follow-up. However, rituximab was associated with a significantly better outcome at two years of follow-up (22). In the case of our patient, mycophenolate mofetil was chosen for maintenance therapy as a drug that reduces the need for glucocorticoids, but also because of the results of studies that showed a lower incidence of disease re-

stavljanju dijagnoze ASS-a. Ukoliko su anti-Jo1 protutijela negativna, a postoji klinička sumnja na ASS, trebalo bi učiniti dijagnostičke testove na ostala antitijela povezana s ASS-om (14).

Kod našeg bolesnika antinuklearna protutijela su bila negativna. Noguchi i sur. u kohortnoj studiji koja je uključivala 51 bolesnika sa ASS-om potvrdili su prisutnost ANA protutijela u samo 12% ispitanika (15).

Liječenje ASS-a uz IBP i dalje nije standardizirano. Prva linija liječenja uključuje primjenu glukokortikoida. Drugu liniju liječenja čine lijekovi koji omogućuju smanjivanje potrebe za glukokortikoidima poput azatioprina, metotreksata, ciklofosfamida te mikofenolat mofetila (16). Multiple randomizirane studije potvrdile su bolju učinkovitost primjene kombinacije prednizona i azatioprina u odnosu na monoterapiju prednizonom (5). Kod ASS-a sa značajnim zahvaćanjem pluća koji ne odgovara na primjenu glukokortikoida i azatioprina treba razmotriti primjenu intravenoznog ciklofosfamida (5, 17). Kod našeg bolesnika prva su linija liječenja bili glukokortikoidi, a azatioprin je uveden kao lijek koji smanjuje potrebu za glukokortikoidima. Međutim, radi razvoja jetrene lezije na primjenu azatioprina i opsega plućnog zahvaćanja odlučili smo se za primjenu intravenoznog ciklofosfamida. Qureshi i sur. su prikazali bolesnika s ASS-om i IBP-om po tipu NSIP kod kojega se na primjenu ciklofosfamida pratilo značajno kliničko i laboratorijsko poboljšanje (18). Kumar i sur. su također opisali značajno poboljšanje kod bolesnika s ASS-om i IBP-om po tipu NSIP koji je primao ciklofosfamid kroz sedam ciklusa (19). Sličan prikaz bolesnika objavili su Cleetus i sur. Njihov bolesnik se inicijalno javio zbog respiratornih tegoba, nije bilo znakova miozitisa, HRCT toraksa je potvrdio IBP po tipu NSIP uzorka, međutim u imunološkim nalazima pristigao je pozitivan anti-PL12 (20). Bolesnici s ASS-om koji su anti-Jo1 negativni imaju lošije preživljenje od onih bolesnika koji su anti Jo-1 pozitivni (13). Brulhart i sur. su prikazali 57-godišnjeg bolesnika s ASS-om koji je inicijalno dobro odgovorio na primjenu metotreksata i prednizona, međutim tri mjeseca kasnije pratio se relaps bolesti te je primijenjen rituksimab s dobrim odgovorom (21). Langlois i sur. su objavili rezultate opservacijske studije koja je uključivala 62 bolesnika s ASS-om i IBP-om, od kojih su 34 bolesnika liječena ciklusima ciklofosfamida, dok je 28 bolesnika primalo rituksimab. Rezultati su pokazali jednaku učinkovitost na preživljenje bez plućne progresije nakon šest mjeseci praćenja, međutim rituksimab je bio povezan sa značajno boljim ishodom nakon dvije godine praćenja (22). Kod našeg bolesnika mikofenolat mofetil je odabran za terapiju održavanja kao lijek koji omogućava smanjivanje potrebe za glukokortikoidima, ali i zbog rezultata studija koje su pokazale manju

lapse with the use of mycophenolate mofetil compared to prednisone monotherapy (23).

In conclusion, antisynthetase syndrome is a rare autoimmune systemic disease that, if left unrecognised, can lead to the development of irreversible pulmonary fibrosis as the main cause of poor prognosis and mortality. The timely application of immunosuppressive therapy can improve the quality of life and prognosis of these patients.

CONFLICT OF INTEREST STATEMENT: The authors declare no conflict of interest.

pojavnost relapsa bolesti uz mikofenolat mofetil u odnosu na monoterapiju prednisonom (23).

Zaključno, antisintetazni sindrom je rijetka autoimunosna sustavna bolest koja, ukoliko ostane neprepoznata, dovodi do razvoja ireverzibilne plućne fibroze kao glavnog uzroka loše prognoze i smrtnog ishoda. Pravovremenom primjenom imunosupresivne terapije može se poboljšati kvaliteta života i prognoza tih bolesnika.

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80TH ANNIVERSARY OF THE DEPARTMENT OF RHEUMATOLOGY, PHYSICAL AND REHABILITATION MEDICINE OF THE SESTRE MILOSRDNICE UHC IN ZAGREB*

OSAMDESETA OBLJETNICA KLINIKE ZA REUMATOLOGIJU, FIZIKALNU MEDICINU I REHABILITACIJU KBC-A SESTRE MILOSRDNICE U ZAGREBU*

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INTRODUCTION

The Department of Rheumatology, Physical and Rehabilitation Medicine is the oldest and largest department that simultaneously encompasses two related fields, rheumatology, and physical and rehabilitation medicine, and which operates as part of one of the largest university hospital centres (UHCs) in Croatia. The operation of the Department is focused on the diagnosis, treatment and rehabilitation of adults and children with various diseases and conditions, mainly those of the locomotor system. In addition to that, the operation of the Department is based on a multidisciplinary approach and teamwork, while putting the patient in the centre of all activities. The employees of the Department are leading experts in their fields, who play an important role in shaping the future of our profession, in education, as well as in scientific research. The Department is the Referral Centre for Spondyloarthropathies of the Ministry of Health of the Republic of

UVOD

Klinika za reumatologiju, fizikalnu medicinu i rehabilitaciju najstarija je i najveća klinika koja istovremeno obuhvaća dva srodna područja, reumatologiju i fizikalnu medicinu i rehabilitaciju, a djeluje u sklopu jednoga od najvećih kliničkih bolničkih centara (KBC) u Hrvatskoj. U klinici se provodi dijagnostika, liječenje i rehabilitacija odraslih i djece s različitim bolestima i stanjima, uglavnom onima koja se manifestiraju na lokomotornom sustavu. Temelj je djelovanja klinike multidisciplinarnost i timski rad, s bolesnikom u središtu. Djelatnici klinike su vodeći stručnjaci iz područja svog djelovanja, koji imaju važnu ulogu u oblikovanju struke, u edukaciji, kao i u znanstvenom radu. Klinika je referentni je centar za spondiloartritis Ministarstva zdravstva Republike Hrvatske i jedna je od svega tri takve organizacijske jedinice iz područja reumatologije u Hrvatskoj. Više od deset godina centar je obuke Europskog odbora za fizikalnu i rehabilitacijsku

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Croatia, and it is one of only three such organisational units in the field of rheumatology in Croatia. It has been the training centre of the European Board for Physical and Rehabilitation Medicine for over ten years and it is the only such centre in Croatia. The employees of the Department are active members of various professional societies in Croatia, and they are also actively involved in the work of various international associations and organisations. The Department is the teaching base of the School of Medicine of the University of Zagreb, and it also serves as the institution in which teaching activities are performed for several other institutions of higher education. The employees of the Department have organised and actively participated in several national and international professional meetings and conducted numerous courses and other forms of education, including public health initiatives. They have participated in various projects, published many books/textbooks or book chapters, as well as articles (including articles published in scientific journals with a high impact factor), which contributes to the scientific status of the Department. The Department of Rheumatology, Physical and Rehabilitation Medicine has reached a high level of quality in professional, scientific, and educational terms in its overall areas of activity in Croatia, and it has become an internationally renowned institution.

This article provides an overview of the Department's history, present and future, with an emphasis on the last twenty years of its operation, i.e., the period after the publication of the last major published work – the monograph of the institution.

HISTORICAL DEVELOPMENT OF THE DEPARTMENT

The Department of Rheumatology, Physical and Rehabilitation Medicine is the oldest organisational unit in Croatia that is a part of a hospital. Physical therapy was first introduced in Croatia in the early 1920s, when Lujo Thaller, MD, an internist, started practising this therapy at the Department of Internal Medicine of the then hospital, "Bolnica Milosrdnih sestara". In 1938, the then Department of Internal Medicine, whose head was Lujo Thaller, MD, was renovated and partly expanded, and, at the time, it was the most modern hospital department with a total of 135 beds. On 1 August 1938, the Division of Physical Therapy and Rheumatism was established as part of the Department of Internal Medicine, and Aleksandar Kraut, MD was appointed its head. Jozo Budak, MD, who will later become an expert in the field of physical medicine and rehabilitation, was one of the four physicians who volunteered as part of their medical specialisation training (residency) at the then Department of Internal Medicine. On 19 March 1940, Budak was appointed

medicinu i jedini je takav centar u Hrvatskoj. Djelatnici klinike su vrlo aktivni u nekoliko stručnih društava u Hrvatskoj, kao i u radu međunarodnih udruga i organizacija. Klinika je nastavna baza Medicinskoga fakulteta Sveučilišta u Zagrebu, a na njoj se provodi i nastava nekoliko drugih visokoškolskih ustanova. Djelatnici klinike organizirali su više domaćih i međunarodnih skupova na kojima su bili aktivni sudionici te su proveli brojne tečajeve i ostale oblike edukacije, uključivo i javnozdravstvene akcije. Sudjelovanje u projektima, objava više knjiga/udžbenika ili poglavlja u njima, kao i članci (uključivo i u časopisima s visokim čimbenikom utjecaja) doprinose znanstvenom statusu klinike. Svojim sveukupnim djelovanjem Klinika za reumatologiju, fizikalnu medicinu i rehabilitaciju ima visok stupanj kvalitete u stručnom, znanstvenom i edukativnom pogledu u područjima svoga djelovanja u Hrvatskoj, a prepoznata je i u međunarodnim okvirima.

U ovom članku daje se pregled povijesti klinike, s naglaskom na zadnjih dvadeset godina, odnosno nakon objave zadnje veće publikacije – monografije bolnice, te njezina sadašnjost i budućnost.

POVIJEST KLINIKE

Klinika za reumatologiju, fizikalnu medicinu i rehabilitaciju najstarija je organizacijska jedinica iz tog područja medicine koja je dio jedne bolnice u Hrvatskoj. Prvi početci uvođenja fizikalne terapije u nas bili su početkom dvadesetih godina 20. stoljeća, u sklopu Internog odjela tadašnje Bolnice Milosrdnih sestara, kada se tom problematikom počeo baviti internist dr. Lujo Thaller. Godine 1938. tadašnji Interni odjel, čiji je voditelj bio upravo dr. Thaller, bio je adaptiran i uređen, a dijelom i dograđen te je u to vrijeme bio najsuvremeniji bolnički odjel s ukupno 135 kreveta. Na tom je odjelu 1. kolovoza 1938. započeo s radom Odsjek za fizikalnu terapiju i reumatizam, a njegov je voditelj bio dr. Aleksandar Kraut. Među četvero liječnika – volontera na specijalizaciji tadašnjeg Internog odjela bio je i dr. Jozo Budak, koji će se usmjeriti u područje fizikalne medicine i rehabilitacije. On će 19. ožujka 1940. postati i voditelj toga Odsjeka, koji se od tada počinje i intenzivnije razvijati. Odsjek je bio smješten u tadašnjoj III. kući (danas Klinika za unutarnje bolesti), a imao je dvanaest kreveta i kabinet za elektroterapiju u okviru kojega su bolesnici liječeni galvanoterapijom, Faradayevim strujama i fototerapijom, a tu je započela i galvansko-faradska elektrodijagnostika. U podrumu Internog odjela provođeno je liječenje hidroterapijom i blatnim kupkama, uključivo, između ostaloga, kupelji s ugljičnim dioksidom, „enterocleanerima“ (irigacijska metoda čišćenja crijeva). U početku su zaprimani samo bolnički pacijenti, a već sljedeće godine i ambulantni. Proširenjem na tadašnju IV. kuću (danas Klinika za

the head of that Division, which started to develop more intensively since his appointment. The Division was located at the then Third House (today known as the Department of Internal Medicine) and it was equipped with twelve beds and an office for electrotherapy, where the patients were treated with galvanotherapy, faradaic current and phototherapy, and it was also the place where galvanofaradic electrodiagnostic testing first started to be used. In the basement of the Department of Internal Medicine, treatment was carried out in the form of hydrotherapy and mud baths, including, among other things, baths with carbon dioxide, that is "enterocleaners" (a bowel irrigation method). At the beginning, only inpatients were admitted, and outpatient admission started one year after its establishment. The Department was given another annex in the form of the then Fourth House (today known as the Department of Ophthalmology) where the office for electrotherapy was located, and the Third House was equipped with additional six beds and a laboratory. The Division became an independent unit, and it was upgraded to the Department of Physical Therapy and Rheumatology, which was officially established and started operating on 19 March 1941. It was the first independent department in Croatia for patients with rheumatic diseases. Due to wartime conditions in 1942, the premises of the Department were confiscated for military purposes, and the patients were moved to other departments of the hospital. After World War II, on 15 April 1946, the Department started operating again, at the same premises where it operated prior to the war. This was followed by a brief period in which the Department stopped operating, and then, due to the large number of disabled people, and at the instigation of UNICEF and the World Health Organization (WHO), the Secondary Medical School was established, and in connection with this, the Department was reopened in 1948 as the Department of Physical Medicine and Rehabilitation. The Department was located at the Eleventh House of the hospital, after these premises were no longer used as the student dormitory. The hospital had previously stopped using that building and deemed it unusable, and the Red Cross adapted it to serve as a student dormitory.

Prof. Jozo Budak was a unique individual with innovative ideas and far-sighted in his work. One could rightly say that the concept of modern physical medicine and rehabilitation in Croatia began to take shape precisely due to his professional work. Prof. Budak, MD, PhD, obtained his professional qualification abroad (he graduated in Graz and completed his medical residency in Vienna, Frankfurt am Main, Wiesbaden and Paris). He passed the specialty examination in Zagreb (on 17 October 1939) and was the first specialist in Physical Therapy, Balneology and Climatolo-

očne bolesti), gdje se smješta kabinet za elektroterapiju, u III. kući dobiva se prostor za još šest kreveta i laboratorij. Odsjek postaje samostalan i prerasta u Odjel za fizikalnu terapiju i reumatologiju, koji je službeno počeo s radom 19. ožujka 1941. Bio je to prvi samostalni odjel u našoj zemlji za bolesnike koji su bolovali od reumatskih bolesti. Zbog ratnih prilika 1942. godine prostorije Odjela bile su oduzete za vojne svrhe, a bolesnici su bili preseljeni po drugim odjelima bolnice. Nakon Drugoga svjetskog rata Odjel ponovo započinje s radom, 15. travnja 1946. u prijeratnim prostorima. Usljedio je kraći prekid rada, a potom je zbog velikog broja invalida, a na poticaj UNICEF-a i Svjetske zdravstvene organizacije (SZO) osnovana Srednja medicinska škola, te je u vezi s tim Odjel ponovo otvoren 1948. godine pod nazivom Odjel za fizikalnu medicinu i rehabilitaciju. Bio je smješten u XI. kući bolnice, nakon iseljenja đakčkog doma. Naime, tu je zgradu Bolnica prethodno bila napustila kao neupotrebljivu, a Crveni križ ju je adaptirao za potrebe đakčkog doma.



FIGURE 1. / SLIKA 1.
Prof. dr. Jozo Budak,
Head of the Department / Predstojnik klinike
1940.–1966.

Prof. Jozo Budak bio je, inače, jedinstvena osoba, inovativan i dalekovidan. S pravom se može reći da se suvremena koncepcija fizikalne medicine i rehabilitacije u Hrvatskoj počela oblikovati upravo njegovim profesionalnim radom. Dr. Budak je stručnu kvalifikaciju stekao u inozemstvu (diplomirao u Grazu, a specijalizirao u Beču, Frankfurtu na Majni, Städtu i u Parizu), dok je specijalistički ispit položio u Zagrebu (17. listopada 1939.) i bio je prvi specijalist iz fizikalne terapije, balneologije i klimatologije u tadašnjoj državi. Iz Beča je bio poslao za objavu svoj članak „Današnje stanje primjene niskofrekventnih struja u medicini i njihovo značenje“, koji je objavljen u *Liječničkom vjesniku*

gy in Croatia at that time. While he was in Vienna, he sent his article *Današnje stanje primjene niskofrekventnih struja u medicini i njihovo značenje* (in English: "Today's state of application of low-frequency currents in medicine and their meaning"), which was published 1938, in the third issue of the *Liječnički vjesnik* medical journal. On the 14 March 1939, he held a lecture *Bit djelovanja visokofrekventnih struja i glavni principi metoda aplikacije* (in English: "Mechanism of action of high-frequency currents and main principles of application methods") at the meeting of the Croatian Medical Association (in Croatian *Zbor liječnika*). As early as 1940, he designed a device for electrotherapy at the then laboratory of the Division, and he later designed a device for sound therapy. Furthermore, he performed experiments with electronarcosis, used pyrotherapy, extensively investigated physical therapy methods for the treatment of lymphedema, studied the biology of disabled persons and their adaptation to environmental factors (including performing experiments on animal models). Under the guidance of Prof. Budak, in the period from 1948 to 1954, an experimental study of treatment of approximately 300 patients with rheumatoid arthritis, which was conducted using freshly extracted pituitary glands originating from young animals, was carried out, along with a follow-up of their therapeutic response using clinical and laboratory parameters. In general, Prof. Budak advocated the use of active kinesitherapy (dynamic rehabilitation) as the most valuable part of treatment and rehabilitation. He was an avid advocate of occupational therapy, and the founder of the *Dug život u radu* (in English: "Long Active Life") society.

In 1942, Prof. Budak started teaching physical therapy at the School of Medicine in Zagreb as a visiting lecturer (he was later appointed Associate Professor), at the Department of Neurology and Psychiatry. It should be noted that in 1946, Prof. Budak proposed to the School of Medicine in Zagreb to establish an independent Department of Physical Therapy, which was unfortunately not realised at the time. Prof. Budak was an active member of numerous professional societies and organisations. He was one of the founders and the first chairman of the Section of Rheumatology, Physical Medicine and Balneoclimatology (1947 – 1949), which was founded on 30 June 1947. Other founders of this Section, along with Prof. Budak, were Prof. Josip Breitenfeld, MD (neurologist), Prim. Drago Čop, MD (rheumatologist), Herman Jurak, MD (rheumatologist), Prof. Danko Riessner, MD (neurosurgeon), Prof. Dinko Sučić, MD (internist), Prim. Lujo Thaller, MD (internist), Leo Trauner, MD (balneologist) and Anka Zdunić-Orešković, MD (physiatrists). Prof. Budak had a prominent role in that professional society, i.e., in that Section, and he was also its vice-chairman (1949

br. 3, 1938., dok je u Zboru liječnika u Zagrebu 14. ožujka 1939. održao predavanje „Bit djelovanja visokofrekventnih struja i glavni principi metoda aplikacije“. Još 1940. konstruirao je aparat za elektroterapiju u tadašnjem laboratoriju Odsjeka, a potom i aparat za terapiju zvukom, provodio je pokuse s elektronarkozom, primjenjivao piroterapiju, intenzivno proučavao metode fizikalne terapije za liječenje limfedema, istraživao biologiju invalidnosti i adaptacije na vanjske čimbenike (uključivo i pokuse na eksperimentalnim životinjskim modelima). Pod njegovim vodstvom u razdoblju od 1948. do 1954. u oko 300 bolesnika s reumatoidnim artritisom proveo je pionirsko istraživanje liječenja svježim hipofizama mladih životinja, a terapijski odgovor praćen je klinički i laboratorijski. Općenito, prof. Budak se najviše zalagao za primjenu aktivne kineziterapije (dinamička rehabilitacija), kao najvrjednijeg dijela u liječenju i rehabilitaciji. Zalažući se za liječenje radom osnovao je društvo „Dug život u radu“.

Prof. Budak je još 1942. počeo predavati na Medicinskom fakultetu fizikalnu terapiju kao honorarni nastavnik (do zvanja izvanrednog profesora), u sklopu Katedre za neurologiju i psihijatriju. Vrijedno je napomenuti da je 1946. prof. Budak predložio Medicinskom fakultetu u Zagrebu osnivanje samostalne Katedre za fizikalnu terapiju, što nažalost tada nije realizirano. Prof. Budak je bio vrlo aktivan u mnogim stručnim društvima i organizacijama. Tako je bio jedan od utemeljitelja i prvi predsjednik Sekcije za reumatologiju, fizikalnu medicinu i balneoklimatologiju (1947. – 1949.), osnovane 30. lipnja 1947. Uz prof. dr. Budaka osnivači sekcije bili su prof. dr. Josip Breitenfeld (neurolog), prim. dr. Drago Čop (reumatolog), dr. Herman Jurak (reumatolog), prof. dr. Danko Riessner (neurokirurg), prof. dr. Dinko Sučić (internist), prim. dr. Lujo Thaller (internist), dr. Leo Trauner (balneolog) i dr. Anka Zdunić-Orešković (fizijatar). U tome stručnom društvu – sekciji prof. Budak je imao istaknutu ulogu te je, između ostaloga, bio i njezin dopredsjednik (1949. – 1956.). U prosincu 1949. Sekcija je organizirala svoj „Prvi naučni sastanak“, održan u Hrvatskome liječničkom zboru, na kojem je prof. Budak bio nositelj jedne od glavnih tema „Organizacija zdravstvene službe u reumatologiji, balneoklimatologiji i fizikalnoj medicini“. Pod njegovim se vodstvom u nas, napose od 1951., počelo sa suvremenom rehabilitacijom kao samostalnim oblikom zdravstvene zaštite utemeljenim na koncepcijama SZO-a. Prof. Budak bio je najvažniji pokretač, utemeljitelj i predavač Škole za fizikalnu medicinu i rendgen, osnovane 1. kolovoza 1947., koja je bila prva takva škola u tadašnjoj državi, a 1957. proširena je Odsjekom za radne terapeute i medicinske elektroničare. Iako je tada u inozemstvu bio običaj da se edukacija iz fizioterapije i radne terapije upisuje s navršениh 19 godina, prof. Budak je inzistirao na upisu nakon osnovne

– 1956). In December 1949, the Section organised its First Scientific Meeting (in Croatian: *Prvi naučni sastanak*), which was held at the premises of the Croatian Medical Association (CMA), and at that event, Prof. Jozo Budak held a lecture on one of the main topics. Prof. Budak presented one of the main topics *Organizacija zdravstvene službe u reumatologiji, balneoklimatologiji i fizikalnoj medicini* ("Organisation of health services in rheumatology, balneoclimatology and physical medicine"). Under his guidance, especially since 1951, modern rehabilitation started to be performed as an independent form of healthcare based on the concepts of WHO. Prof. Jozo Budak was the main instigator, founder and lecturer at the School of Physical Therapy and X-Ray, which was established on 1 August 1947. This was the first school of that type in Croatia, and in 1957 it was expanded with the addition of the Division of Occupational Therapy and Medical Electronics. Although, at the time, it was a customary practice abroad for students to enrol in the physiotherapy and occupational therapy classes at the age of 19, Prof. Budak insisted on the initiation of the enrolment process after the completion of elementary school (that is, after year eight), because he believed that for the development of abilities and the mastery of knowledge and skills, it is better to be of young age. Numerous employees of the then Department/Divisions were lecturers at the aforementioned School. In 1949, Prof. Budak became the founder of the health resort *Igalo* in Montenegro, which offered peloid mud treatments as well as mineral water baths.

On 1 August 1958, the Department of Physical Medicine and Rehabilitation became the Republic Department of Physical Medicine and Rehabilitation of the People's Republic of Croatia, and Prof. Budak became its first head. On 1 March 1959, the Department had officially separated from the former "Dr. Mladen Stojanović" hospital and became an independent institution. Nevertheless, the Department continued to operate at the same location on the hospital grounds and collaborate with the organisational units of the hospital. The establishment and operation of the Department were a major shift in the quality of rehabilitation of patients with special needs. Comprehensive multidisciplinary rehabilitation, including occupational rehabilitation (more than 30 occupations), was carried out at the Department. In addition to that, occupational therapy, and music therapy, as well as cybernetics started to be applied in the rehabilitation and education of children with developmental disorders. In 1963, the first experimental electronic classroom for frontal programmed teaching in the country was designed and presented. The classroom was equipped with 30 communicators, and it was designed in collaboration with the engineer, Branimir Makanac. This classroom

škole (osmoljetke), jer je držao da je za razvoj sposobnosti i savladavanje znanja i vještina potrebna što mlađa životna dob. Inače, u toj su školi predavali brojni djelatnici tadašnjeg Odjela/Zavoda. Još ranije, 1949. godine prof. Budak je bio osnivač peloidnog i mineralnog kupališnog lječilišta *Igalo* u Crnoj Gori.

Odjel 1. kolovoza 1958. prerasta u Republički zavod za fizikalnu medicinu i rehabilitaciju NR Hrvatske, čiji ravnatelj postaje prof. Budak, a od 1. ožujka 1959. godine Zavod se i formalno odvaja od tadašnje Bolnice „Dr. Mladen Stojanović“ i postaje samostalna ustanova, iako uvijek radi na istoj lokaciji u bolničkom krugu te surađuje s organizacijskim jedinicama bolnice. Osnivanje i rad Zavoda značili su velik pomak u kvaliteti rehabilitacije osoba s posebnim potrebama. U Zavodu se provodila sveobuhvatna multidisciplinarna rehabilitacija, uključivo i onu profesionalnu (više od 30 zanimanja), počele su se primjenjivati radna terapija i terapija glazbom (muzikoterapija), kao i kibernetika u rehabilitaciji i edukaciji djece ometene u razvoju. Godine 1963. izrađena je prva elektronička eksperimentalna učionica za frontalnu programiranu nastavu u tadašnjoj državi, s 30 komunikatora, izrađena u suradnji s ing. Branimirom Makancem, koja je uvedena u rad sljedeće godine (poslije je darovana Tehničkomu muzeju u Zagrebu). Godine 1960. Zavod se proširuje izgradnjom stacionara u kojemu su smješteni Odjel za reumatske bolesti i fizikalnu terapiju i Odsjek za rehabilitaciju djece, kao i montažne zgrade za profesionalnu rehabilitaciju (obrađa drva, obrađa metala – precizna mehanika, radiomehanika i dr.). Otvara se i Odjel za dijagnostiku i uvode suvremene elektrodijagnostičke metode. Naime, u nas se EMG kao dijagnostička metoda pojavio 1958. kad je prof. Budak dobio na dar od UNICEF-a trokanalni elektromiografski uređaj DISA, prvi takav na Balkanu. Tako je u Zavodu razvijana elektromiografija pod vodstvom dr. Franje Gračanina (prvi službeni nalaz izišao je 1963.), a uz njega se tom metodom bavila i dr. Ruža Sabol. Kraće je vrijeme 1963. trajala intenzivna suradnja s pedijatrima (P. Žeškov), odnosno dijagnostika u djece. U suradnji sa specijalistima ORL-a (F. Marinović) rađene su pretrage na otvorenom larinksu, a u suradnji s okulistima (dr. N. Laktić i dr. S. Padovan) ispitivani su vanjski i unutarnji mišići oka. Također s dermatolozima (dr. A. Gospodnetić) ispitivane su promjene mišića u bolesnika s polimiozitisom i sistemskim lupusom, a s neurolozima miastenije (tenzilonski test). Odlaskom dr. Gračanina u Ljubljani jedno se vrijeme u Zavodu dijagnostikom bavi prof. Zlatko Domljan, a od 1968. prim. dr. Čedo Ljubić (nakon specijalističkog ispita i edukacije u Ljubljani). Od 1963. započinje veće zanimanje neurologa i suradnja Zavoda s našom poznatom stručnjakinjom iz tog područja prof. Anicom Jušić, koja tu dobiva prvu edukaciju i koja, uočivši vrijednost metode, odlazi

was put into operation in the following year (it was later donated to the Technical Museum in Zagreb). In 1960, the Department was further expanded by building an inpatient facility that housed the Department for Rheumatic Diseases and Physical Therapy and the Division for the Rehabilitation of Children, as well as prefabricated buildings for professional rehabilitation (wood finishing, metalworking – precision mechanics, radio mechanics, etc.). The Department of Diagnostics was also established and modern electrodiagnostic methods were introduced. EMG started to be used as a diagnostic method in Croatia in 1958, when Prof. Budak received a three-channel electromyography device called DISA, the first of its kind in the Balkans, as a gift from UNICEF. The development of electromyography at the Department was carried out under the expert guidance of Franjo Gračanin, MD (the first official tests were performed in 1963), and Ruža Sabol was also one of the experts who were using this method. For a brief period of time, intense cooperation was established with the paediatricians (P. Žeškov), regarding diagnostics in children. In collaboration with ORL specialists (F. Marinović), tests were performed on the laryngeal inlet, and in collaboration with the ophthalmologists (N. Laktić, MD and S. Padovan), the extraocular and intraocular muscles were examined. In addition to that, in collaboration with the dermatologists (A. Gospodnetić) muscle changes in patients with polymyositis and systemic lupus erythematosus were examined, and cases of myasthenia gravis were examined in collaboration with the neurologists (using the Tensilon test). After the departure of Prof. Gračanin, MD to Ljubljana, Prof. Zlatko Domljan took over the diagnostic testing activities at the Department, and in 1968 Prim. Čedo Ljubić was entrusted with this task (after he completed his specialty examination and training in Ljubljana). In 1963, neurologists started getting increasingly intrigued by this method, and this was also the year in which the collaboration with our renowned expert in this field, Prof. Anica Jušić started. Her first training in this field was done at this Department, and after she realised just how valuable the method is, she went to Munich for the purpose of further professional development. At the same time as the EMNG method, diagnostics using low-frequency currents, the I/t curve (intensity-time curve) or electrostimulation, was developed, which was first performed in Croatia in 1962 by Ruža Sabol, MD. Prim. Ljubić worked at the laboratory for electromyography and electrodiagnosis, and this work was later performed by several specialists such as Prim. Maja Dubravica, MD, PhD, Prim. Astrid Marčić, MD, and Prim. Fani Doko Guina, PhD. According to the criteria of the World Health Organization, the institute was a model institution for physical medicine and rehabilitation. Due to

1964. u München na daljnje usavršavanje. Istodobno s metodom EMNG-a razvijala se i dijagnostika niskofrekventnim strujama I/t-krivulja (intenzitetno-vremenska krivulja) ili elektrostimulogram, koji je prvi u Hrvatskoj 1962. učinila dr. Ruža Sabol. U laboratoriju za elektromiografiju i elektrodijagnostiku uz prim. Ljubina poslije su radili i liječnici specijalisti prim. dr. sc. Maja Dubravica, prim. dr. Astrid Marčić, a kasnije i prim. dr. sc. Fani Doko Guina. Zavod je, prema kriterijima SZO-a, bio ogledna ustanova za fizikalnu medicinu i rehabilitaciju. Tako je u toku turneje po tada Istočnoj Europi 1963. Zagreb posjetio ekspert SZO-a prof. Howard Rusk, predstojnik Odjela za fizikalnu medicinu i rehabilitaciju Medicinskog fakulteta Sveučilišta u New Yorku, koji je dao najbolje ocjene za rad i organizaciju Zavoda. Zavod i prof. Budak osobno dali su važan doprinos podizanju stručne razine defektologa (danas rehabilitatora), kao i u osnivanju tadašnje Više defektološke škole, danas Edukacijsko-rehabilitacijskog fakulteta, 1962. godine. Reorganizacijom zdravstvenog sustava od 31. prosinca 1966., Zavod 1. siječnja 1967. ponovno postaje dio Bolnice, djeluje kao Odjel za fizikalnu medicinu i rehabilitaciju, sa 64 postelje u stacionaru i s polikliničkom službom.

Nakon prof. Budaka u prijelaznom razdoblju predstojnik Odjela bio je dr. Mijo Rudar, a od 1. svibnja 1967. za predstojnika je izabran prof. dr. sc. Ferdo Licul, koji je došao iz Rijeke, gdje je u Općoj bolnici



FIGURE 2. / SLIKA 2.
Prof. dr. Ferdo Licul,
Head of the Department / Predstojnik klinike
1967–1981.

»Braća dr. Sobol« osnovao i razvio službu fizikalne medicine, rehabilitacije i reumatologije. Od 21. siječnja 1971. Odjel postaje Klinika za fizikalnu medicinu i rehabilitaciju Stomatološkog fakulteta Sveučilišta u Zagrebu (1973.), a voditelj katedre istoimenog predmeta

this, in 1963, the prominent expert and physician of the World Health Organization and the chairman of the Institute of Physical Medicine and Rehabilitation at New York University, Howard Rusk, visited Zagreb during his tour of the then territory of Eastern Europe. During his visit, Husk assessed that the operation and organisation of the Department were at the highest level possible. The Department and Prof. Budak played a significant role in raising the professional level of special education teachers (today known as educational rehabilitators), as well as in the establishment of the then College of Special Education, today known as the Faculty of Education and Rehabilitation Sciences, which was founded in 1962. With the reorganisation of the healthcare system on 31 December 1966, the Department became a part of the hospital once again, on 1 January 1967. It started operating as the Department of Physical Medicine and Rehabilitation, with 64 inpatient beds and an outpatient service.

In the transitional period, after the departure of Prof. Budak, Mijo Rudar, MD became the head of the Department, and on 1 May 1967 this role was assigned to Prof. Ferdo Licul, MD, PhD, who came to work at the Department from Rijeka, where he founded and developed the Unit of Physical Therapy, Rehabilitation and Rheumatology at the *Braća dr. Sobol* General Hospital. On 21 January 1971, the Department became the Department of Physical Medicine and Rehabilitation of the School of Dental Medicine of the University of Zagreb (1973). The head of this Department, which bore the same name as its course, was Prof. Licul, who became an Associate Professor at the School of Dental Medicine in 1974. Prof. F. Licul was also the author of several books such as *Elektroterapija, elektrodijagnostika* (in English: "Electrotherapy, Electrodiagnostics") (published in 1971) and *Elektrodijagnostika i elektroterapija* ("Electrodiagnostics and Electrotherapy") (published in 1981), which was the first book of this kind in our region. Moreover, Prof. Licul devoted the first part of the second book to the foundations of physics, biophysics, electrical technology, electronics, and the physiology of the neuromuscular system. Teamwork, focused on the field of physical medicine and rehabilitation, continued to be the main focal point of the Department. It is definitely worth mentioning that one of the segments of the Department's operation that developed the most during that time, was the (re)habilitation of children with neurodevelopmental disorders. Our hospital is still the leading institution in this field, and it has an exceptionally long tradition in dealing with topics related to it. In the beginning, the segment of (re)habilitation of children was under the guidance of Prof. Ruža Sabol. Soon after, Prof. Milena Stojčević Polovina, MD, PhD, in collaboration with her colleagues Prim. Margita Klobučar,

bio je prof. Licul, koji je na istom fakultetu 1974. postao izvanredni profesor. F. Licul je napisao knjige *Elektroterapija, elektrodijagnostika* (1971.) te *Elektrodijagnostika i elektroterapija* (1981.), prve knjige u nas iz tog područja, pri čemu je prvi dio drugonavedene knjige posvetio temeljima fizike, biofizike, električnoj tehnologiji, elektronici i fiziologiji neuromišićnoga sustava. I dalje je glavni smjer Klinike timski rad, usredotočen na fizikalnu medicinu i rehabilitaciju. Napose je vrijedno istaknuti jedan segment djelovanja klinike koji se najviše razvio u tom vremenu, a to je (re)habilitacija djece s neurorazvojnim smetnjama, u čemu naša bolnica prednjači i ima vrlo dugu tradiciju. U početku je segment (re)habilitacije djece bio pod vodstvom prof. Ruže Sabol, a ubrzo je prof. dr. sc. Milena Stojčević Polovina u suradnji s prim. dr. Margitom Klobučar i kasnije prim. dr. sc. Fani Doko Guina razvila intenzivnu i značajnu aktivnost u smislu razvoja polivalentne (re)habilitacije djece ometene u razvoju. Prof. Stojčević Polovina bila je voditeljica organizacijske jedinice (najprije odsjeka, a potom odjela) za rehabilitaciju i rehabilitaciju djece ometene u razvoju od 1973., kao i Poliklinike za djecu ometenu u razvoju od 1974. do 2004. godine. Prof. Stojčević Polovina još 1973. uviđa važnost i započela je s uvođenjem rane i super-rane rehabilitacije djece, tada kao novine u medicinskoj literaturi i kliničkoj praksi. Godine 1974. prvi put su primijenjene rehabilitacijske tehnike kod djeteta u inkubatoru, a od 1975. se započinje s rehabilitacijom u rodilištu Bolnice, kao i s interdisciplinarnim timskim praćenjem djece s čimbenicima rizika, što je nastavljeno sve do danas.

Nažalost, nema cjelovitog popisa liječnika koji su radili u Klinici, a uz već prethodno navedene vrijedno je spomenuti liječnike specijaliste za koje je poznato da su radili i ostavili trag na klinici, neki još od vremena kad je predstojnik bio prof. Budak, a potom i prof. Licul. Uz ranije spomenute to su: dr. Aleksandar Klimek, dr. Vladimir Pajas, dr. Valerija Pavletić, dr. Ljerka Gruis-Globarević, dr. Drago Radej, dr. Mateja Ivetta i prim. dr. Fatima Krajina.

Od 1. veljače 1981. do 1. lipnja 1985. predstojnik Klinike bio je prof. dr. sc. Franjo Gračanin. On je naglasak aktivnosti usmjerio na neurološku rehabilitaciju, a posebno je razvijao funkcionalnu elektrostimulaciju i biološku povratnu spregu, u kojim je područjima napose stekao velik međunarodni ugled. Utemeljio je Jedinicu za bol, a jedini je naš stručnjak iz fizikalne medicine i rehabilitacije koji je napisao poglavlje u tako prestižnoj knjizi kao što je tada bila *Krusen's Handbook of Physical Medicine and Rehabilitation*.

Od 1. kolovoza 1985. predstojnik Klinike bio je prof. dr. sc. Ivo Jajić. Njegovim dolaskom Klinika postaje klinikom Medicinskog fakulteta Sveučilišta u Zagrebu (22. listopada 1987.). Preimenovana je najprije u Klini-

MD, and Prim. Fani Doko Guina, PhD, developed an intensive and significant activity in terms of the development of polyvalent (re)habilitation of children with developmental disorders. In 1973, Prof. Stojčević Polovina became the head of the organisational unit (at first, she was the head of the Division's OU, and following that, the head of the Department's OU) for habilitation and rehabilitation of children with developmental disorders. From 1974 to 2004 she was the head of the Polyclinic for children with developmental disorders. As early as 1973, Prof. Stojčević Polovina recognised the importance of and started introducing the early and super-early rehabilitation of children, which was then a novel method in medical literature and clinical practice. In 1974, rehabilitation techniques were used for the first time on a child in an incubator, and in 1975, rehabilitation was introduced as a new method at the maternity ward of our hospital, as well as in the interdisciplinary team follow-up of children with risk factors, and it is still used to this day.

Unfortunately, there is no complete list of doctors who worked at the Department. In addition to the aforementioned experts, it is worth mentioning the specialists who worked at the Department and left their mark on it. Some of these experts were employees of the Department at the time when Prof. Budak was its head, and some of them worked there when Prof. Licul was assigned this title. In addition to the aforementioned experts, the physicians who are worth mentioning are the following: Aleksandar Klimek, MD, Vladimir Pajas, MD, Valerija Pavletić, MD, Ljerka Gruis-Globarević, MD, Drago Radej, MD, Mateja Iveta, and Prim. Fatima Krajina, MD.

From February 1981 to 1 June 1985, Prof. Franjo Gračanin, MD, PhD was the head of the Department. He focused his activities on neurological rehabilitation, and his work was especially centred around the development of functional electro-stimulation and biological feedback. The mentioned areas were the fields in which he became internationally renowned. In addition to that, he founded the Clinical Unit for Pain, and he was the only specialist in Physical Medicine and Rehabilitation in our country to ever write a chapter in the most prestigious physiatry book of the time – *Krusen's Handbook of Physical Medicine and Rehabilitation*.

On 1 August 1985, Prof. Ivo Jajić, MD, PhD became the head of the Department. After his appointment, on the 22 October 1987, the Department became the University Department of the School of Medicine, University of Zagreb. The Department was first named the Department of Physical Medicine, Rehabilitation and Rheumatology, and it was later renamed the Department of Rheumatology, Physical and Rehabilitation Medicine because, when Prof. Jajić was the head of the Department, the professional and scientific activities



FIGURE 3. / SLIKA 3.
Prof. dr. Franjo Gračanin,
Head of the Department / Predstojnik klinike
1981–1985.

ku za fizikalnu medicinu, rehabilitaciju i reumatologiju, a poslije u Kliniku za reumatologiju, fizikalnu medicinu i rehabilitaciju, jer su pod njegovim vodstvom stručne i znanstvene aktivnosti općenito usmjerene više prema reumatologiji. U vrijeme Domovinskoga rata klinika je bila uključena u rehabilitaciju ozljeđenika, a vrijedno je napomenuti da su pojedini njezini sadašnji djelatnici bili istaknuti aktivni sudionici u ratu. Godine 1999. Klinika je postala Referentni centar za upalne reumatske bolesti Ministarstva zdravstva RH. Uz stručni rad i nastavu na Medicinskom fakultetu i nekim drugim visokoškolskim ustanovama prof. Jajić je razvio opsežnu publicističku djelatnost, uključivo i objavljivanje većeg broja knjiga iz područja reumatologije, fizikalne medicine i rehabilitacije. Posebno je vrijedno istaknuti njegove pivotalne radove o razumijevanju etiopatogeneze, kliničkoj i radiološkoj prezentaciji ankilozantnoga spondilitisa i hipertrofične osteoartropatije. Prof. Jajić je organizirao brojne stručno-znanstvene skupove, intenzivirao je međunarodnu suradnju, a bio je član Britanskog društva reumatologa (*British Society of Rheumatology*) i začasni član nekoliko europskih reumatoloških društava, te naš predstavnik u više međunarodnih foruma i odbora. Također, prof. Jajić je bio predsjednik Sekcije za reumatologiju Hrvatskoga liječničkog zbora (od 1977. do 1985.), predsjednik i potpredsjednik Udruženja reumatologa Jugoslavije (1982. – 1986.), predsjednik Hrvatskoga reumatološkog društva HLZ-a (1996. – 1998.) i drugi po redu predsjednik Hrvatskoga vertebralnog društva HLZ-a (nakon prof. dr. Pavla Dürriгла). Utemeljio je prvi registar reumatskih bolesti u Hrvatskoj, koji, nažalost, nije uspio zaživjeti. Klinika je od 1996. do 1998. bila sjedište Katedre za fizikalnu medicinu i opću rehabili-

of the Department were more focused on rheumatology. During the Croatian War of Independence, the Department was involved in the rehabilitation of the injured, and it is worth noting that some of the current employees of the Department served in the military during the war. In 1999, the Department became the Referral Centre for Inflammatory Rheumatic Diseases of the Ministry of Health of the Republic of Croatia. Prof. Jajić did not only participate in the professional and scientific activities of the School of Medicine, University of Zagreb. He was also one of the lecturers at this institution and he was involved in the publication of various works and numerous books in the field of rheumatology, physical medicine, and rehabilitation. It is extremely important to highlight his pivotal works on etiopathogenesis, clinical and radiological presentation of ankylosing spondylitis and hypertrophic osteoarthropathy. Furthermore, Prof. Jajić organised numerous professional and scientific meetings, and intensified international cooperation. He was a member of the British Society for Rheumatology and a temporary member of several European societies for rheumatology, and he represented Croatia in several international forums and committees. In addition to that, Prof. Jajić was the chairman of the Rheumatology Section Board of the Croatian Medical Association (from 1977 to 1985), the president and vice-president of the Rheumatology Association of Yugoslavia (from 1982 to 1986), the president of the Croatian Society for Rheumatology of the Croatian Medical Association (from 1996 to 1998) and the second ever president of the Croatian Society for Vertebrology of the Croatian Medical Association (its first president was Pavao Dürigl). He was the founder of the first Register of Rheumatic Diseases in Croatia, which unfortunately, did not last for a long time. From 1996 to 1998, the Department was the seat of the Department for Physical Medicine and General Rehabilitation of the School of Medicine in Zagreb, and Prof. Jajić was the main instigator and the first head of the postgraduate professional study programme in Physical Medicine and Rehabilitation. He was also the founder of the *Fizikalna medicina i rehabilitacija* journal ("Physical Medicine and Rehabilitation") (established in 1984), and from 1991 to 1998 he was the editor-in-chief of the *Reumatizam* journal ("Rheumatism"). In 1982 he became an active member of the Croatian Academy of Medical Sciences (CAMS, in Croatian: AZMH), an honorary member of the Croatian Medical Association and an honorary member of the Croatian Society for Rheumatology. He was especially renowned for his work in the education of young generations of physiatrists and rheumatologists. All things considered, it can be said that Prof. Ivo Jajić significantly contributed to the improvement of rheumatology and physical medicine and rehabilita-

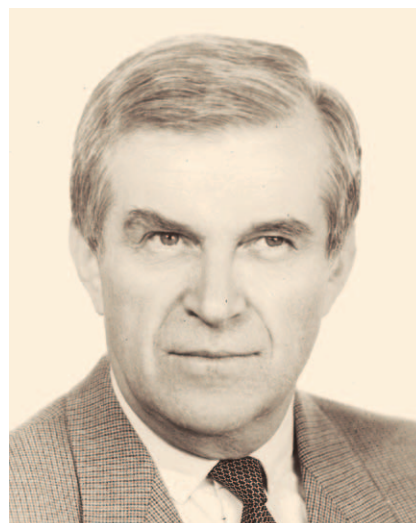


FIGURE 4. / SLIKA 4.
Prof. dr. Ivo Jajić,
Head of the Department / Predstojnik klinike
1985.-2001.

taciju Medicinskog fakulteta u Zagrebu, a prof. Jajić je bio glavni inicijator i prvi voditelj poslijediplomskoga stručnog studija iz fizikalne medicine i rehabilitacije. Utemeljio je časopis *Fizikalna medicina i rehabilitacija* (1984.), a od 1991. do 1998. bio je glavni i odgovorni urednik časopisa *Reumatizam*. Bio je redoviti član Akademije medicinskih znanosti Hrvatske (AMZH) od 1982., počasni član Hrvatskoga liječničkog zbora i počasni član Hrvatskoga reumatološkog društva. Posebno je zapažen njegov rad u edukaciji mladih naraštaja fizijatarata i reumatologa. Sveukupno, prof. Ivo Jajić je značajno pridonio unaprjeđenju reumatologije i fizikalne medicine i rehabilitacije u Jugoslaviji i u Hrvatskoj, te međunarodnoj vidljivosti. Dobitnik je više priznanja među kojima se posebno ističu: nagrada Vlade Republike Hrvatske za znanstveni rad "Ruđer Bošković" (1987.), nagrada Hrvatskoga liječničkog zbora "Ladislav Rakovac" (1993.) i Nagrada grada Zagreba za 2000. godinu. Također, uvršten je u knjigu najpoznatijih svjetskih kliničara i znanstvenika koji su doprinijeli istraživanju ankilozantnog spondilitisa, tadašnjeg vodećeg reumatologa, profesora J. M. H. Molla iz Centra za Reumatske bolesti, Sheffield (UK) (1987.). Prof. Jajić bio je glavni inicijator osnutka i prvi predsjednik Hrvatske lige protiv reumatizma (1992.), tada jedine neprofitne udruge na državnoj razini koja se bavi promicanjem važnosti reumatskih bolesti, a koja je proistekla iz Društva reumatičara, osnovanog 1982. godine. Za vrijeme predstojništva prof. Jajića, a na inicijativu prof. dr. sc. Stojčević Polovine, 2000. godine na klinici je ustanovljen program „Majka – dijete“.

Nakon umirovljenja prof. Jajića 2001. v. d. predstojnika Klinike postala je prim. dr. sc. Maja Dubravica. Dok je prim. Dubravica bila na čelu klinike poboljšani su

tion in former Yugoslavia and Croatia, and he put our country on the map in that field. He received several awards for his work, and some of the most prestigious ones are the following: the Annual Award of the Ruđer Bošković Institute in the category of the Published Scientific Paper (1987), the "Ladislav Rakovac" award of the Croatian Medical Association (1993) and the City of Zagreb Award (2000). In addition to that, he was included in the book of the world's most prominent clinicians and scientists who contributed to the research of ankylosing spondylitis, which was authored by the leading rheumatologist of that time Prof. J. M. H. Moll from the Sheffield Centre for Rheumatic Diseases, Sheffield (UK) (1987). Furthermore, Prof. Jajić was the main initiator of the establishment of the Croatian League against Rheumatism (1992) and its first president. At that time, this was the only non-profit association in the country, dedicated to raising awareness of the importance of rheumatic diseases. Moreover, it was a legal successor of the Association of Rheumatic Patients of the City of Zagreb, which was established in 1982. In 2000, during the time when Prof. Jajić, MD, PhD was the head of the Department, the programme "Mother and Child" was established, on the initiative of Prof. Stojčević Polovina, MD, PhD.

After Prof. Jajić's retirement in 2001, Prim. Maja Dubravica, MD became the acting head of the Department. During the time when Prim. Dubravica was the head of the Department, the working conditions of the outpatient unit for the rehabilitation of children were improved and the unit was given the space located on the fifth floor of building number 5 (in 2004). In addition to that, an Outpatient Unit for the Diagnostic Ultrasound of the Locomotor System was established at the Department, and Tomislav Nemčić, MD was appointed as its head in 2002.

When Prim. Dubravica took on another job at another institution in 2005, Professor Simeon Grazio, MD, PhD, who was appointed head of the Department on 7 October 2005, took on her role. In addition to that, he continued to act as the head of the Department and accepted his mandate for the following four terms: 2009, 2011, 2015 and 2019. From that moment on, the general activities of the Department became more focused on the early diagnosis and treatment with the application of the newest treatment modalities, and the principle of multidisciplinary continued to be used in processing and treatment. The casuistry remained the same in the basic segments, but with an even greater emphasis on spondyloarthritis, vertebral and vertebrogenic syndromes, osteoporosis, rare diseases, as well as post-traumatic and oncological rehabilitation. The latter two were introduced in accordance with the expansion of the Department, that is, its joining with the Department of Traumatology and the Institute for Tu-

prostorni uvjeti polikliničkog dijela namijenjenog rehabilitaciji djece, dobivanjem prostora na V. katu zgrade br. 5 (2004.). Također, na klinici je ustanovljena redovita ambulanta za dijagnostički ultrazvuk lokomotornoga sustava, s kojom je započeo dr. Tomislav Nemčić (2002.).

Odlaskom prim. dr. sc. Dubravice u drugu ustanovu 2005., na njezino mjesto došao je doc. dr. sc. Simeon Grazio, koji je imenovan prestojnikom klinike 7. listopada 2005., a svoj mandat je potvrdio u sljedeća četiri navrata (2009., 2011., 2015. i 2019.). Sveukupne aktivnosti klinike naglašenije su usmjerene na ranu dijagnostiku i liječenje uz primjenu najsuvremenijih modaliteta, a nastavljeno je s načelom multidisciplinarnosti u obradi i liječenju. Kazuistika je u osnovnim segmentima ostala ista, ali, s još većim naglaskom na spondiloartritise, vertebralne i vertebrogene sindrome, osteoporozi, rijetke bolesti, kao i posttraumatološku i onkološku rehabilitaciju (potonje dvoje sukladno proširenju, tj. udruživanju s Klinikom za traumatologiju i Institutom za tumore i formiranjem kliničkoga bolničkoga centra). Pod vodstvom prof. Grazija klinika je 2007. postala Referentni centar za spondiloartropatije Ministarstva zdravstva Republike Hrvatske, a naziv je u suvremenijoj inačici kao Referentni centar za spondiloartritise zadnji put obnovljen 2019. na razdoblje od pet godina. Sukladno tomu naglasak u radu je na dijagnostici, liječenju i rehabilitaciji bolesnika s tom grupom upalnih reumatskih bolesti, gdje je klinika postigla značajne stručne i znanstvene rezultate i u čemu je prepoznata u Hrvatskoj i šire. Uz „velike“ vizite (jedanput na tjedan), obnovljena je praksa održavanja redovitih sastanaka stručnog kolegija i stručnih predavanja (za liječnike i za fizioterapeute) te tjednih kliničko-radioloških sastanaka (u suradnji s radiolozima specijaliziranim za lokomotorni sustav). Uvedeno je kvantificirano praćenje bolesnika s upalnim reumatskim bolestima, što je važno u provođenju načela liječenja prema cilju (engl. *Treat to Target* – T2T). U vezi s tim reumatološke bolesnike pratimo uporabom validiranih indeksa – upitnika (npr. DAS, HAQ, SF-36, BASDAI, BASFI, WOMAC), a doprinos naše Klinike jest da smo validirali i publicirali hrvatsku inačicu upitnika specifičnih za ankilozantni spondilitis (BASFI, BASDAI), što je za sada jedina formalna validacija upitnika za jednu reumatsku bolest u Hrvatskoj (objavljeno u časopisu *Reumatizam*, 2009.). U segmentu (re)habilitacije djece u kliničku praksu naše klinike uveden je test neuromotoričkih sposobnosti za djecu od prohodavanja do šeste godine života, koji je izradila prof. dr. sc. Valentina Matijević.

Godine 2012. oformljena je Dnevna bolnica za odrasle, čime su dobiveni uvjeti za primjenu diferentne terapije, ponajprije bioloških lijekova intravenskim putem, kao i dijagnostičke obrade, liječenja i rehabilitacije bolesnika koji ne trebaju prekonoćni boravak u Kli-

mours and the establishment of the University Hospital Centre. In 2007, during the time when Prof. Grazio was its head, the Department became the Referral Centre for Spondyloarthropathies of the Ministry of Health of the Republic of Croatia, and its name was last changed in 2019, when it was renamed the Referral Centre for Spondyloarthritis, and it was decided that it shall bear the same name for the following period of five years. In accordance with that, the Department is mainly focused on the diagnosis, treatment, and rehabilitation of patients with this group of inflammatory rheumatic diseases. This is the field in which the Department has achieved significant professional and scientific results and gained national and international recognition. In addition to the reintroduction of making grand rounds (once a week), the practice of holding regular meetings of the professional board and expert lectures (for doctors and physiotherapists) and weekly clinico-radiological meetings (in collaboration with radiologists specialising in diseases of the locomotor system) had been reintroduced as well. Quantified follow-up of patients with inflammatory rheumatic diseases was introduced, which is important in implementing the *Treat to Target* strategy (T2T). In this regard, we performed the follow-up of patients with rheumatic diseases using validated disease activity indices – questionnaires (such as DAS, HAQ, SF-36, BASDAI, BASFI, WOMAC). Another special contribution of our Department is that we have validated and published the Croatian version of questionnaires specific for ankylosing spondylitis (BASFI, BASDAI), which is currently the only formal validation of a questionnaire for a rheumatic disease in Croatia (published in the *Rheumatism* journal in 2009). In the field of (re)habilitation of children, the neuromotor skills test for children from their initial gait stage to the age of six was introduced into the clinical practice of our Department. This test was created by Prof. Valentina Matijević, MD, PhD.

In 2012, the Outpatient Clinic for Adults was established, which helped create appropriate conditions for the application of different therapies, primarily of biologic drugs administered intravenously, as well as diagnostic processing, treatment and rehabilitation of patients who do not have to stay overnight at the Department. In 2015, the Outpatient Clinic for Children was also established, and due to the different casuistry, the Outpatient Clinic for Children and the Outpatient Clinic for Adults were created as two separate units. As an example of multidisciplinary approach, we must mention the unit dedicated to the care of patients with an extremely rare hereditary disease, fibrodysplasia ossificans progressiva, which was established at the Sestre milosrdnice UHC over 15 years ago, under the guidance of Prof. Grazio. This unit, that is, team, con-

nici. Godine 2015. ustanovljena je i Dnevna bolnica za djecu, a zbog različitosti kazuistike odvojene su Dnevna bolnica za djecu i Dnevna bolnica za odrasle. Kao primjer multidisciplinarnoga rada navodimo primjer tima za skrb bolesnika s vrlo rijetkom nasljednom bolešću, *fibrodysplasia ossificans progressiva*, koja je prije više od 15 godina osnovana pod vodstvom prof. Grazija u sklopu KBC-a Sestre milosrdnice i u kojem surađuju specijalisti raznih specijalnosti (fizijatar, reumatolog, otorinolaringolog, onkolog – radioterapeut, pulmolog, urolog, dermatolog, radiolog i dr.), a uključen je i Laboratorij za kalcificirana tkiva Zavoda za anatomiju / Zavod za proteomiku Centra za translacijska klinička ispitivanja Medicinskog fakulteta u Zagrebu. U zadnjih petnaestak godina povećan je kapacitet, napose specijalističko-konzilijarne zaštite, pa su na Klinici uvedene nove ambulate (Ambulanta za spondiloartritise, Ambulanta za osteoporozu – lokacija Vinogradska 29). Kao primjer angažiranosti naših djelatnika vrijedno je navesti da je doc. dr. sc. Valentina Matijević 2015. godine dobila priznanje Ministarstva zdravstva RH za najučinkovitiju liječnicu u specijalnosti fizikalne medicine i rehabilitacije, što ju je prema evidenciji HZZO-a uvrstilo među deset najučinkovitijih liječnika te godine. Glede dijagnostičkih mogućnosti nastavljena je tradicija, a provedena su i poboljšanja u radu laboratorija za elektrofiziološku dijagnostiku, dok su primjenom dijagnostičkog ultrazvuka s osnaženim *dopplerom*, uz nabavu novoga suvremenoga uređaja i edukaciju liječnika značajno unaprijeđene mogućnosti u ranom i preciznom dijagnosticiranju različitih bolesti i stanja lokomotornoga sustava. Stoga je na poticaj i podršku prof. Grazija edukaciju u tom smislu završilo još troje liječnika klinike.

U farmakološkom liječenju od 2006. na klinici se primjenjuju biološki lijekovi za liječenje bolesnika s teškim oblicima najčešćih upalnih reumatskih bolesti. Time se naša Klinika svrstala uz bok drugih vodećih ustanova. Također, napretci su postignuti i glede nefarmakoloških modaliteta dijagnostike, liječenja i rehabilitacije. Tako su pojedini liječnici i fizioterapeuti educirani u najvažnijim funkcionalnim dijagnostičkim i terapijskim metodama (npr. Bobath, Vojta, McKenzie, metoda prisilno induciranog pokreta i dr.), što osigurava visoku razinu kvalitete dijagnostike i (re)habilitacije. Osim toga, učinkovitost fizikalne terapije povezana je s nabavom novih uređaja za fizikalnu terapiju, uključivo laser, izvantjelesni udarni val, trakciju s računalnom potporom itd. Od 2011. godine započeli smo s organiziranjem fizioterapije prema najsuvremenijemu integriranom modelu pružanja usluga, dok je u zadnjih petnaestak godina poboljšana dostupnost fizioterapijskog tretmana na više organizacijskih djelova KBC-a i u svim jedinicama intenzivnog liječenja, uključivo i vikendom.

sists of various specialists (such as physiatrists, rheumatologists, otorhinolaryngologists, oncologists – radiotherapists, pulmonologists, urologists, dermatologists, radiologists, etc.) who collaborate on various cases, and the Laboratory for Mineralised Tissues of the Department of Anatomy / Department for Proteomics of the Centre for Translational and Clinical Research of the School of Medicine, University of Zagreb are also included in this collaboration. In the last fifteen years, the capacity has been increased, especially in the area of specialist consultative healthcare, so new outpatient units have been introduced at the Department (Outpatient Clinic for Spondyloarthritis and Outpatient Clinic for Osteoporosis, located at Vinogradska 29). As an example of the engagement of our employees, it is worth mentioning that, in 2015, Prof. Valentina Matijević, MD, PhD received an award from the Ministry of Health of the Republic of Croatia as the most effective doctor in the specialty of Physical Medicine and Rehabilitation. According to the records of the Croatian Health Insurance Fund (CHIF), this made her one of the ten most effective doctors of that year. Regarding the diagnostic possibilities, the Department continued to use traditional methods, and improvements have been made in the operation of the Laboratory for Electrophysiological Diagnostics, while the use of contrast-enhanced power Doppler ultrasound, along with the acquisition of a new modern device and the training of physicians, have significantly improved the possibilities for early and precise diagnosis of various diseases and conditions of the locomotor system. In accordance with the aforementioned, it is worth noting that three more doctors who worked at the Department completed their training with the encouragement and support of Prof. Grazio.

Biologic drugs for the treatment of patients with severe forms of the most common inflammatory rheumatic diseases have been used at the Department since 2006. This put our Department on the map and helped it get on the list of the world's leading institutions in this field. In addition to that, progress has been made regarding non-pharmacological modalities of disease diagnosis, treatment, and rehabilitation. Thus, certain doctors and physiotherapists received training in the most important functional diagnostic and therapeutic methods (such as the Bobath, Vojta and McKenzie methods, constraint-induced movement therapy, etc.), which insures a high level of quality in the area of diagnosis and (re)habilitation. In addition to that, the effectiveness of physical therapy was related to the acquisition of new physical therapy devices, including laser, extracorporeal shock wave, computer-assisted traction, etc. In 2011, we have started organising our physiotherapy treatment according to the most modern integrated model of service provision, while in the last

Uočivši potrebu za izjednačavanjem s europskom kvalitetom i kriterijima rada u medicini, Klinika je aplicirala i ispunila kriterije Europske unije koji jamče kvalitetu i održivost specifične djelatnosti kojom se bave te od 9. travnja 2009. ima certifikat za sustav upravljanja prema EN ISO 9001:2000 za dijagnostiku i konzervativno liječenje lokomotornog sustava (zadnja je inačica 9001:2015). Time je postala jedna od svega nekoliko organizacijskih jedinica našeg KBC-a koja ima taj certifikat. Riječ je o međunarodno priznatoj normi koju je uvela Organizacija za standardizaciju (ISO) radi uspostave međunarodnih zahtjeva za Sustave upravljanja kvalitetom. Certifikat se redovito obnavlja te u tom smislu Klinika usmjerava svoje napore.

Klinika je oduvijek imala važnu ulogu u edukaciji. Njezini su djelatnici bili i jesu poticatelji edukacije i edukatori na svim razinama. Nastava na Medicinskom fakultetu Sveučilišta u Zagrebu uključuje diplomski studij, studij na engleskom jeziku, studij sestrinstva i poslijediplomski specijalistički studij iz fizikalne medicine i rehabilitacije, a voditeljica potonjega je prof. dr. sc. Zrinka Jajić. Na istom Fakultetu na poticaj prof. Grazija realiziran je izborni predmet *Križobolja – najčešći problem lokomotornog sustava u primarnoj zdravstvenoj zaštiti*. Dolaskom na čelo klinike prof. Grazija, uz proširenje prethodne suradnje s Edukacijsko-rehabilitacijskim fakultetom i Kineziološkim fakultetom, obnovljena je suradnja sa Zdravstvenim veleučilištem u Zagrebu, sa Stomatološkim fakultetom u Zagrebu, Fakultetom za dentalnu medicinu i zdravstvo u Osijeku, kratko vrijeme je provedena i nastava Odjela za lingvistiku Filozofskog fakulteta u Zagrebu, dok su nedavno naši liječnici započeli provođenje nastave za fizioterapeute Sveučilišta Libertas u Zagrebu i Visoke škole u Ivanić Gradu.

Klinika ima dugo iskustvo u provođenju edukacije specijalista i užih specijalista. Tako se na klinici provodila i provodi edukacija specijalizanata (fizikalna medicina i rehabilitacija i manji dio nekih drugih specijalizacija) i užih specijalizanata iz reumatologije. Kontinuirano smo sudjelovali i sudjelujemo u edukaciji liječnika, fizioterapeuta, medicinskih sestara i drugih zdravstvenih djelatnika.

Djelatnici naše Klinike (prof. S. Grazio i prof. Z. Jajić) sudjelovali su u izradi novih programa specijalizacije iz reumatologije, odnosno fizikalne medicine i rehabilitacije, koje su usklađene s europskom regulativom, a prije ulaske Hrvatske u Europsku uniju. Od ožujka 2012. do veljače 2019. prof. Grazio je bio voditelj specijalističkog usavršavanja iz fizikalne medicine i rehabilitacije pri Nacionalnom povjerenstvu za specijalističko usavršavanje doktora medicine Ministarstva zdravstva RH, što je priznanje i samoj klinici, a od veljače 2019. nadalje član je radne grupe za specijalističko usavršavanje iz fizikalne medicine i rehabilitacije

fifteen years, the availability of physiotherapy treatment has been improved in several organisational units of the UHC and in all intensive care units, including on the weekends.

The Department recognised the need to get on the same level of quality and work-related criteria in medicine as other European institutions. In accordance with the aforementioned, it applied for a certain kind of certification and fulfilled the criteria of the European Union that guarantee the quality and sustainability of the particular activity that the Department has been dealing with. Due to this, since 9 April 2009, the Department has been the holder of the **quality** management system certificate in accordance with the EN ISO 9001:2000 standard for the diagnosis and conservative treatment of the locomotor system (the latest version of the certificate is in line with the ISO 9001:2015 standard). Due to this, the Department became one of the few organisational units of our UHC that holds this certificate. This is an internationally recognised standard introduced by the International Organisation for Standardization for the purpose of establishing international requirements for Quality Management Systems. The certificate is regularly renewed, and the Department has given its best efforts in order to keep its activities on the level required by the aforementioned certificate.

Furthermore, the Department has always had an important role in the training and education of its employees, who were and remain to be the instigators of education and educators providing training and education at all levels. The study programmes of the School of Medicine, University of Zagreb include the following programmes: the *Medical Studies in English* graduate study programme, the professional study programme in Nursing and the professional study programme in Physical Medicine and Rehabilitation. The head of the aforementioned study programme is Prof. Zrinka Jajić, MD, PhD. At the incentive of Prof. Grazio, an elective course titled "Low back pain – the most common problem of the locomotor system in primary health care" (in Croatian: *Križobolja – najčešći problem lokomotornog sustava u primarnoj zdravstvenoj zaštiti*) was introduced in the curriculum of the School of Medicine, University of Zagreb. When Prof. Grazio became the head of the Department, in addition to the realisation of more extensive cooperation with the Faculty of Education and Rehabilitation Sciences and the Faculty of Kinesiology, the cooperation with the University of Applied Health Sciences in Zagreb, the School of Dental Medicine, University of Zagreb, the Faculty of Dental Medicine and Health in Osijek, was renewed. Furthermore, the courses of the Department of Linguistics of the Faculty of Humanities and Social Sciences of the University of Zagreb were taught for a

pri istom Ministarstvu. Također, u ime Hrvatskoga društva za fizikalnu i rehabilitacijsku medicinu HLZ-a prof. Grazio je bio koordinator zajedničkoga prijedloga za četiri uže specijalizacije iz fizikalne i rehabilitacijske medicine, kao i voditelj prijedloga uže specijalizacije iz Reumatološko-ortopedske rehabilitacije, čiji je član radne grupe bio doc. Grubišić, dok je voditeljica radne grupe za prijedlog uže specijalizacije iz dječje rehabilitacije bila prof. Matijević (2018.).

U siječnju 2011. Klinika je nakon akreditacijskog postupka i posjeta predstavnika mjerodavnih tijela dobila naziv Centra obuke Europskog odbora za fizikalnu i rehabilitacijsku medicinu (*Training Centre of the European Board for Physical and Rehabilitation Medicine*), što je obnovljeno u veljači 2016. i studenom 2020. godine. U vezi s tim prim. T. Nemčić, prim. T. Nikolić i doc. F. Grubišić stekli su, nakon postupka certifikacije, naslove *Fellow of the European Board of Physical and Rehabilitation Medicine* i *Board Certified Trainer*, isti je naslov polaganjem europskog ispita stekla i dr. J. Marunica Karšaj, dok je prof. Grazio uz naslov *Board Certified Trainer* u međuvremenu dobio naslov *Senior Fellow of the European Board of Physical and Rehabilitation Medicine*.

Djelatnici Klinike aktivno su sudjelovali na brojnim radionicama i tečajevima trajne edukacije te brojnim domaćim i međunarodnim stručno-znanstvenim skupovima. Tako su na primjer u zadnjih dvadesetak godina djelatnici Klinike imali ključnu ulogu u organizaciji, kao članovi znanstvenog i/ili organizacijskoga odbora te kao predavači na godišnjim kongresima Hrvatskoga reumatološkoga društva, kongresima Hrvatskoga društva za fizikalnu i rehabilitacijsku medicinu te nekoliko Mediteranskih kongresa (prof. Grazio je bio član znanstvenog odbora i suvoditelj sekcija Mediteranskih reumatoloških kongresa 2009., 2011., 2014., 2016. i 2018.), te kao predsjednik lokalnog Organizacijskoga odbora Srednjoeuropskoga reumatološkog kongresa, 2018. godine. Djelatnici klinike su od 2006. organizatori i aktivni sudionici tečaja Medicinskog fakulteta u Zagrebu *Izvanzglobni reumatizam – novosti u dijagnostici i liječenju*, održanog pet puta (suvoditelj: prof. Grazio). Također, klinika je bila suorganizator, a prof. Grazio suvoditelj tečaja I. kategorije Medicinskoga fakulteta u Zagreba iz područja osteoartritisa koljena, održanoga dva puta. Doc. Grubišić je bio suvoditelj simpozija *Od sustavnih preglednih radova do Cochrane kliničkih sažetaka u fizikalnoj i rehabilitacijskoj medicini*, održanoga u Zagrebu 2019. godine. Klinika je kao Referentni centar bila suorganizator tečaja *MRI training* u području promjena na sakroilijakalnim zglobovima održanoga u Zagrebu 2019., na kojem je prof. Grazio održao i predavanje i vodio radionicu. Klinika je bila značajno uključena u aktivnosti svjetske kampanje *Desetljeća kostiju i zglobova* od samog početka djelovanja

brief period of time. Moreover, our physicians have only recently started teaching classes for physiotherapists at the Libertas International University in Zagreb and at the "Ivanić-Grad College" institution of higher education in Ivanić Grad (in Croatian: *Visoka škola Ivanić-Grad*).

The Department has a long tradition and experience in conducting training and education for specialists and subspecialists. Thus, residency training (in the field of Physical Medicine and Rehabilitation and a few other medical specialties) and subspecialty fellowship training in Rheumatology was conducted and continues to be conducted at the Department. We have continuously participated and continue to participate in the training of physicians, physiotherapists, nurses and other health professionals.

The employees of our Department (Prof. S. Grazio and Prof. Z. Jajić) participated in the establishment of new medical specialty programmes in Rheumatology, i.e., Physical Medicine and Rehabilitation, which were harmonised with EU regulations, even before Croatia joined the EU. From March 2012 to February 2019, Prof. Grazio was the head of the specialist training in Physical Medicine and Rehabilitation of the National Authority for Specialty Training of Medical Doctors in Croatia of the Ministry of Health of the Republic of Croatia, which is a tremendous accomplishment for the Department. In addition to that, he is the member of the Working Group for Specialist Training in Physical Medicine and Rehabilitation of the Ministry of Health of the Republic of Croatia. Moreover, on behalf of the Croatian Society of Physical and Rehabilitation Medicine of the Croatian Medical Association, Prof. Grazio served as a coordinator of the joint proposal for four subspecialties in Physical and Rehabilitation Medicine, as well as the initiator of the proposal for the subspecialty in the field of Rheumatology and Orthopaedic Rehabilitation. Assistant Professor Grubišić, MD was the member of the Working Group for Rheumatology and Orthopaedic Rehabilitation, while Prof. Matijević was the head of the Working Group for the proposal of the subspecialty in the Rehabilitation of Children. (2018).

In January 2011, after the accreditation procedure and the official visit of the competent authorities, the Department was named the Training Centre of the European Board of Physical and Rehabilitation Medicine, and this name was renewed in February 2016 and November 2020. In accordance with the aforementioned and after the certification process, Prim. T. Nemčić, Prim. T. Nikolić and Assistant Prof. F. Grubišić have obtained the following titles: *Fellow of the European Board of Physical and Rehabilitation Medicine* and *Board Certified Trainer*. Furthermore, J. Marunica Karšaj, MD, passed the exam of the European Board of

Nacionalnoga odbora u Hrvatskoj, 2004., dok je prof. Grazio bio tajnik Hrvatskoga nacionalnog odbora *De-setljeća kostiju i zglobova 2010. – 2020.* (od 2011. s dodatnim nazivom *Saveza za mišićnokoštano zdravlje*). Tako je naša klinika bila organizator ili suorganizator svih simpozija povodom Svjetskog dana kralježnice, koji se održava svake godine u lipovnju, a u posljednjih sedam godina pod pokroviteljstvom Hrvatske akademije znanosti i umjetnosti. Voditelj svih simpozija, osim prvoga (voditeljica prof. Z. Jajić), bio je prof. Grazio. Na simpozijima su liječnici Klinike uvijek imali zapaženu ulogu te su redovito aktivno sudjelovali. Na simpozijima su obrađene vrlo raznolike teme iz područja vertebrologije, bili su vrlo dobro posjećeni i od struke ocijenjeni kao visokokvalitetni. Također, klinika je bila suorganizator više simpozija povodom obilježavanja Svjetskog dana traume. Djelatnici klinike su napose bili aktivni u organiziranju i provođenju mnogobrojnih predavanja, tečajeva i radionica s ciljem ranog prepoznavanja i odgovarajućeg liječenja i rehabilitacije bolesnika s upalnim reumatskim bolestima, križoboljom, osteoporozom i djece s neurorazvojnim poremećajima. Na primjer, u sklopu akcije „Ne okrećite leđa križobolji“, to se nastojalo još više osnažiti. Naime, Klinika je, uz Hrvatsku ligu protiv reumatizma, prvi put u Hrvatskoj 2015. obilježila Svjetski dan spondiloartritisa (29. travnja), što je bio i početak te akcije, koja je imala za cilj rano prepoznavanje i odgovarajuće liječenje bolesnika s ovom grupom upalnih reumatskih bolesti. Akcija je bila usmjerena na opće pučanstvo, bolesnike s kroničnom križoboljom, kao i na liječnike, ponajprije one obiteljske medicine, a postoji mogućnost narudžbe i pregleda bolesnika s upalnom križoboljom i sumnjom na aksijalni spondiloartritis kod subspecialista reumatologa izvan redovite liste čekanja. Od prosinca 2016. provodeći je neprofitni projekt „Quantum PsA – Hrvatska“, prvenstveno usmjeren na dermatologe i reumatologe, a koji je implementiran u KBC-u Sestre milosrdnice. U okviru obaju projekata ustanovljen je postupnik što ranijeg i pravilnijeg upućivanja, prepoznavanja i odgovarajućeg liječenja bolesnika s aksijalnim spondiloartritisom odnosno psorijatičnim artritisom, s ciljem smanjenja stupnja nesposobnosti i podizanja kvalitete života tih bolesnika. Radi podizanja sveukupne svijesti o važnosti radne sposobnosti u bolesnika s mišićno-koštanim bolestima i stanjima osnovana je Nacionalna koalicija „Sposoban za rad – Hrvatska“ (*Fit for Work Croatia*) u sklopu projekta EU-a *Fit for Work*, a sve radi podizanja sveukupne svijesti o važnosti radne sposobnosti i ostvarenja njezina što duljeg trajanja u bolesnika s mišićno-koštanim bolestima i stanjima. Djelatnici naše Klinike (prof. dr. sc. Simeon Grazio i doc. dr. sc. Frane Grubišić) njezini su aktivni sudionici i prisustvovali su osnivačkom sastanku u Hrvatskom saboru 13. svibnja 2015., dok je na sljedećoj sjednici Koalicije prof. Grazio izabran za

Physical and Rehabilitation Medicine, and by doing so she was awarded the same title as the aforementioned physicians. Moreover, in addition to the title of *Board Certified Trainer*, Prof. Grazio was also awarded the title of *Senior Fellow of the European Board of Physical and Rehabilitation Medicine*.

The employees of the Department actively participated in numerous workshops and courses of continuing education, as well as various national and international scientific and professional meetings. Over the last twenty years, the employees of the Department played a key role in the organisation of committees, as members of scientific and/or organisational committees and as lecturers at the annual congresses of the Croatian Society for Rheumatology, the congresses of the Croatian Society of Physical and Rehabilitation Medicine and several Mediterranean Congresses of Rheumatology. Prof. Grazio was the member of the Scientific Advisory Committee and the co-leader of various sections at the Mediterranean Congress of Rheumatology in 2009, 2011, 2014, 2016 and 2018. In addition to that, he was the president of the local Organisational Committee at the Central European Congress of Rheumatology in 2018. Since 2006, the employees of the Department have been organising and actively participating in the course titled "Extra-Articular Rheumatism and Related Conditions – Novelities in Diagnosis and Treatment" (in Croatian: *Izvanzglobni reumatizam – novosti u dijagnostici i liječenju*) of the School of Medicine of the University of Zagreb. The co-leader of this course was Prof. Grazio. In addition to that, the Department was the co-organiser and Prof. Grazio was the co-leader of the 1st category course of the School of Medicine, University of Zagreb in the field of osteoarthritis of the knee, which was held two times. Assistant Professor Grubišić was the co-leader of the "From Systematic Reviews to Cochrane Clinical Abstracts in Physical and Rehabilitation Medicine" Symposium (in Croatian: *Od sustavnih preglednih radova do Cochrane kliničkih sažetaka u fizikalnoj i rehabilitacijskoj medicini*), which was held in Zagreb in 2019. As a Referral Centre, the Department was the co-organiser of the "MRI Training" course in the field of sacroiliac joint changes, which was held in Zagreb in 2019. Prof. Grazio held a lecture and a workshop at that same course. The Department was extremely involved in the activities of the global campaign titled The Bone and Joint Decade ever since the establishment of the National Board of the Bone and Joint Decade in Croatia in 2004, while Prof. Grazio was the secretary of the Croatian National Board of the Bone and Joint Decade from 2010 to 2020 (from 2011 with the addition of the Alliance for Musculoskeletal Health). Thus, our Department was the organiser or co-organiser of all symposia on the occasion of the World Spine

voditelja Radne grupe za križbolju. Također, održane su i radionice s temom ranog otkrivanja djece sa neurorizičnim simptomima, jer su istraživanja pokazala da se pravovremenim uključivanjem takve djece u programe postižu optimalni rezultati habilitacije. Prof. Grazio je bio suorganizator i jedan od predavača na tečajevima o pisanju znanstvenih radova, komunikaciji i recenziranju održanih u sklopu godišnjega kongresa Hrvatskoga reumatološkoga društva ili Srednjoeuropskoga reumatološkog kongresa 2017., 2018. i 2019. godine, a u suradnji s prof. Armenom Y. Gasparyanom i prof. Olenom Zimba, kao i tečaja „Pisanje i kritičko čitanje znanstvenoga rada“ održanoga tri puta 2018. godine, u organizaciji Hrvatskoga reumatološkog društva. Slijedi popis stručno-znanstvenih skupova na kojima su liječnici Klinike imali važnu organizacijsko-znanstvenu ulogu.

Značajniji stručni znanstveni skupovi u kojima su članovi klinike imali važnu organizacijsko-znanstvenu ulogu (2000. – 2020.)

- 15. – 17. 10. 2003. 6. godišnji kongres Hrvatskoga reumatološkog društva, Hvar
- 5. 10. 2004. "Prvi hrvatski dan posvećen križbolji", Zagreb, povodom obilježavanja Svjetskog dana kraljeznice
- 18. 10. 2005. Simpozij „Križbolja – biopsihosocijalni aspekt“, Zagreb, povodom obilježavanja Svjetskog dana kraljeznice
- 14. – 16. 10. 2005. 7. godišnji kongres Hrvatskoga reumatološkog društva, Rovinj
- 4. 10. 2006. Simpozij „Dijagnostika i liječenje hernije lumbalnog diska“, Zagreb, povodom obilježavanja Svjetskog dana kraljeznice
- 20. – 22. 10. 2006. 8. godišnji kongres Hrvatskoga reumatološkog društva, Opatija
- 16. 10. 2007. Simpozij „Prognoza i ishod križbolje: medicina temeljena na dokazima“, Zagreb, povodom obilježavanja Svjetskog dana kraljeznice
- 19. – 21. 10. 2007. 9. godišnji kongres Hrvatskoga reumatološkog društva, Split
- 2. 10. 2008. Simpozij „Vratobolja: od uzroka do rehabilitacije“, Zagreb, povodom obilježavanja Svjetskog dana kraljeznice
- 17. – 19. 10. 2008. 10. godišnji kongres Hrvatskoga reumatološkog društva, Primošten
- 5. 3. 2009. „Izvanzglobni reumatizam i srodna stanja – novosti u dijagnostici i liječenju“, poslijediplomski tečaj stalnog medicinskog usavršavanja, Zagreb
- 6. 10. 2009. Simpozij „Torakalna kralježnica – zane-mareni dio kralježnice“, Zagreb, povodom obilježavanja Svjetskog dana kraljeznice
- 18. – 21. 11. 2009. 13th Mediterranean Congress of Rheumatology, Cavtat

Day, which is held every year in October, and for the last seven years it has been sponsored by the Croatian Academy of Sciences and Arts. The chairperson of all symposia, except the first one (which was chaired by Prof. Z. Jajić) was Prof. Grazio. The physicians of our Department always had a significant role at these symposia, and they have actively participated in them on a regular basis. At the symposia, very diverse topics from the field of vertebrology were covered. They also included a great number of participants, and the opinion of the professional and academic community was that they were events of a remarkably high quality. In addition to that, the Department was the co-organiser of numerous symposia on the occasion of the World Trauma Day. The employees of the Department were particularly active in organising and conducting numerous lectures, courses, and workshops with the aim of early recognition and appropriate treatment and rehabilitation of patients with inflammatory rheumatic diseases, low back pain, osteoporosis and children with neurodevelopmental disorders. One of the ways in which we have tried to draw more attention to this topic was the "Don't turn your back on low back pain" campaign (in Croatian: *Ne okrećite leđa križbolji*). In 2015, in collaboration with the Croatian League against Rheumatism, the Department celebrated the World Ankylosing Spondylitis Day (on 29 April) for the first time in Croatia. This was the beginning of the aforementioned campaign, which aimed at early recognition and appropriate treatment of patients with this group of inflammatory rheumatic diseases. The campaign was aimed at the general public, patients with chronic low back pain, as well as doctors, primarily family practice doctors. There was also the possibility of scheduling appointments for patients and performing examinations on patients with inflammatory low back pain and suspected axial spondyloarthritis. These examinations were to be carried out by subspecialists in rheumatology, and they were to be scheduled with no connection to the regular waiting list. Since December 2016, the non-profit project "Quantum PsA – Croatia" has been implemented, which is primarily aimed at dermatologists and rheumatologists. The project has been implemented at the Sestre milosrdnice UHC. As part of both projects, a procedure for early and correct referral, recognition, and appropriate treatment of patients with axial spondyloarthritis or psoriatic arthritis was established, with the aim of reducing the degree of disability and improving the quality of life of these patients. In order to raise awareness of the importance of work ability of patients with musculoskeletal diseases and conditions, the National Coalition titled "Fit for Work Croatia" was established as part of the EU project "Fit for Work". This initiative was established for the purpose of raising awareness of the importance of

21. – 22. 11. 2009. 11. godišnji kongres Hrvatskoga reumatološkog društva, Cavtat

19. – 21. 3. 2010. *European interdisciplinary rheumatology conference*, Dubrovnik, Hrvatska

14. – 17. 10. 2010. 12. godišnji kongres Hrvatskoga reumatološkog društva, Zadar

19. 10. 2010. Simpozij „Novosti i perspektive u vertebrologiji“, Zagreb, povodom obilježavanja Svjetskog dana kralježnice

25. 2. 2011. „Izvanzglobni reumatizam i srodna stanja – novosti u dijagnostici i liječenju“, poslijediplomski tečaj stalnog medicinskog usavršavanja, Zagreb

18. 10. 2011. Simpozij „Smjernice za dijagnostiku, konzervativno i invazivno/operacijsko liječenje križbolje“, Zagreb, povodom obilježavanja Svjetskog dana kralježnice

20. – 23. 10. 2011. 13. godišnji kongres Hrvatskoga reumatološkog društva, Cavtat

10. – 13. 5. 2012. 5. hrvatski kongres fizikalne i rehabilitacijske medicine s međunarodnim sudjelovanjem, Zagreb

16. 10. 2012. Simpozij „Neuspjeh kirurških postupaka na slabinskoj kralježnici – uzroci i rješenja“, Zagreb, povodom obilježavanja Svjetskog dana kralježnice

1. 3. 2013. „Izvanzglobni reumatizam i srodna stanja – novosti u dijagnostici i liječenju“, poslijediplomski tečaj stalnoga medicinskog usavršavanja, Zagreb

15. 10. 2013. Simpozij „Medicinske vježbe u križbolji“, Zagreb, povodom obilježavanja Svjetskog dana kralježnice

17. – 20. 10. 2013. 15. Godišnji kongres Hrvatskoga reumatološkog društva, Split

24. 10. 2013. Simpozij „Prijelomi kuka – sekundarna prevencija osteoporotskih prijeloma“, Zagreb, povodom Svjetskog dana traume

28. – 31. 8. 2014. XV. *Mediterranean Congress of Rheumatology* (MCR), Istanbul, Turska; S. Grazio član Znanstvenoga savjetodavnog odbora (*Scientific Advisory Committee*) i suvoditelj sekcije Spondiloartropatije

16. 10. 2014. Simpozij „Sportske ozljede kralježnice“, Zagreb, povodom Svjetskog dana kralježnice

23. – 26. 10. 2014. 16. godišnji kongres Hrvatskoga reumatološkog društva, Šibenik

31. 10. 2014. Simpozij „Prijelomi gornjeg okrajka bedrene kosti“, Zagreb, povodom Svjetskog dana traume

7. – 9. 11. 2014. 17. godišnja Europska konferencija organizacije bolesnika s artritisom i reumatizmom (PARE) Europske lige protiv reumatizma (EULAR), Hotel Esplanade, Zagreb

13. 10. 2015. Simpozij „Atlanto-aksijalna regija – bolesti i ozljede“, Zagreb, povodom Svjetskog dana kralježnice

15. – 18. 10. 2015. 17. godišnji kongres Hrvatskoga reumatološkog društva Hrvatskoga liječničkog zbora, Poreč

work ability and achieving its long-lasting effect in patients with musculoskeletal diseases and conditions. The employees of our Department (Prof. Simeon Grazio, MD, PhD and Assistant Prof. Frane Grubišić, MD) have actively participated in this initiative, and they have also attended the meeting held at the Croatian Parliament on 13 May 2015, at which this Coalition was established. At the next session of the Coalition, Prof. Grazio was appointed head of the Working Group for Low Back Pain. Moreover, workshops were held on the topic of early detection of children with neurological risk symptoms, as research has shown that the timely inclusion of such children in programmes is beneficial for achieving optimal habilitation results. Furthermore, Prof. Grazio was the co-organiser and one of the lecturers at the courses on writing scientific papers, communication and peer review which were held as part of the annual congress of the Croatian Society for Rheumatology in 2017, 2018 and 2019. These courses were held in collaboration with Prof. Armen Y. Gasparian and Prof. Olena Zimba. In addition to that, Prof. Grazio was the co-organiser and lecturer at the "Writing and Critical Reading of Scientific Papers" course (in Croatian: *Pisanje i kritičko čitanje znanstvenoga rada*), which was held three times in 2018, and which was organised by the Croatian Society for Rheumatology. In the following part, we shall present the list of significant professional and scientific meetings in which the employees of the Department played an important organisational and scientific role.

Significant professional and scientific meetings in which the employees of the Department played an important organisational and scientific role (2000 – 2020)

15 – 17 October 2003 – 6th Annual Congress of the Croatian Society for Rheumatology, Hvar

5 October 2004 – The First Croatian Low Back Pain Day, Zagreb, held on the occasion of the World Spine Day

18 October 2005 – "Low Back Pain – Biopsychosocial Aspect" Symposium, Zagreb, held on the occasion of the World Spine Day

14 – 16 October 2005 – 7th Annual Congress of the Croatian Society for Rheumatology, Rovinj

4 October 2006 – "Diagnosis and Treatment of Lumbar Disc Herniation" Symposium, Zagreb, held on the occasion of the World Spine Day

20 – 22 October 2006 – 8th Annual Congress of the Croatian Society for Rheumatology, Opatija

16 October 2007 – "Prognosis and Outcome of Low Back Pain: Evidence-based Medicine" Symposium, Zagreb, held on the occasion of the World Spine Day

19 – 21 October 2007 – 9th Annual Congress of the Croatian Society for Rheumatology, Split

30. 10. 2015. Simpozij „Liječenje prijeloma proksimalnog humerusa“, Zagreb, povodom Svjetskog dana traume

14. – 17. 4. 2016. 7. hrvatski kongres fizikalne i rehabilitacijske medicine s međunarodnim sudjelovanjem, Šibenik

1. – 4. 9. 2016. 16. mediteranski reumatološki kongres, Sarajevo

13. 10. 2016. Simpozij „Stenoza spinalnog kanala lumbalne regije“, Zagreb, povodom obilježavanja Svjetskog dana kralježnice

20. – 23. 10. 2016. 18. kongres Hrvatskoga reumatološkog društva, Šibenik

21. 10. 2016. Simpozij „Osteoporotski prijelomi – dijagnostika, liječenje i rehabilitacija“, Zagreb, povodom obilježavanja Svjetskog dana traume

22. – 23. 9. 2017. AGORA meeting (platforma za organizacije bolesnika s reumatskim i koštano-mišićnim bolestima južne Europe / platform representing patient organizations of people with Rheumatic and Musculoskeletal Diseases (RMDs) in Southern Europe), Zagreb, Hrvatska.

17. 10. 2017. Simpozij „Smjernice za dijagnostiku i liječenje bolesnika s vratoboljom“, Zagreb, povodom Svjetskog dana kralježnice

18. 10. 2017. Simpozij „Prijelomi u području ručnog zgloba i šake – dijagnostika, liječenje i rehabilitacija“, Zagreb, povodom Svjetskog dana traume

26. – 29. 10. 2017. 19. godišnji kongres Hrvatskoga reumatološkog društva s međunarodnim sudjelovanjem, Dubrovnik

12. – 14. 4. 2018. 14. Mediterranean Congress of Rheumatology, Genova, Italija

19. – 22. 4. 2018. 7. hrvatski kongres fizikalne i rehabilitacijske medicine, Šibenik

4. 10. 2018. tečaj I. kategorije Medicinskog fakulteta u Zagrebu „Novosti u liječenju osteoartritisa koljena“, Zagreb

16. 10. 2018. Simpozij „Sakrolijakalni zglobovi“, Zagreb, povodom Svjetskog dana kralježnice

17. 10. 2018. Simpozij „Ozljeđe kralježnice“, Zagreb, povodom Svjetskog dana traume

6. – 8. 12. 2018. Srednjoeuropski reumatološki kongres (Central European Congress of Rheumatology), 2018., Zagreb

8. 12. 2018. 20. godišnji kongres Hrvatskoga reumatološkog društva, Zagreb

24. 5. 2019. Simpozij „Od sustavnih preglednih radova do Cochrane kliničkih sažetaka u fizikalnoj i rehabilitacijskoj medicini“, Zagreb

16. 10. 2019. Simpozij „Biološki i medicinski aspekti degenerativnih promjena intervertebralnog diska“, Zagreb, povodom Svjetskog dana kralježnice

2 October 2008 – “Neck pain: causes and rehabilitation” Symposium, Zagreb, held on the occasion of the World Spine Day

17 – 19 October 2008 – 10th Annual Congress of the Croatian Society for Rheumatology, Primošten

5 March 2009 – “Extra-articular Rheumatism and Related Conditions – Novelties in Diagnosis and Treatment”, postgraduate course of continuing medical education, Zagreb

6 October 2009 – “Thoracic Spine – A Neglected Portion of the Spine” Symposium, Zagreb, held on the occasion of the World Spine Day

18 – 21 November 2009 – 13th Mediterranean Congress of Rheumatology, Cavtat

21 – 22 November 2009 – 11th Annual Congress of the Croatian Society for Rheumatology, Cavtat

19 – 21 March 2010 – European Interdisciplinary Rheumatology Conference, Dubrovnik, Croatia

14 – 17 October 2010 – 12th Annual Congress of the Croatian Society for Rheumatology, Zadar

19 October 2010 – “News and Perspectives in Vertebrology”, Zagreb, held on the occasion of the World Spine Day

25 February 2011 – “Extra-articular Rheumatism and Related Conditions – Novelties in Diagnosis and Treatment”, postgraduate course of continuing medical education, Zagreb

18 October 2011 – “Guidelines for the Diagnosis, Conservative and Invasive/Operative Treatment of Low Back Pain” Symposium, Zagreb, held on the occasion of World Spine Day

20 – 23 October 2011 – 13th Annual Congress of the Croatian Society for Rheumatology, Cavtat

10 – 13 May 2012 – 5th Croatian Congress of Physical and Rehabilitation Medicine with international participation, Zagreb

16 October 2012 – “Failure of Surgery on the Lumbar Spine – Causes and Solutions” Symposium, Zagreb, on the occasion of World Spine Day

1 March 2013 – “Extra-articular Rheumatism and Related Conditions – Novelties in Diagnosis and Treatment”, postgraduate course of continuing medical education, Zagreb

15 October 2013 – “Medical Exercises for Low Back Pain” Symposium, Zagreb, held on the occasion of the World Spine Day

17 – 20 October 2013 – 15th Annual Congress of the Croatian Society for Rheumatology, Split

24 October 2013 – “Hip Fractures – Secondary Prevention of Osteoporotic Fractures” Symposium, Zagreb, held on the occasion of the World Trauma Day

28 – 31 August 2014 – XV Mediterranean Congress of Rheumatology (MCR), Istanbul, Turkey, S. Grazio, member of the Scientific Advisory Committee and co-leader of the “Spondyloarthropathies” section

„European Prospective Osteoporosis Study (EPOS)“ – leader and principal investigator for Croatia (voditelj i glavni istraživač za Hrvatsku): prof. dr. sc. Ivo Jajić; financed by European Union Concerted Action Grant pod Biomed-1 (BMH1CT920182) and EU grants C1P-DCT925102 i ERBC1PDCT 930105 i 940229 (financiranje: Komisija za znanost Europske unije i EU grants), supported by the Wellcome Trust (uz potporu Wellcome Trusta); 1996–2002.

„Molecular mechanisms of the effects of immune disorders on bone (Molekularni mehanizmi učinaka imunskih poremećaja na kost)“ – collaborator (suradnik): prof. dr. sc. Zrinka Jajić; financed by (financiranje): Ministry of Science, Education and Sports of the Republic of Croatia (Ministarstvo znanosti, obrazovanja i športa RH); project code (šifra projekta): 108-1080229-0142); 2007–2011.

“Effects of work environmental factors on musculo-skeletal system (Utjecaji čimbenika radnog okoliša na mišićno-koštani sustav)“ – collaborator (suradnik): prof. dr. sc. Simeon Grazio; financed by (financiranje): Ministry of Science, Education and Sports of the Republic of Croatia (Ministarstvo znanosti, obrazovanja i športa RH); project code (šifra projekta): 022.0222411-2409; 2007–2013.

„Psoriatic arthritis – epidemiology and risk factors (Psorijatični artritis – epidemiologija i čimbenici rizika)“ – lead investigator (voditelj): prof. dr. sc. Simeon Grazio; financed by (financiranje): Ministry of Science, Education and Sports of the Republic of Croatia (Ministarstvo znanosti, obrazovanja i športa RH); project code (šifra projekta): 134-0000000-3531); 2008–2011.

„Development and validation of a new patient-reported outcome (PRO) questionnaire to estimate vitamin D status (D-PRO) and its correlation with quality of life, disease activity and disability in rheumatoid arthritis patients in Europe“ – leader and principal investigator for Croatia (voditelj i glavni istraživač za Hrvatsku): prof. dr. sc. Simeon Grazio; financed by (financiranje): European League Against Rheumatism – EULAR (Europska liga protiv reumatizma – EULAR); number (broj): CLI064; 2012–2016.

„A multinational observational study to investigate the impact of treatment recommendation for the treatment of patients with rheumatoid arthritis using web-based monitoring“ – associate (suradnik): prof.

17. – 20. 10. 2019. 21. godišnji kongres Hrvatskoga reumatološkog društva s međunarodnim sudjelovanjem, Šibenik

22. 10. 2019. Simpozij „Revizijski zahvati kod protetike kuka: dijagnostika, liječenje i rehabilitacija“, Zagreb, povodom Svjetskog dana traume

dr. sc. Zrinka Jajić; financed by (financiranje): International Recommendation Implementation Study, Leiden University Medical Center, Merit Foundation, Netherlands; 2012–2014.

„Coxib and traditional NSAID Trialist (CNT) Collaboration“ – collaborator (suradnik): prof. dr. sc. Zrinka Jajić; financed by (financiranje): Medical Research Council and the British Heart Foundation, and coordinated by researchers at the MRC Clinical Trial Service Unit & Epidemiological Studies Unit (CTSU) at the University of Oxford; 2012–2013.

„ASAS Health Indeks – a new tool to measure health in patients with spondyloarthritis based on the International Classification of Functioning, Disability and Health (ICF)“ – leader and principal investigator for Croatia (voditelj i glavni istraživač za Hrvatsku): prof. dr. sc. Simeon Grazio; collaborators (suradnici): doc. dr. sc. Frane Grubišić, dr. Hana Skala Kavanagh; financed by (financiranje): Assessment of Spondyloarthritis International Society (ASAS); 2013–2018.

„Proteomic profiling of blood plasma proteins associated with rheumatoid arthritis, psoriatic arthritis and non-inflammatory arthritis (Proteomsko profiliranje proteina krvne plazme povezanih s reumatoidnim artritisom, psorijatičnim artritisom i ne-upalnim artritisom)“ – collaborator / leader of the research unit (suradnik / voditelj na istraživačkoj jedinici): prof. dr. sc. Simeon Grazio; financed by (financiranje): research project by the Department of Proteomics, Centre for Translational and Clinical Medicine, School of Medicine, University of Zagreb (istraživački projekt Odjela za proteomiku, Centra za translacijsku i kliničku medicinu Medicinskog fakulteta u Zagrebu); 2013–

„EULAR Recommendations for the use and interpretation of laboratory diagnostic tests for the management of systemic autoimmune rheumatic diseases“ – collaborator (suradnik): prof. dr. sc. Simeon Grazio; financed by (financiranje): European League Against Rheumatism – EULAR (Europska liga protiv reumatizma – EULAR); number (broj): SCI016; 2017–2020.

„Determination of differences in the proteomic profile and occurrence of inflammatory mediators in the blood and urine of patients with FOP, and examination of the induction of ossification by egg extract in cell culture of fibrocytic-adipose progenitors (Određivanje razlika u proteomskom profilu te pojavnosti upalnih medijatora u krvi i urinu pacijenata sa FOP te ispiti-

vanje indukcije okoštavanja ekstraktom jaja u staničnoj kulturi fibrocitno-adipoznih progenitora)“ – collaborator (suradnik): prof. dr. sc. Simeon Grazio; financed by (financiranje): project supported by the University of Zagreb (projekt potpore Sveučilišta u Zagrebu); 2018–

„Classification of Axial Spondyloarthritis Inception Cohort“ – leader and principal investigator for Croatia (voditelj i glavni istraživač za Hrvatsku): prof. dr. sc. Simeon Grazio; collaborators (suradnici): doc. dr. sc. Frane Grubišić, dr. Hana Skala Kavanagh, dr. sc. Ines Doko Vajdić; financed by (financiranje): Assessment of Spondyloarthritis International Society (ASAS); 2018–

„Activity of bone progenitor cells in bone metabolism disorders caused by inflammation (Aktivnost koštanih progenitorskih stanica u poremećajima koštanog metabolizma uzrokovanih upalom)“ – collaborator (suradnik): prof. dr. sc. Zrinka Jajić; financed by (financiranje): University of Zagreb (Sveučilište u Zagrebu); 2015–

„Notch signaling pathway in rheumatoid arthritis-induced osteoclast progenitors (Notch signalni put u osteoklastnim progenitorima potaknutim reumatoidnim artritisom)“ – collaborator (suradnik): prof. dr. sc. Zrinka Jajić; financed by (financiranje): Croatian Science Foundation (Hrvatska zaklada za znanost) (IP-2018-01-2414); 2018–

„Analysis of cytokines and proteomic profile of microvesicles in biological fluids of patients with rare bone diseases and bone fractures and hampered bone healing (Analiza citokina i proteomskog profila mikrovezikula u biološkim tekućinama pacijenata s rijetkim koštanim bolestima te kod koštanih prijeloma i otežanog koštanog cijeljenja)“ – collaborator (suradnik): prof. dr. sc. Simeon Grazio; financed by (financiranje): research project by the Department of Proteomics, Centre for Translational and Clinical Medicine, School of Medicine, University of Zagreb (istraživački projekt Odjela za proteomiku, Centra za translacijsku i kliničku medicinu Medicinskog fakulteta u Zagrebu); 2020–

„GRAPPA (Group for Research in Assessment of Psoriasis and Psoriatic Arthritis) recommendation 2021“ – collaborator (suradnik): prof. dr. sc. Simeon Grazio; financed by (financiranje): GRAPPA; 2020–

FIGURE 5. – SLIKA 5. Research projects (2000 – 2020) / Znanstveni projekti (2000. – 2020.)

16 October 2014 – “Sports-related Spine Injuries” Symposium, Zagreb, held on the occasion of the World Spine Day

23 – 26 October 2014 – 16th Annual Congress of the Croatian Society for Rheumatology, Šibenik

25. 10. 2019. tečaj I. kategorije Medicinskog fakulteta u Zagrebu „Novosti u liječenju osteoartritisa koljena“, Zagreb

22. 11. 2019. „MRI training“, Zagreb

27. – 30. 8. 2020. 8. hrvatski kongres fizikalne medicine i rehabilitacije, Šibenik / webinar

31 October 2014 – “Fractures of the Upper Part of the Femur” Symposium, Zagreb, held on the occasion of the World Trauma Day

7 – 9 November 2014 – 17th EULAR Annual European Conference of PARE, Hotel Esplanade, Zagreb

13 October 2015 – “Atlanto-axial Joint – Diseases and Injuries” Symposium, Zagreb, held on the occasion of the World Spine Day

15 – 18 October 2015 – 17th Annual Congress of the Croatian Society for Rheumatology of the Croatian Medical Association, Poreč

30 October 2015 – “Treatment of Proximal Humerus Fracture” Symposium, held on the occasion of the World Trauma Day

14 – 17 April 2016 – 7th Croatian Congress of Physical and Rehabilitation Medicine with international participation, Šibenik

1 – 4 September 2016 – XVI Mediterranean Congress of Rheumatology, Sarajevo

13 October 2016 – “Lumbar Spinal Stenosis” Symposium, Zagreb, held on the occasion of the World Spine Day

20 – 23 October 2016 – 18th Congress of the Croatian Society for Rheumatology, Šibenik

21 October 2016 – “Osteoporotic Fractures – Diagnosis, Treatment and Rehabilitation” Symposium, Zagreb, held on the occasion of the World Trauma Day

22 – 23 September 2017 – The AGORA meeting – a platform representing patient organizations of people with Rheumatic and Musculoskeletal Diseases (RMDs) in Southern Europe, Zagreb, Croatia

17 October 2017 – “Guidelines for the Diagnosis and Treatment of Patients with Neck Pain” Symposium, Zagreb, held on the occasion of the World Spine Day

18 October 2017 – “Wrist and Hand Fractures – Diagnosis, Treatment and Rehabilitation” Symposium, Zagreb, held on the occasion of the World Trauma Day

26 – 29 October 2017 – 19th Annual Congress of the Croatian Society for Rheumatology of the Croatian Medical Association with international participation, Dubrovnik

12 – 14 April 2018 – 14th Mediterranean Congress of Rheumatology, Genoa, Italy

19 – 22 April 2018 – 7th Croatian Congress of Physical and Rehabilitation Medicine, Šibenik

4 October 2018 – 1st category course of the School of Medicine, University of Zagreb: “New Procedures in the Treatment of Osteoarthritis of the Knee”, Zagreb

16 October 2018 – “Sacroiliac Joints” Symposium, Zagreb, held on the occasion of the World Spine Day

17 October 2018 – “Spine Injuries” Symposium, Zagreb, held on the occasion of the World Trauma Day

6 – 8 December 2018 – Central European Congress of Rheumatology, 2018, Zagreb

8 December 2018 – 20th Annual Congress of the Croatian Society for Rheumatology, Zagreb

13. 10. 2020. Simpozij „Osteoporoza kralježnice“, Zagreb (*webinar*), povodom Svjetskog dana kralježnice

16. – 17. 10. 2020. 22. godišnji kongres Hrvatskoga reumatološkog društva s međunarodnim sudjelovanjem – virtualni kongres

Klinika je niz desetljeća bila jedna od vodećih u znanstvenoj aktivnosti u svojim područjima djelovanja, a posljednjih desetljeća to je još osnaženo, napose većim udjelom u bazičnim istraživanjima, dok je broj djelatnika koji se bave znanstvenim radom značajno proširen. Iako su područja znanstvenog istraživanja dominantno klinička, iz područja reumatologije te fizikalne medicine i rehabilitacije (u odraslih i u djece), u zadnjih desetak godina primjetan je porast broja bazičnih istraživanja, napose iz područja patofizioloških procesa upalnih reumatskih bolesti i biologije bolesti karakteriziranih poremećajima osifikacije. Velika većina liječnika stekla je titulu primarijusa u zadnjih 15 godina, kao i sedam od deset liječnika doktorat znanosti, uz jedan magisterij (većini je mentor/voditelj bio prof. Grazio), što govori u prilog poticajnog i pozitivnog ozračja za stručni i znanstveni razvoj na Klinici.

U Klinici je provedeno više projekata i neprofitnih istraživanja te kliničkih studija. Posebno je vrijedno istaknuti projekte financirane od strane Ministarstva znanosti, obrazovanja i sporta RH i Hrvatske zaklade za znanost, kao i činjenicu da su neki od projekata i istraživanja u zadnjih petnaestak godina realizirani u suradnji s uglednim domaćim i međunarodnim ustanovama i organizacijama. To su na primjer Centar za translacijska i klinička istraživanja – Odjel za proteomiku, Zavod za fiziologiju i imunologiju i Hrvatski institut za istraživanje mozga Medicinskog fakulteta u Zagrebu, Institut za medicinska istraživanja i medicinu rada Republike Hrvatske u Zagrebu, Institut „Ruđer Bošković“ u Zagrebu ili *Assessment of SpondyloArthritis International Society*. Od 2019. klinika je kao nacionalni centar uključena u mrežu europskih referentnih centara (ERN – *European Reference Network*) iz područja rijetkih imunodeficiencija, autoinflamatornih i autoimunih bolesti RITA (*Rare Immunodeficiency autoimmune Inflammatory Autoimmune*), s ciljem omogućavanja zdravstvenim profesionalcima i bolesnicima u Europskoj uniji pristup najboljoj ekspertizi i pravovremenoj razmjeni znanja. Na slici 5. dan je popis projekata u razdoblju od 2000. do 2020. godine.

Djelatnici Klinike sudjelovali su u više multicentričnih intervencijskih studija, čime su stečene nove spoznaje i iskustva o novim mogućnostima liječenja, poglavito upalnih i neupalnih reumatskih bolesti, osteoporoze i traumatologije.

Znanstvena se aktivnost odražava i u broju aktivnih sudjelovanja na znanstvenim skupovima i objavljenih publikacija, u čemu Klinika ima zavidnu tradiciju. Dje-

24 May 2019 – “From Systematic Reviews to Cochrane Clinical Abstracts in Physical and Rehabilitation Medicine” Symposium, Zagreb

16 October 2019 – “Biological and Medical Aspects of Intervertebral Disc Degenerative Changes” Symposium, Zagreb, on the occasion of the World Spine Day

17 – 20 October 2019 – 21st Annual Congress of the Croatian Society for Rheumatology with international participation, Šibenik

22 October 2019 – “Revision Procedures in Hip Prosthetics: Diagnosis, Treatment and Rehabilitation” Symposium, Zagreb, held on the occasion of the World Trauma Day

25 October 2019 – 1st category course of the School of Medicine, University of Zagreb: “New Procedures in the Treatment of Osteoarthritis of the Knee”, Zagreb

22 November 2019 – MRI training, Zagreb

27 – 30 August 2020 – 8th Croatian Congress of Physical and Rehabilitation Medicine, Šibenik (webinar)

13 October 2020 – “Osteoporosis of the Spine” Symposium, Zagreb (webinar), held on the occasion of the World Spine Day

16 – 17 October 2020 – 22nd Annual Congress of the Croatian Society for Rheumatology of the Croatian Medical Association with international participation (virtual congress)

For several decades, the Department has been one of the leaders in scientific activity in its fields, and in recent decades this has been further strengthened, especially with a larger share of operations in basic research, while the number of employees who engage in scientific work increased significantly. Although the areas of scientific research are predominantly focused on the clinical field, in the last decade there has been a noticeable increase in the number of basic research studies in the field of Rheumatology and Physical Medicine and Rehabilitation (in adults and in children), and especially in the field of Pathophysiology of Inflammatory Rheumatic Diseases and the biology of diseases characterised by ossification disorders. In the period of the last 15 years, most of our physicians obtained the title of primarius (Prim.), seven of our ten physicians obtained a title of PhD and one of them got a Master's degree (most of them were mentored by Prof. Grazio), which speaks in favour of a stimulating and positive atmosphere for the professional and scientific development at the Department.

Several projects and non-profit research and clinical studies were conducted at the Department. It is important to highlight the projects funded by the Ministry of Science, Education and Sports of the Republic of Croatia and the Croatian Science Foundation, as well as the fact that some of the projects and research studies conducted in the last fifteen years have been carried out in cooperation with reputable national and international

latnici Klinike su autori, koautori i urednici više knjiga ili poglavlja u knjigama, a mnoge od njih su nastavni i/ili sveučilišni udžbenici/tekstovi. Djelatnici Klinike pojavljuju se oko 400 puta kao autori ili koautori stručno-znanstvenih radova *in extenso*, od čega više od 150 puta u časopisima koji se citiraju u najprestižnijim bazama podataka, a s oko 600 radova sudjelovali su na domaćim i međunarodnim skupovima (objavljeni sažetci), što sve govori o značajnoj stručno-znanstvenoj i publicističkoj aktivnosti djelatnika klinike, najvećim dijelom u zadnjih petnaestak godina. Kao primjer interesa stručne javnosti za visokokvalitetne radove proistekle iz rada djelatnika klinike vrijedno je spomenuti rad o perzistenciji tjednog alendroanata (Grazio i sur., 2008.), koji je u tjednu objavljivanja bio drugi najčitaniji rad u tjednu objave uopće. Na slici 6. dan je popis poglavlja u knjigama, a na slici 7. izbor značajnijih radova (*in extenso*).

Liječnici klinike članovi su više domaćih i međunarodnih stručnih udruga i organizacija kao što su Hrvatsko reumatološko društvo, Hrvatsko društvo za fizikalnu i rehabilitacijsku medicinu, Hrvatsko vertebrološko društvo, Hrvatsko društvo za liječenje boli, Hrvatsko društvo za palijativnu medicinu, Hrvatsko društvo za sportsku medicinu, Hrvatsko društvo za neuromuskularne bolesti i kliničku elektromioneurografiju, Hrvatsko društvo za reanimatologiju, Hrvatsko logopedsko društvo, Hrvatsko udruženje za bihevioralno-kognitivne terapije, Hrvatski olimpijski odbor, kao i nekoliko međunarodnih udruga i organizacija, kao što su Britansko reumatološko društvo, Europska liga protiv reumatizma (*European League Against Rheumatism* – EULAR), Europsko društvo za fizikalnu i rehabilitacijsku medicinu (*European Society for Physical and Rehabilitation Medicine* – ESPRM), Međunarodna zaklada za osteoporozu (*International Osteoporosis Foundation*), Međunarodno društvo za ortotiku i protetiku (*International Society for Prosthetic and Orthotic* – ISPO), međunarodna grupa ASAS (*Assessment of Spondyloarthritis*), međunarodna grupa GRAPPA (*Group for Research and Assessment of Psoriasis and Psoriatic Arthritis*). Fizioterapeuti i medicinske sestre članovi su svojih stručnih udruga.

Neki od zaposlenika obavljali su i obavljaju dužnosti u stručnim društvima i organizacijama, domaćim i međunarodnim. Tako je, na primjer, prof. Grazio predsjednik Hrvatskoga vertebrološkog društva HLZ-a (od 2013.), prvi je dopredsjednik Hrvatskog društva za fizikalnu i rehabilitacijsku medicinu HLZ-a (od 2013.) i prvi dopredsjednik Hrvatskoga reumatološkog društva HLZ-a (od 2015.); doc. Grubišić član je Upravnog odbora Hrvatskog društva za fizikalnu i rehabilitacijsku medicinu i Hrvatskoga vertebrološkoga društva (aktualno je i tajnik potonjeg stručnoga društva), a bio je član Upravnog odbora Hrvatskoga reumatološkoga

institutions and organisations. These include: the Centre for Translational and Clinical Research – the Department of Proteomics, the Department of Physiology and Immunology and the Croatian Institute for Brain Research of the School of Medicine, University of Zagreb, Institute for Medical Research and Occupational Health of the Republic of Croatia in Zagreb, the Ruđer Bošković Institute in Zagreb, or the Assessment of SpondyloArthritis international Society. Since 2019, the Department has been included in the European Reference Network (ERN) as a national centre in the field of Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases (RITA), with the aim of enabling health professionals and patients in the European Union to get the best expert advice and the timely exchange of knowledge. Figure 5. present a list of significant research projects conducted in the period from 2000 to 2020.

The employees of the Department participated in several multicentre intervention studies, which helped them gain new knowledge and experience about the new treatment options, especially in the area of inflammatory and non-inflammatory rheumatic diseases, osteoporosis, and traumatology.

Scientific activity is also reflected in the number of active participations in scientific meetings and published publications, and the Department has a long tradition of partaking in both of these areas. The employees of the Department are authors, co-authors and editors of several books or book chapters, many of which are educational textbooks and/or university textbooks/articles. Furthermore, employees of the Department are mentioned approximately 400 times as authors or co-authors of scientific papers in extenso. In that total number of honourable mentions, they appear over 150 times in journals that are cited in the most prestigious databases. Moreover, with approximately 600 papers, they participated in national and international meetings (published abstracts). which speaks volumes about the significant scientific and publishing activity of the Department's employees, mostly over the last fifteen years. As an example of the academic community's interest in high-quality papers resulting from the work of the Department's employees, it is worth mentioning the paper on the persistence of weekly alendronate (Grazio et al., 2008), which was the second most read paper in the week of its publication. Figure 6. present the list of book chapters and figure 7. present significant papers (in extenso).

The Department's physicians are members of several national and international professional associations and organisations such as the Croatian Society for Rheumatology, the Croatian Society of Physical and Rehabilitation Medicine, the Croatian Society for Vertebrology, the Croatian Society for the Treatment of

Grazio S. Thermal therapy (Toplinska terapija). In: Jajić I et al, editors. Physical Medicine and General Rehabilitation (Fizikalna medicina i opća rehabilitacija). 2nd ed. Zagreb: Medicinska naklada; 2000, pp. 185–209.

Grazio S. Light therapy (Svjetlosna terapija). In: Jajić I et al, editors. Physical Medicine and General Rehabilitation (Fizikalna medicina i opća rehabilitacija). 2nd ed. Zagreb: Medicinska knjiga; 2000, pp. 210–26.

Grazio S. Heliotherapy (Helioterapija). In: Jajić I et al, editors. Physical Medicine and General Rehabilitation (Fizikalna medicina i opća rehabilitacija). 2nd ed. Zagreb: Medicinska naklada; 2000, pp. 227–30.

Grazio S. Intermittent pneumatic compression (Intermitentna pneumatska kompresija). In: Jajić I et al, editors. Physical Medicine and General Rehabilitation (Fizikalna medicina i opća rehabilitacija). 2nd ed. Zagreb: Medicinska naklada; 2000, pp. 277–80.

Jajić I. History (Povijest). In: Jajić I et al, editors. Physical Medicine and General Rehabilitation (Fizikalna medicina i opća rehabilitacija). 2nd ed. Zagreb: Medicinska naklada; 2000, pp. 1–5.

Jajić I. Short-wave and microwave diathermy (Kratkovalna i mikrovalna dijatermija). In: Jajić I et al, editors. Physical Medicine and General Rehabilitation (Fizikalna medicina i opća rehabilitacija). 2nd ed. Zagreb: Medicinska naklada; 2000, pp. 43–71.

Jajić I. Therapeutic ultrasound (Terapijski ultrazvuk). In: Jajić I et al, editors. Physical Medicine and general rehabilitation (Fizikalna medicina i opća rehabilitacija). 2nd ed. Zagreb: Medicinska naklada; 2000, pp. 72–92.

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Jajić I. Ultrasonophoresis (Ultrasonoforeza). In: Jajić I et al, editors. Physical Medicine and General Rehabilitation (Fizikalna medicina i opća rehabilitacija). 2nd ed. Zagreb: Medicinska naklada; 2000, pp. 113–5.

Jajić I. Pain (Bol). In: Jajić I et al, editors. Physical Medicine and General Rehabilitation (Fizikalna medicina i opća rehabilitacija). 2nd ed. Zagreb: Medicinska naklada; 2000, pp. 123–38.

Jajić I. Transcutaneous electrical nerve stimulation (Transkutana električna živčana stimulacija). In: Jajić

I et al, editors. Physical medicine and general rehabilitation (Fizikalna medicina i opća rehabilitacija). 2nd ed. Zagreb: Medicinska naklada; 2000, pp. 139–53.

Jajić I. Balneotherapy (Balneoterapija). In: Jajić I et al, editors. Physical Medicine and General Rehabilitation (Fizikalna medicina i opća rehabilitacija). 2nd ed. Zagreb: Medicinska naklada; 2000, pp. 296–301.

Jajić I. Zdravstveni turizam (Zdravstveni turizam). In: Jajić I et al, editors. Physical Medicine and General Rehabilitation (Fizikalna medicina i opća rehabilitacija). 2nd ed. Zagreb: Medicinska naklada; 2000, pp. 302–4.

Jajić I. Physical therapy at home (Fizikalna terapija u kući). In: Jajić I et al, editors. Physical Medicine and General Rehabilitation (Fizikalna medicina i opća rehabilitacija). 2nd ed. Zagreb: Medicinska naklada; 2000, pp. 309–10.

Jajić I. Electrical injuries (Električne ozljede). In: Jajić I et al, editors. Physical Medicine and General Rehabilitation (Fizikalna medicina i opća rehabilitacija). 2nd ed. Zagreb: Medicinska naklada; 2000, pp. 404–5.

Jajić I, Grazio S. Basics of kinesitherapy (Osnove kineziterapije). In: Jajić I et al, editors. Physical Medicine and General Rehabilitation (Fizikalna medicina i opća rehabilitacija). 2nd ed. Zagreb: Medicinska naklada; 2000, pp. 244–55.

Jajić Z. Electrotherapy (Elektroterapija). In: Jajić I et al, editors. Physical Medicine and General Rehabilitation (Fizikalna medicina i opća rehabilitacija). 2nd ed. Zagreb: Medicinska naklada; 2000, pp. 6.

Jajić Z. Galvanization (Galvanizacija). In: Jajić I et al, editors. Physical Medicine and General Rehabilitation (Fizikalna medicina i opća rehabilitacija). 2nd ed. Zagreb: Medicinska naklada; 2000, pp. 7–14.

Jajić Z. Intermittent galvanization (Isprekidana galvanizacija). In: Jajić I et al, editors. Physical Medicine and General Rehabilitation (Fizikalna medicina i opća rehabilitacija). 2nd ed. Zagreb: Medicinska naklada; 2000, pp. 15.

Jajić Z. Iontophoresis (Iontoforeza). In: Jajić I et al, editors. Physical Medicine and General Rehabilitation (Fizikalna medicina i opća rehabilitacija). 2nd ed. Zagreb: Medicinska naklada; 2000, pp. 16–22.

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Jajić Z. Traction (Trakcija). In: Jajić I et al, editors. Physical Medicine and General Rehabilitation (Fizikalna medicina i opća rehabilitacija). 2nd ed. Zagreb: Medicinska naklada; 2000, pp. 256–65.

Jajić Z. Thalassotherapy (Talasoterapija). In: Jajić I et al, editors. Physical Medicine and General Rehabilitation (Fizikalna medicina i opća rehabilitacija). 2nd ed. Zagreb: Medicinska naklada; 2000, pp. 307–8.

Grazio S. Musculoskeletal manifestations of acromegaly (Mišićno-koštane manifestacije akromegalije). In: Vrkljan M, Čerina V, editors. Acromegaly – excess and lack of growth hormone (Akromegalija – suvišak i nedostatak hormona rasta). Zagreb: Birotisak d.o.o.; 2004, pp. 281–90.

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Nikolić V, Nikolić T. Biomechanics (Biomehanika). In: Duraković Z et al, editors. Geriatrics, Medicine of the elderly (Gerijatrija, medicina starije dobi). Zagreb: C.T. – Poslovne informacije; 2007, pp. 473–86.

Grazio S. Palindromic rheumatism (Palindromski reumatizam). In: Vrhovac B, Jakšić B, Reiner Ž, Vučelić B, editors. Internal Medicine (Interna medicina). 4th ed. Zagreb: Naklada Ljevak; 2008, pp. 14–22.

Grubišić F. High voltage electrotherapy (Visokovoltna elektroterapija). In: Jajić I, Jajić Z et al, editors. Physical and Rehabilitation Medicine (Fizikalna i rehabilitacijska medicina: osnove i liječenje). Zagreb: Medicinska naklada; 2008, pp. 172–4.

Grubišić F. Electrostimulation therapy (Elektrostimulacijska terapija). In: Jajić I, Jajić Z et al, editors. Physical and Rehabilitation Medicine: Basics and Treatment (Fizikalna i rehabilitacijska medicina: os-

FIGURE 6. Significant books and book chapters (2000 – 2020)
SLIKA 6. Značajnije knjige – poglavlja (2000. – 2020.)

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FIGURE 6. Nastavak
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Pain, the Croatian Society for Palliative Medicine, the Croatian Sports Medicine Society, the Croatian Society for Neuromuscular Diseases and Clinical Electromyoneurography, Croatian Resuscitation Council, Croatian Logopedics Association, Croatian Association for Behavioral-Cognitive Therapies, Croatian Olympic Committee, as well as several international associations and organisations, such as the British Society for Rheumatology, the European League against Rheumatism (EULAR), European Society for Physical and Rehabilitation Medicine (ESPRM), International Osteoporosis Foundation (IOF), International Society for Prosthetics and Orthotics (ISPO), the Assessment of SpondyloArthritis international Society (ASAS), and the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA). Physiotherapists and nurses are members of their official professional associations.

Some of the employees of the Department have carried out and continue to carry out their duties in professional societies and organisations, both national and international. So, for example, Prof. Grazio is the president of the Croatian Society for Vertebrology of the Croatian Medical Association (he was appointed in 2013), he is the first vice-president of the Croatian Society of Physical and Rehabilitation Medicine of the Croatian Medical Association (he was appointed in 2013 as well), and the first vice-president of the Croatian Society for Rheumatology of the Croatian Medical Association (he was appointed in 2014). In addition to that, Assistant Prof. Grubišić is a member of the Management Board of the Croatian Society of Physical and Rehabilitation Medicine and the Croatian Society for Vertebrology (he is currently the secretary of the aforementioned professional society), and he was a member of the Management Board of the Croatian Society for Rheumatology. Furthermore, Prof. Matijević is a member of the Management Board and the head of the Section for the Rehabilitation of Children of the Croatian Society of Physical and Rehabilitation Medicine, Prim. Nemčić is a member of the Management Board of the Croatian Society for Vertebrology, and Prim. Tatjana Nikolić was a member of the Management Board of the Croatian Society of Physical and Rehabilitation Medicine and a member of the Management Board of the Croatian Society for Vertebrology (she is currently the treasurer of the aforementioned professional society). In addition to that, from 2008 to 2011, Prof. Grazio was a representative of the Croatian Society for Rheumatology at the EULAR Standing Committee on Investigative Rheumatology (ESCIR), and from 2011 to 2015 he was a member of the EULAR Standing Committee on Epidemiology and Health Services. Furthermore, as of 2014, Assistant Prof. Grubišić has been the national delegate of the Croatian Society of

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FIGURE 7. Nastavak
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FIGURE 7. Nastavak
SLIKA 7. Continued

Physical and Rehabilitation Medicine of the CMA at the European Society of Physical and Rehabilitation Medicine (ESPRM), in which he is the chairman of the Special Interest Scientific Committee (SISC) in implementing evidence-based medicine (EBM) in everyday practice, as well as one of the initiators and advocates for the Cochrane Rehabilitation Field. The employees of the Department have received numerous awards, diplomas and certificates of appreciation from professional societies, institutions and non-profit organisations. In 2020, Prof. Grazio was granted the title of honorary member by the European Society of Physical and Rehabilitation Medicine (ESPRM) and he is one of the first members who have obtained this honourable title.

In accordance with the activities of the national and international associations and organisations, it is important to mention some of the activities that our employees have significantly contributed to over the last twenty years. For example, Prof. Grazio is the coordinator of the proposal for subspecialties in physical and rehabilitation medicine (which is one of the activities of the Croatian Society of Physical and Rehabilitation Medicine of CMA), the coordinator and head of the Working Group for the language adaptation and translation of ICF (a clinical tool for rehabilitation medicine) to Croatian (members of the Working Group: Associate Prof. Grubišić and Ana Šečić, educational rehabilitator). Furthermore, Prof. Matijević is the main initiator of the National Register of Children with Neurodevelopmental Risk Factors (one of the activities of the Croatian Society of Physical and Rehabilitation Medicine), and Assistant Prof. Grubišić is the head of the Cochrane Physical and Rehabilitation Medicine Field (one of the activities as part of the collaboration with the Croatian Society for Physical and Rehabilitation Medicine of the CMA).

The employees of the Department have also had an important role in the creation of guidelines/recommendations for the most important entities in the rheumatology and physiatry practice. Some of the guidelines that especially stand out are the following: the 2010 Guidelines of the Croatian Medical Association for the Treatment of Knee and Hip Osteoarthritis (the first author of these Guidelines: Prof. Grazio), the 2017 Recommendation Proposal of the Croatian Society for Rheumatology of the CMA for the Treatment of Adults with Axial Spondyloarthritis and Psoriatic Arthritis with Biologic Drugs and Targeted Synthetic Drugs (the first author of this Recommendation Proposal: Prof. Grazio, the co-author: Assistant Prof. Grubišić), the 2017 Recommendation Proposal of the Croatian Society for Rheumatology of the CMA for the Treatment of Patients with Rheumatoid Arthritis with Biologic Drugs and Targeted Synthetic Drugs (the co-

društva; prof. Matijević je članica Upravnoga odbora i voditeljica je Sekcije za rehabilitaciju djece Hrvatskoga društva za fizikalnu i rehabilitacijsku medicinu; prim. Nemčić član je Upravnoga odbora Hrvatskoga vertebraloškoga društva, prim. Tatjana Nikolić bila je članica Upravnog odbora Hrvatskog društva za fizikalnu i rehabilitacijsku medicinu i članica je Upravnoga odbora Hrvatskoga vertebraloškoga društva (aktualno i blagajnica potonjeg stručnoga društva). Također, prof. Grazio je od 2008. do 2011. bio predstavnik Hrvatskoga reumatološkog društva u Europskome znanstvenom odboru istraživanja u reumatologiji (EULAR *Scientific Committee on Investigative Rheumatology – ESCIR*) Europskoga reumatološkog društva (EULAR), od 2011. do 2015. bio je član Stalnog odbora za epidemiologiju i istraživanje zdravstvenih servisa (*The Standing Committee of Epidemiology and Health Services Research*) EULAR-a, dok je F. Grubišić od 2014. nacionalni delegat Hrvatskog društva za fizikalnu i rehabilitacijsku medicinu HLZ-a pri Europskom društvu za fizikalnu i rehabilitacijsku medicinu (engl. *European Society of Physical and Rehabilitation Medicine*, skr. ESPRM) unutar kojega vodi Znanstveni odbor za implementaciju medicine temeljene na dokazima u kliničkoj praksi (engl. *Special Interest Scientific Committee in implementing evidence based medicine in everyday practice*) te je jedan od inicijatora i promotora *Cochrane Rehabilitation*. Djelatnici Klinike dobitnici su povelja, diploma i zahvalnica stručnih društava, institucija i neprofitnih udruga, dok je prof. Graziju 2020. godine dodijeljeno začasno članstvo Europskoga društva za fizikalnu i rehabilitacijsku medicinu (engl. skr. ESPRM) kao jednome od prvih članova koji su dobili tu počast.

U skladu s aktivnostima u sklopu domaćih i međunarodnih udruga i organizacija vrijedno je spomenuti neke od njih, kojima su u zadnjih dvadesetak godina značajno pridonijeli djelatnici klinike. Na primjer, prof. Grazio je koordinator prijedloga užih specijalizacija iz fizikalne medicine i rehabilitacije (u sklopu aktivnosti Hrvatskoga društva za fizikalnu i rehabilitacijsku medicinu HLZ-a), koordinator i voditelj radne grupe za prijevod i jezičnu adaptaciju ICF-a – kliničkog alata za rehabilitacijsku medicinu na hrvatski jezik (članovi radne skupine: doc. Grubišić i Ana Šečić – rehabilitator). Prof. Matijević je glavni inicijator Nacionalnog registra neurorizične djece (u sklopu aktivnosti Hrvatskoga društva za fizikalnu i rehabilitacijsku medicinu), a doc. Grubišić je voditelj Cochrane grupe za područje rehabilitacijske medicine (u sklopu aktivnosti suradnje s Hrvatskim društvom za fizikalnu i rehabilitacijsku medicinu HLZ-a).

Djelatnici klinike imali su i važnu ulogu u kreiranju smjernica/preporuka za najvažnije entitete iz reumatološke i fizijatrijske prakse. Među njima posebno se ističu one za liječenje osteoartritis kuka i koljena Hrvat-

authors of this Recommendation Proposal: Prof. Grazio and Assistant Prof. Grubišić), the 2012 guidelines titled "Diagnosis and Treatment of Low Back Pain: review and guidelines of the Croatian Vertebrologic Society of the CMA" (the first author of these Guidelines: Prof. Grazio, co-authors: Prim. Nemčić and Assistant Prof. Grubišić), the 2015 Guidelines of the Croatian Society for Physical and Rehabilitation Medicine of the CMA for the Treatment of Patients with Osteoarthritis of the Hip and/or Knee (the first author of these Guidelines: Prof. Grazio), Guidelines of the Croatian Society for Vertebrology of the CMA for the Diagnosis and Treatment of Patients with Neck Pain (the first author of these Guidelines: Prof. Grazio, co-authors: Assistant Prof. Grubišić, Prim. Nemčić, Prim. Nikolić, Dubravka Sajković, MD, H. Skala Kavanagh, MD), and the Guidelines (Re)habilitation of Children with Neurodevelopmental Disorders (the first author: Prof. Valentina Matijević, co-author: Jelena Marunica Karšaj, MD). When it comes to international guidelines/recommendations it is important to note Prof. Grazio's involvement in the recently published 2021 guidelines of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) and in the validation of the Assessment of SpondyloArthritis international Society (ASAS) health index (along with his collaborators: Assistant Prof. Grubišić and Hana Skala Kavanagh, MD).

The employees of the Department have always been active in the process of editing scientific journals. The Department is the seat, that is, the place of origin of two peer-reviewed journals – the *Rheumatism* journal and the *Physical and Rehabilitation Medicine* journal. *Rheumatism*, the journal of the Croatian Society for Rheumatology of the Croatian Medical Association (CMA), is one of our longest-running journals (it has been published continuously since 1954) and it is the sixteenth journal on the list of the world's top rheumatology journals. Up until 2017, it was indexed in PubMed, but with the reform of that database it was omitted from the list. However, the process of its re-indexing is currently underway. The employees of our Department were also members of the Editorial Board of the *Rheumatism* journal, and, in 2014 Prof. Grazio took on the role of its editor-in chief, thus succeeding Prof. I. Jajić, who had previously carried out this duty. The Department is also the seat, i.e., the place of origin of the *Physical and Rehabilitation Medicine* journal of the Croatian Society of Physical and Rehabilitation Medicine. In its beginnings, this journal was intended for physiotherapists, and at a later time, physicians became its target audience. Since 2011, this journal has been indexed in the Croatian e-journal databases *Hrčak* and *Index Copernicus*. All of the editors-in-chief of this journal (except for one) were employees of our

skoga reumatološkoga društva HLZ-a iz 2010. (prvi autor: prof. Grazio), za liječenje bolesnika s aksijalnim spondiloartritisom i psorijatičnim artritisom biološkim lijekovima i ciljanim sintetskim molekulama iz 2017. Hrvatskoga reumatološkoga društva HLZ-a (prvi autor: prof. Grazio; koautor: doc. Grubišić), za liječenje bolesnika s reumatoidnim artritisom biološkim lijekovima i ciljanim sintetskim molekulama iz 2017. Hrvatskoga reumatološkoga društva HLZ-a (koautori: prof. Grazio i doc. Grubišić), za dijagnostiku i liječenje bolesnika s križoboljom Hrvatskoga vertebrološkoga društva HLZ-a iz 2012. (prvi autor: prof. Grazio; koautori: prim. Nemčić i doc. Grubišić), za liječenje osteoartritisa kuka i/ili koljena Hrvatskoga društva za fizikalnu i rehabilitacijsku medicinu HLZ-a iz 2015. (prvi autor: prof. Grazio), za dijagnostiku i liječenje vratobolje Hrvatskoga vertebrološkoga društva HLZ-a (prvi autor: prof. Grazio; koautori: doc. Grubišić, prim. Nemčić, prim. Nikolić, dr. Sajković, dr. H. Skala Kavanagh) i za (re)habilitaciju djece s neurorazvojnim poremećajima (prvi autor: prof. Matijević, koautor: dr. Marunica Karšaj). Među međunarodnim smjernicama/preporukama vrijedno je spomenuti sudjelovanje prof. Grazija u recentnim smjernicama *Group for Research and Assessment of Psoriasis and Psoriatic Arthritis* (engl. skr. GRAPPA) 2021. i validaciji Indeksa zdravlja međunarodne organizacije eksperata *Assessment of SpondyloArthritis International Society* (engl. skr. ASAS) (suradnici: doc. Grubišić i dr. Skala Kavanagh).

Djelatnici klinike uvijek su bili aktivni u uređivanju stručno-znanstvenih časopisa. Na Klinici je sjedište dva-ju časopisa – *Reumatizam* i *Fizikalna i rehabilitacijska medicina*. *Reumatizam*, časopis Hrvatskoga reumatološkog društva Hrvatskoga liječničkog zbora, jedan je od naših najdugovječnijih časopisa (izlazi u kontinuitetu od 1954.) i šesnaesti je po redu među reumatološkim svjetskim časopisima; do 2017. bio je indeksiran u *PubMedu*, a reformom te baze je izostavljen te je u tijeku njegovo ponovno indeksiranje. Djelatnici naše Klinike bili su uključeni u uređivački odbor časopisa *Reumatizam*, a uz prof. I. Jajića, koji je bio i njegov glavni i odgovorni urednik, od 2014. glavni i odgovorni urednik je prof. Grazio. Na Klinici je i sjedište časopisa Hrvatskog društva za fizikalnu i rehabilitacijsku medicinu pri HLZ-u *Fizikalna medicina i rehabilitacija*, koji je u svojim počecima bio namijenjen fizioterapeutima, a kasnije je namijenjen liječnicima. Časopis je od 2011. indeksiran u hrvatskoj bazi časopisa *Hrčak* i *Index Copernicus*. Glavni i odgovorni urednici časopisa, uz jedan izuzetak, bili su djelatnici Klinike: prof. I. Jajić (1984. – 1998.; ujedno i pokretač časopisa), prim. T. Nemčić (2005. – 2008.), prof. S. Grazio (2009. – 2012.), a od 2013. glavni i odgovorni urednik je doc. F. Grubišić. Prof. Grazio je od 2005. do 2015. bio član Uredničkog odbora časopisa *Acta Clinica Croatica* (indeksiran u SCIE), a od druge polovine 2015.

Department: Prof. I. Jajić (1984 – 1998, who was also the founder of this journal), Prim. T. Nemčić (2005 – 2008), Prof. S. Grazio (2009 – 2012), and Assistant Prof. F. Grubišić (2013 – present). Furthermore, from 2005 to 2015, Prof. Grazio was the member of the Editorial Board of the *Acta Clinica Croatica* journal (indexed in the SCIE (Science Citation Index Expanded) journal database), and since the second half of 2015 to the present day he has been the member of the Editorial Council of the journal. Moreover, from 2016 to 2020 he was the member of the Editorial Board of the *European Journal of Physical and Rehabilitation Medicine* (indexed in the Current Contents (CC) database), from 2016 to the present day he has been the member of the Editorial Board of the *Mediterranean Journal of Rheumatology* (indexed in the Scopus database), and from 2018 to the present day he has been the member of the Editorial Board of the *Rheumatology International* journal (indexed in the Current Contents (CC) database). The employees of the Department have reviewed several papers for national and international medical journals. From 2011 to July 2019, Prof. Grazio was the president of the Library Committee of the Sestre milosrdnice UHC, and from July 2019 to the present day he has been a member of the Expert Council of the Sestre milosrdnice UHC Library.

It is important to mention the chief physiotherapists of the Department who played an important role in this segment of the Department's activities with their expertise and organisation of work. They are (mentioned in order, from the establishment of the Department to the present day): Marta (surname unknown), Marija Barbić, Vera Došen, Mateja Znika and Ivan Anzulović (he has been working at the Department from 2011).

In the last fifteen years, the working conditions of the Department have been improved, primarily in the aspect of the level of comfort of hospitalised patients. Moreover, architectural, that is, physical barriers have been overcome, and the area of the Outpatient Clinic for Adults has been expanded and renovated (it was given an annex on the first floor of building number 7). Unfortunately, some of our worksites were extremely damaged in the 2020 earthquakes, so they need to be restored. The IT equipment and support at the Department have been significantly improved in accordance with modern trends, and especially in the last fifteen years, and recently, at the instigation of the head of the Department, tablet computers were purchased for the purpose of facilitating the everyday work duties of physicians and other health professionals.

Following the establishment of the Sestre milosrdnice University Hospital Centre in 2010, the University Department got several associated departments in the form of the following units: the Department of Phys-

nadalje je član Uredničkog savjeta časopisa), 2016. – 2020. časopisa *European Journal of Physical and Rehabilitation Medicine* (indeksiran u CC-u), od 2016. nadalje i *Mediterranean Journal of Rheumatology* (indeksiran u Scopusu), a od 2018. član je Uredničkog odbora časopisa *Rheumatology International* (indeksiran u CC-u). Djelatnici klinike recenzirali su više radova za domaće i međunarodne medicinske časopise. Prof. Grazio je od 2011. do srpnja 2019. bio predsjednik Knjižničnog odbora KBC-a Sestre milosrdnice, a od srpnja 2019. nadalje član je Stručnog vijeća Knjižnice KBC-a Sestre milosrdnice.

Vrijedno je navesti glavne fizioterapeute Klinike, koji su svojom stručnošću i organizacijom rada imali važnu ulogu u tom segmentu djelatnosti. To su od početka Klinike do danas redom: Marta (prezime nepoznato), Marija Barbić, Vera Došen, Mateja Znika i Ivan Anzulović (potonji od 2011. do danas).

U posljednjih petnaestak godina poboljšani su prostorni uvjeti Klinike, a ponajprije komfor hospitaliziranih bolesnika, savladane su arhitektonske zapreke, proširen je i uređen prostor Poliklinike za odrasle bolesnike (na I. katu zgrade broj 7). Nažalost, potresi iz 2020. značajno su oštetili neka od naših radilišta pa je potrebna njihova sanacija. Shodno suvremenim trendovima, a napose u zadnjih petnaestak godina informatička oprema i podrška na klinici značajno su poboljšane, a nedavno su na poticaj predstojnika nabavljena i tablet-računala za lakši svakodnevni rad liječnika i ostalih stručnih djelatnika.

Nakon formiranja Kliničkoga bolničkog centra Sestre milosrdnice (2010.) Klinici su pridružene fizijatrijske službe Klinike za traumatologiju (Draškovićeva 19) i Klinike za tumore (Ilica 197), što je potvrđeno sistematizacijom 2011., kada su u sklopu Zavoda za reumatologiju, fizikalnu medicinu i rehabilitaciju u Klinici tadašnji odsjeci postali zasebni odjeli (odrasli i djeca). U nastavku ukratko slijedi povijesni razvoj i doprinos tih pridruženih dijelova Klinike.

Provođenje fizikalne medicine i rehabilitacije u Bolnici, Kliničkoj bolnici, a naposljetku Klinici za traumatologiju počelo je 1951. u ranim godinama rada Bolnice, u sklopu rehabilitacije ozljeđenika. Odjel za fizikalnu medicinu i rehabilitaciju osnovan je 1964. godine, kada je dogradnjom i preuređenjem starog dijela Bolnice dobio i svoje prostore u podrumu zgrade, gdje je smješten i danas. Od tog vremena raspolaže uređajima za elektroterapiju i dvoranom za kineziterapiju. Vrijedno je napomenuti da je u sklopu fizikalne medicine i rehabilitacije bila napose razvijena radna terapija. Voditelji Službe, a poslije Odjela bili su redom prim. dr. Branko Haramustek, dr. Marijan Hlavka, dr. Vladimir Vinceković, prim. dr. Ružica Nikolić, prim. dr. Dušanka Kostenarović Živković (od 1984. do 2004.), dr. Nina Bival Fak (od 2004. do 2012.), a od 2012. prim. dr. Ta-

iatry of the University Hospital for Traumatology (Draškovićeva 19) and the Department of Physiatry of the University Hospital for Tumours (Ilica 197). This structure was confirmed by the systematisation process in 2011, when the divisions which were a part of the Department of Rheumatology, Physical Medicine and Rehabilitation became separate departments (for adults and children) at the University Department. In the following part we shall briefly present the historical development and the contribution of these associated departments that are a part of the overall structure of our University Department.

The treatment of physical medicine and rehabilitation was first introduced in 1951, during the early years of the University Hospital operation, as part of the rehabilitation of trauma patients. The Department of Physical Medicine and Rehabilitation was established in 1964, when the old part of the University Hospital was renovated and rebuilt. The offices of the Department were located in the basement of the building, where they remain to this day. Ever since that period, the Department has been equipped with electrotherapy devices and a kinesiotherapy room. It is also worth noting that occupational therapy was developed as part of the physical medicine and rehabilitation. The heads of this Unit, which was later the Department of Physical Medicine and Rehabilitation were the following experts (mentioned in order): Prim. Branko Harmustek, MD, Marijan Hlavka, MD, Vladimir Vinceković, MD, Prim. Ružica Nikolić, MD, Prim. Dušanka Kostenarović-Živković (from 1984 to 2004), Nina Bival Fak (from 2004 to 2012), and Prim. Tatjana Nikolić (from 2012 to the present day). Two major renovations of the Department took place in 1987 and in 2004. The aforementioned renovation process was carried out from 2004 to 2005 (donation was made by the people of Japan), and at that time the new equipment and devices for electrotherapy and rehabilitation were purchased, which were in accordance with the modern requirements. During the Croatian War of Independence, the University Hospital for Traumatology and the Department played a special role in the treatment and rehabilitation of the injured. As part of the activities of physiatry, rehabilitation and specialist consultative healthcare, osteoporosis was also one of the main activities carried out at the Department, so in 2000, the Outpatient Clinic for Osteoporosis was officially established at the University Hospital for Traumatology. From 2000 to 2004, the following doctors took turns working at the Outpatient Clinic for Osteoporosis: Dolores Car, MD (internist) and Tatjana Nikolić, MD (specialist in Physical Medicine and Rehabilitation), and in 2004 Gordana Tajsić joined their team (specialist in Physical Medicine and Rehabilitation). In 2012, a reorganisation of the physical therapy programme was

tjana Nikolić. Dva velika preuređenja Odjela bila su 1987. godine i 2004. – 2005. (donacija japanskog naroda) kada je nabavljena nova oprema i uređaji za elektroterapiju i rehabilitaciju, čime je učinjena prilagodba suvremenim zahtjevima. U Domovinskom su ratu Klinika za traumatologiju, a time i Odjel imali posebnu ulogu u zbrinjavanju ozljeđenika. U sklopu fizijatrijsko-rehabilitacijske specijalističko-konzilijarne djelatnosti u žarištu je djelovanja i osteoporoza pa je 2000. godine u Klinici za traumatologiju službeno osnovana Ambulanta za osteoporozu. Od 2000. do 2004. u Ambulanti su se izmjenjivale dr. Dolores Car (internistica) i dr. Tatjana Nikolić (spec. fizikalne medicine i rehabilitacije), a od 2004. godine priključuje im se i dr. Gordana Tajsić (spec. fizikalne medicine i rehabilitacije). Od 2012. u Kliničkoj jedinici za rehabilitaciju traumatoloških bolesnika dolazi do reorganizacije rada fizikalne terapije, kada se uvodi koncept rada po fizioterapijskim jedinicama. Tada se reorganizira i prostor, uz manju obnovu postojećih prostorija. Od jeseni 2014. godine dolazi do daljnjeg unaprjeđenja rada Kliničke jedinice za rehabilitaciju traumatoloških bolesnika, jer se uvodi rad u dvije smjene, i liječničkih ambulanta i fizikalne terapije.

Služba za rehabilitaciju onkoloških bolesnika osnovana je u sklopu Instituta za tumore u Zagrebu 1979. godine. Utemeljiteljica Službe, a istodobno i hrvatske onkološke rehabilitacije jest prof. dr. sc. Ruža Sabol, specijalistica fizikalne medicine i rehabilitacije i profesorica defektologije, koja je prethodno do 1974. radila na tadašnjem Odsjeku za rehabilitaciju djece naše Bolnice, a potom u Bolnici za rehabilitaciju djece Goljak. Odmah nakon osnivanja koncepcija rada usmjerena je na medicinsku i psihosocijalnu rehabilitaciju kao integralne dijelove kompleksnog liječenja onkološkog bolesnika. Dugogodišnjom suradnjom s Edukacijsko-rehabilitacijskim fakultetom i Visokom zdravstvenom školom/Zdravstvenim veleučilištem provodilo se i kontinuirano se provodi stručno usavršavanje i znanstveni rad u onkološkoj rehabilitaciji. Djelatnici Službe od početka su aktivno uključeni u rad različitih udruga onkoloških bolesnika, a profesorica Sabol bila je glavni inicijator uvođenja i dvaju neprofitnih, humanitarnih programa vezanih za rak dojke (1993.). To su *Reach to Recovery*, svjetski program u kojem rehabilitirana i stručno educirana bolesnica pruža psihosocijalnu potporu novooboljeloj; drugi je *Europa Donna Hrvatska*, u sklopu *Europske koalicije protiv raka dojke*, a odnosi se ponajprije na ranu dijagnostiku i liječenje te promicanje kvalitete života bolesnica s karcinomom dojke. Nakon umirovljenja profesorice Sabol 1990. voditeljica Službe (kasnije Kliničke jedinice) postaje mr. sc. Nada Kraljević do umirovljenja u ožujku 2020., kad ju je zamijenila dr. Senija Brnić. U posljednjih desetak godina djelatnost je izrazitije unaprijeđena zahvaljujući većem

carried out at the Unit for the Rehabilitation of Trauma Patients, due to the introduction of a different concept of work in which work duties were carried out in various physiotherapy units. Following that, the premises of the Unit were reorganised as well, and the existing rooms had undergone a small-scale renovation. In 2014, the working conditions at the Unit for the Rehabilitation of Trauma Patients have further improved with the introduction of shift work (the employees could work in two shifts). The working conditions of the outpatient units and physical therapy programme have improved as well.

The Unit for the Rehabilitation of Cancer Patients was established as part of the Institute for Tumours in Zagreb, in 1979. The founder of the Unit, as well as the person responsible for the introduction of the rehabilitation of cancer patients in Croatia (which was introduced at the same time) is Prof. Ruža Sabol, MD, PhD, a specialist in Physical Medicine and Rehabilitation and a professor of Special Education. Prior to this, up until 1974, Prof. Sabol, MD, PhD worked at the then Division for Rehabilitation of Children at our hospital, and following that, she worked at the Goljak Hospital, a special hospital for the rehabilitation of children. Immediately after its establishment, the concept of work at the Unit was focused on medical and psychosocial rehabilitation as integral parts of the complex treatment of cancer patients. Through long-term cooperation with the Faculty of Education and Rehabilitation Sciences and the College / University of Applied Health Sciences, professional training and scientific work was carried out and continues to be carried out in the field of rehabilitation of cancer patients. From the beginning, the employees of the Unit have been actively involved in the work of various associations of cancer patients, and Professor Sabol was the main initiator of the implementation and establishment of two non-profit, humanitarian programmes related to breast cancer (1993). The first programme is the *Reach to Recovery* programme, a worldwide programme in which a volunteer who has experienced a certain kind of breast cancer, who went through the rehabilitation process and is educated on the topic offers psychosocial support to a newly diagnosed patient. The second one is the *Europa Donna Croatia* programme, which is part of the European Breast Cancer Coalition, and which primarily refers to early diagnosis and treatment as well as the promotion of the quality of life of patients with breast cancer. Following the retirement of Prof. Sabol in 1990, Nada Kraljević, MSc became the head of the Unit (which later named the Clinical Unit), who continued to carry out that duty until her retirement in March 2020, when she was succeeded by Senija Brnić, MD. In the last decade. The activity has been significantly improved due to a larger number of employees,

broju djelatnika, novim fizikalnim postupcima uvedenim na listu HZZO-a, a napose dobivanjem novih većih i prikladnijih prostora preseljenjem u novi dio zgrade Klinike za tumore (2012. godine), nakon čega su nabavljeni i novi uređaji. Najnovije organizacijske promjene dogodile su se sistematizacijom 2015. godine, kada su ukinute Klinička jedinica za rehabilitaciju traumatoloških bolesnika i Klinička jedinica za rehabilitaciju onkoloških bolesnika te uklopljene u Polikliniku.

Klinika za reumatologiju, fizikalnu medicinu i rehabilitaciju povezana je s Hrvatskom ligom protiv reumatizma, najmasovnijom neprofitnom udrugom na državnoj razini koja okuplja bolesnike s reumatskim bolestima, kao i stručnjake koji se bave tom problematikom. Od osnutka sjedište joj je u klinici, a dosadašnji predsjednici bili su: I. Jajić (1992. – 2001.), T. Nemčić (2001. – 2009.), S. Grazio (2009. – 2013.) te F. Grubišić (2013. – 2017.). Više djelatnika Klinike bilo je ili trenutno jesu članovi Upravnog odbora Lige. Liga provodi brojne aktivnosti, među kojima su organizacija popularnih predavanja i tribina (od 2004. do 2020. u sklopu obilježavanja „Desetljeća kostiju i zglobova“), a djelatnici Klinike u njima su vrlo često aktivno sudjelovali. Liga je objavila 28 priručnika za bolesnike (u 21 su autori ili koautori djelatnici Klinike), kao i dvije knjige (koautori su također djelatnici Klinike), a od 1992. do 2016. objavljivala je svoje glasilo *Reuma* (ranije *Reumatičar*) (glavni i odgovorni urednik: 1992. – 1998. I. Jajić, a 1998. – 2016. S. Grazio). Liga je članica udruge pacijenata pri EULAR-u (PARE) (predstavnik Lige je od 2008. F. Grubišić), Međunarodne udruge za ankilozantni spondilitis (ASIF) i Međunarodne zaklade za osteoporozu (IOF) (predstavnik Lige S. Grazio). Posljednjih desetak godina intenzivirale su se međunarodne aktivnosti Lige. Tako je Liga jedan od utemeljitelja AGORA-e, platforme za organizacije osoba s reumatskim bolestima južne Europe (u sklopu PARE-a) (član Stalnog odbora od 2011. do 2017. godine bio je F. Grubišić). Njezini predstavnici redovito sudjeluju na EULAR-ovoj godišnjoj konferenciji PARE-a. Liga je u svibnju 2011. organizirala međunarodni projekt, izložbu *Working Wonders Exhibition*, koja je održana pod visokim pokroviteljstvom predsjednika Republike Hrvatske, dok je u studenome 2014. organizirala vrlo uspješnu konferenciju PARE-a koja je okupila predstavnike svih udruga bolesnika iz Europe. Hrvatska liga protiv reumatizma bila je jedan od inicijatora tematske sjednice Odbora za zdravstvo Hrvatskog sabora posvećene koštano-mišićnim bolestima (listopad 2009.), kada je i u Hrvatskoj predstavljena i prihvaćena Europska povelja o radu bolesnika s koštano-mišićnim bolestima. Također, Liga je jedan od utemeljitelja inicijative *Fit for work – Hrvatska*.

U daljnjem dijelu ovog priloga o klinici navedeni su stručni i znanstveni skupovi u čijoj smo organizaciji



FIGURE 8. Medical doctors of the Department – March 2016. Seated (from left to right): prim. Tomislav Nemčić, MD, PhD; Assistant Professor Valentina Matijević, MD, PhD; Diana Balen, MD, MSc; Professor Simeon Grazio, MD, PhD; Nada Kraljević, MD, MSc; prim. Tatjana Nikolić, MD. Standing (from left to right): Senija Brnić, MD; Iva Popović, MD, PhD; Vedran Brnić, MD; Gordana Tajsić, MD; Dubravka Sajković, MD; prim. Frane Grubišić, MD, MSc; Ines Doko, MD; Hana Skala Kavanagh, MD. Missing: Professor, Zrinka Jajić, MD, PhD; Velimir Šušak, MD; Jelena Marunica Karšaj, MD.

SLIKA 8. Liječnici klinike – ožujak 2016. Sjede slijeva nadesno: prim. dr. sc. Tomislav Nemčić, doc. dr. sc. Valentina Matijević, mr. sc. Diana Balen, prof. dr. sc. Simeon Grazio, mr. sc. Nada Kraljević, prim. dr. Tatjana Nikolić; stoje slijeva nadesno: dr. Senija Brnić, dr. sc. Iva Popović, dr. Vedran Brnić, dr. Gordana Tajsić, dr. Dubravka Sajković, prim. mr. sc. Frane Grubišić, dr. Ines Doko, dr. Hana Skala Kavanagh. (nedostaju: prof. dr. sc. Zrinka Jajić, dr. Velimir Šušak i dr. Jelena Marunica Karšaj).

new physical procedures introduced in the list of programmes by the Croatian Health Insurance Fund (CHIF), and especially by obtaining new, larger, and more suitable premises by moving to a new part of the building of the University Hospital for Tumours (in 2012). Following this move, new devices were purchased as well. The most recent organisational changes took place with the systematisation process in 2015, when the Clinical Unit for the Rehabilitation of Trauma Patients and the Clinical Unit for the Rehabilitation of Cancer Patients were closed as independent units and reintroduced as the associated units of the Outpatient Clinic of the Department.

The Department of Rheumatology, Physical and Rehabilitation Medicine is affiliated with the Croatian League against Rheumatism, the largest non-profit association in the country that brings together patients with rheumatic diseases, as well as experts dealing with this issue. Its seat has been at the Department since its establishment, and its presidents were the following experts: I. Jajić (1992 – 2001), T. Nemčić (2001 – 2009), S. Grazio (2009 – 2013) and F. Grubišić (2013 – 2017). Various employees of the Department were or currently are members of the Management Board of this League. The League carries out numerous activities,

značajno sudjelovali, značajniji udžbenici i knjige, kao i poglavlja u knjigama te značajniji znanstveni radovi, sve u zadnjih dvadesetak godina, a nakon zadnje objavljenih monografija kako Klinike tako i bolnice.

DJELATNOSTI KLINIKE

Sadašnja djelatnost Klinike za reumatologiju, fizikalnu medicinu i rehabilitaciju Medicinskog fakulteta Sveučilišta u Zagrebu povezana je s njezinom dugom tradicijom, ali i s aktivnostima i poboljšanjima koja su učinjena u zadnjih petnaestak godina, te je sve navedeno oblikovalo njezin sadašnji rad.

Na Klinici se provode dijagnostika, liječenje i rehabilitacija različitih bolesti i stanja, ponajprije onih koja se odnose na lokomotorni sustav, kao što su najčešće upalne reumatske bolesti, degenerativne bolesti, bolni sindromi (napose vertebralni i vertebrogeni), neurorazvojni poremećaji djece, posttraumatska stanja, stanja nakon operacija i drugih oblika liječenja onkoloških bolesnika te osteoporoza i njezine posljedice.

Multidisciplinarni pristup temelj je dijagnostike, liječenja i rehabilitacije hospitaliziranih i ambulantnih bolesnika, za što je neophodan timski rad. Suradnja se odnosi na članove tima unutar same klinike (liječnik – specijalist ili uži specijalist, fizioterapeut, radni tera-

including the organisation of popular lectures and discussions (from 2004 to 2020 it was involved in these activities on the occasion of the Bone and Joint Decade) and the employees of the Department often actively participate in these events. The League has published 28 manuals for patients (21 of them are authored or co-authored by the employees of our University Department), and from 1992 to 2016 it published its newsletter *Reuma* (formerly called *Reumatičar*). The editors-in-chief of this newsletter were the following experts: I. Jajić (1992 – 1998) and S. Grazio (1998 – 2016)). The League is a member of the EULAR PARE (People with Arthritis and Rheumatism in Europe) association (since 2008 its representative has been Associate Prof. F. Grubišić), the Axial Spondyloarthritis International Federation (ASIF) and the International Osteoporosis Foundation (IOF) (the representative of the League: S. Grazio). In the last decade, the international activities of the League have been reinforced. Thus, the League became one of the founders of AGORA, a platform of organisations of people with rheumatic diseases in southern Europe (as part of the PARE association) (from 2011 to 2017, F. Grubišić was a member of the Standing Committee). Its representatives are regular and active members at the EULAR PARE annual conference. In May 2011, the League organised an international project, an exhibition titled *Working Wonders Exhibition*, which was held under the auspices of Ivo Josipović, the then president of the Republic of Croatia. Furthermore, in November 2014, the League organised a highly successful PARE conference which was the meeting place of representatives of all patient groups across Europe. The Croatian League against Rheumatism was one of the main initiators of thematic meeting of the Health Committee of the Croatian Parliament which was dedicated to musculoskeletal disorders (in October 2009). At the same time, the European Charter on the work of patients with musculoskeletal disorders was presented and accepted in Croatia. In addition to that, the League is one of the founders of the “Fit for Work Croatia” initiative.

In the following part, also dedicated to the activities of the Department, we shall mention the professional and scientific meetings that we have organised and participated in, the significant textbooks and books, as well as book chapters and significant scientific papers. All of these works were published in the last twenty years, and in the period after the last published monographs of the Department and the UHC.

THE ACTIVITIES OF THE DEPARTMENT

The current activity of the Department of Rheumatology, Physical and Rehabilitation Medicine of the School of Medicine, University of Zagreb is connected

peut, logoped, defektolog – rehabilitator, psiholog, medicinska sestra te bolesnik, odnosno roditelj), ali i izvan nje. Pritom je važno naglasiti da je bolesnik aktivan član tima koji s napredovanjem liječenja i rehabilitacije postaje sve odgovorniji za ishode. Specifičnost za djecu s neurorazvojnim i sličnim poremećajima jest da multidisciplinarni tim pruža potporu i usmjerava roditelje o postupanjima, pravima i mogućnostima njihova participiranja. Krajnji cilj naših djelovanja jest ponov-



FIGURE 9. Children's (re)habilitation – kinesiotherapy
SLIKA 9. Dječja (re)habilitacija – kinezioterapija

no uključivanje bolesnika u obiteljsku, socijalnu i radnu sredinu.

U Klinici je zaposleno 18 liječnika specijalista fizijatar (od toga 5 subspecijalista reumatologa), 3 liječnika na specijalizaciji (jedan iz fizikalne medicine i rehabilitacije i dva liječnika na specijalizaciji iz reumatologije), 1 defektolog-rehabilitator, 2 logopeda, 1 psiholog, 55 fizioterapeuta (2 magistra, 7 diplomiranih i 46 prvostupnika fizioterapije), 2 prvostupnika radne terapije, 18 medicinskih sestara (od toga 3 prvostupnice sestrinstva), 1 tajnica i 2 administratora (u sklopu Poslovnog centra).

Klinika se organizacijski sastoji od Odjela za reumatske bolesti, fizikalnu medicinu i rehabilitaciju odraslih, Odjela za rehabilitaciju djece i Poliklinike.

Odjel za reumatologiju, fizikalnu medicinu i rehabilitaciju odraslih ima 17 postelja. Voditelj odjela je doc. dr. sc. Frane Grubišić. Na odjelu se hospitaliziraju bolesnici kojima je potrebna visokodiferentna dijagnostika i terapija, a prvenstveno se radi o bolesnicima s upalnim i drugim reumatskim bolestima, kao i bolnim sindromima (najčešće vertebrogenim) u fazi pogoršanja. U dijagnosticiranju se koriste sve suvremene metode, koje između ostaloga uključuju laboratorijske pretrage (iz krvi i urina, sinovijske tekućine i/ili drugih tkiva), metode oslikavanja (npr. dijagnostički ultrazvuk s ojačanim dopplerom, klasična radiografija, CT, MR, scintigrafija skeleta) i neurofiziološke pretrage (npr. EMNG). Inter-

with its long tradition, but also with the activities and improvements made over the last fifteen years. Moreover, all of the aforementioned endeavours have helped shape its current operative activities.

The diagnosis, treatment and rehabilitation of various diseases and conditions are carried out at the Department. These conditions mainly include diseases of the locomotor system, the most common inflammatory rheumatic diseases, degenerative diseases, pain syndromes (especially vertebral and vertebrogenic), neurodevelopmental disorders in children, post-traumatic conditions, post-operative conditions, and other forms of treatment of cancer patients, as well as osteoporosis and osteoporosis-related complications.

A multidisciplinary approach is the basis of diagnosis, treatment and rehabilitation of inpatients and outpatients, which requires effective teamwork. The concept of cooperation implies the cooperation between team (staff) members within the Department (physicians – specialists or subspecialists, physiotherapists, occupational therapists, speech therapists, special education teachers – educational rehabilitators, psychologists, nurses and patients or their parents), but also outside of the Department. With this in mind, it is important to highlight the fact that the patient is an active member of the team who, with the progress of treatment and rehabilitation, becomes increasingly responsible for the treatment outcomes. The unique element of the multidisciplinary approach to children with neurodevelopmental and similar disorders is that a multidisciplinary team provides support to the parents of these children and gives them more insight into the procedures, and their rights and opportunities in relation to their participation in this process. The ultimate goal of our activities is the reintegration of patients in their family, social and work environment.

The number of staff members of the University Department is the following: 18 specialists in Physical Medicine and Rehabilitation (5 of them are subspecialists in Rheumatology), 3 residents (1 in the field of Physical Medicine and Rehabilitation and 2 residents in the field of Rheumatology), 1 special education teacher-educational rehabilitator, 2 speech therapists, 1 psychologist, 55 physiotherapists (2 of them hold a Master's degree in Physiotherapy, 7 of them are Graduated Physiotherapists, and 46 of them hold a Bachelor's degree in Physiotherapy), 2 employees who hold a Bachelor's degree in the field of occupational therapy, 18 nurses (3 of them hold a Bachelor's degree in Nursing), 1 secretary and 2 hospital administrators (employed at the Business centre of the Department).

The organisational structure of the University Department consists of the following units: the Division of Rheumatic Diseases, Physical Medicine and Rehabilitation of Adults, the Division for the Rehabilitation of Children, and the Outpatient Clinic.



FIGURE 10. Department Board – April 2021
(from left to right): Ivan Anzulović, mag. physioth.;
Professor Simeon Grazio, MD, PhD (Haed of the Department);
Associate Professor Valentina Matijević, MD, PhD;
Assistant Professor Frane Grubišić, MD, PhD;
Senija Brnić, MD; prim. Tomislav Nemčić, MD, PhD;
prim. Tatjana Nikolić, MD.

SLIKA 10. Stručni kolegij klinike – travanj 2021.
Slijeva na desno: Ivan Anzulović, mag. physioth.;
prof. prim. dr. sc. Simeon Grazio, dr. med. (predstojnik klinike);
izv. prof. prim. dr. sc. Valentina Matijević, dr. med.;
doc. prim. dr. sc. Frane Grubišić, dr. med.; Senija Brnić dr. med.;
prim. dr. sc. Tomislav Nemčić, dr. med.;
prim. Tatjana Nikolić, dr. med.

vencije se odnose na farmakološko liječenje (uključivo i terapiju biološkim lijekovima i ciljanim sintetskim molekulama) i liječenje nefarmakološkim, najčešće fizikalno-terapijskim modalitetima liječenja.

Odjel za rehabilitaciju djece ima 11 postelja, od toga dva u sklopu programa „Majka – dijete“. Voditelj odjela je izv. prof. dr. sc. Valentina Matijević. Odjel je jedina takva organizacijska jedinica u Hrvatskoj koja djeluje u sklopu klinike odnosno kliničkoga bolničkog centra. Na odjelu se hospitaliziraju djeca s neurorazvojnim oštećenjima, a (re)habilitacija se provodi u sklopu multidisciplinarnoga tima (liječnik – specijalist, logoped, rehabilitator, klinički psiholog, fizioterapeut i medicinska sestra) i to od rođenja djeteta (što uključuje i rano dijagnosticiranje poremećaja i rane postnatalne intervencije) do punoljetnosti.

U Dnevnoj bolnici za odrasle (2 stolca/postelje) obrađuju se i liječe uglavnom bolesnici s upalnim reumatskim bolestima, a u Dnevnoj bolnici za djecu (2 stolca/postelje) bolesnici s neurorazvojnim poremećajima. Načela rada (dijagnostika, liječenje/rehabilitacija) za obje Dnevne bolnice ista su kao i za hospitalizirane, s tim da ti bolesnici prvenstveno zbog težine svog zdravstvenoga stanja ne trebaju prekonolni boravak na klinici. Sukladno općem trendu, zadnjih godina broj bolesnika obrađenih i liječenih u okviru Dневnih bolnica stalno se povećava.

Poliklinika u svojem sastavu na lokaciji Vinogradska 29 uključuje specijalističko-konzilijarne djelatnosti za

There are currently 17 beds at the Division of Rheumatology, Physical Medicine and Rehabilitation of Adults. The head of the Division is Associate Prof. Frane Grubišić, MD, PhD. Patients in need of high-quality differential diagnosis and therapy are hospitalised at the Division, and these are primarily patients with inflammatory and other types of rheumatic diseases, as well as pain syndromes (most often vertebro-genic) in the period of exacerbation. All modern methods are used in the diagnosis, which, among other things, include laboratory tests (blood tests, urine tests, synovial fluid analysis and/or the analysis of other tissues), imaging methods (e.g., contrast-enhanced colour Doppler ultrasound, standard radiography, CT, MRI, skeletal scintigraphy) and neurophysiological tests (e.g., electromyoneurography (EMNG)). Interventions are carried out in relation to pharmacological treatment (including therapy with biologic drugs and targeted synthetic drugs) and treatment with non-pharmacological treatment modalities mostly focused on physical therapy.

The Division for the Rehabilitation of Children has 11 beds, and two of them are reserved for the "Mother and Child" programme. The head of the Division is Prof. Valentina Matijević, MD, PhD. The Division is the only organisational unit of its kind in Croatia which operates as a part of a University Department, that is, a University Hospital Centre. Children with neurodevelopmental disorders are hospitalised at the Division, and (re)habilitation is carried out by our multidisciplinary team (physician – specialist, speech therapist, educational rehabilitator, clinical psychologist, physiotherapist, and nurse), from the child's birth (which also includes the early diagnosis of the disorder and early postnatal interventions) to adulthood.

Patients with inflammatory rheumatic diseases are mostly diagnosed and treated at the Outpatient Clinic for Adults (2 chairs/beds) and patients with neurodevelopmental disorders are mostly treated at the Outpatient Clinic for Children (2 chairs/beds). The principles of work (diagnosis, treatment/rehabilitation) for both outpatient clinics are the same as principles of work in inpatient care, with the only exception being that outpatients do not have to stay overnight due to the mild course of their disease. In accordance with the general trend, the number of patients diagnosed and treated at the outpatient clinics has been constantly increasing in recent years.

The activities of specialist consultative healthcare for adults and children are carried out at the Outpatient Clinic (organisational unit) located at Vinogradska 29. The deputy head of the Outpatient Clinic is Prim. Tomislav Nemčić, MD. The Outpatient Clinics for Physiatry for Adults are related to the casuistry of general physiatry, and their activities mainly include deal-

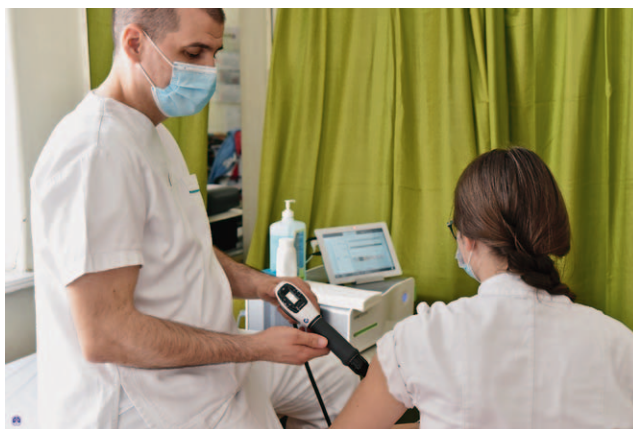


FIGURE 11. Physical therapy – therapy of extracorporeal shock wave

SLIKA 11. Fizikalna terapija – primjena izvantjelesnog udarnoga vala



FIGURE 12. Physical therapy – traction of the lumbar spine

SLIKA 12. Fizikalna terapija – trakcija slabinske kralježnice

odrasle i za djecu. V. d. voditelja Poliklinike je prim. dr. sc. Tomislav Nemčić. Fizijatrijske ambulante za odrasle odnose se na opću fizijatrijsku kazuistiku, a dominiraju bolni sindromi (npr. vertebrogeni), neurološke bolesti i posttraumatska stanja. U tim ambulantama trenutno rade prim. dr. sc. Tomislav Nemčić, prim. dr. sc. Diana Balen i mr. sc. Danijela Klarić, dr. med. Ambulanta za osteoporozu uključuje prevenciju i liječenje osteoporoze i njezinih posljedica kao „tihe epidemije“, odnosno još uvijek nedovoljno prepoznate bolesti suvremenoga svijeta, a u njoj radi prim. dr. sc. Diana Balen. Reumatološke (subspecijalističke) ambulante odnose se na obradu i liječenje bolesnika s upalnim reumatskim bolestima (npr. reumatoidni artritis, psorijatični artritis, ankilozantni spondilitis, enteropatski artritis i dr.), a uključuju posebnu Ambulantu za spon-

ing with pain syndromes (e.g., vertebrogenic), neurological disorders and post-traumatic conditions. The experts who are currently working at these outpatient units are: Prim. Tomislav Nemčić, MD, Prim. Diana Balen, MD, Danijela Klarić, MD. At the Outpatient Clinic for Osteoporosis the procedures of prevention and treatment of osteoporosis and its complications are carried out. Osteoporosis is also known as a “silent epidemic”, i.e., a disease which severely affects the world population today and which is still not sufficiently researched. Prim. Diana Balen, MD is working at this Outpatient Clinic. At the Outpatient Clinics for Rheumatology (subspecialist clinics) the procedures of diagnosis and treatment of patients with rheumatic diseases are carried out (e.g., rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, enteropathic arthritis, etc.). In addition to that, a special Outpatient Clinic for spondyloarthritis also operates as part of the aforementioned clinics, considering that, as a Referral Centre of the Ministry of Health of the Republic of Croatia, the University Department has a special interest in this group of inflammatory rheumatic diseases. The experts who are working at this Outpatient Clinic are: Prof. Simeon Grazio, MD, PhD, Assistant Prof. Frane Grubišić, MD, PhD, Hana Skala Kavanagh, MD and Ines Doko Vajdić, PhD). At the Outpatient Clinic for Electromyoneurography, the EMNG test is performed by using the most up-to-date, recently acquired device, and currently this test is performed by two specialists (Prim. Tomislav Nemčić, MD and Prim. Diana Balen, MD). The Outpatient Clinic for the ultrasound of the locomotor system greatly facilitates the diagnosis of various diseases and conditions, and the contrast-enhanced Doppler helps in identifying increased blood flow, which is present in inflammation. At the University Department, this test is currently carried out by four specialists and subspecialists (Prim. Tomislav Nemčić, MD, Hana Skala Kavanagh, MD, Ines Doko Vajdić, PhD, and Prim. Diana Balen, MD).

The Outpatient Clinics for Physiatry are focused on the diagnosis and indication of therapeutic and rehabilitation methods for neurodevelopmental disorders, and three of our physicians currently work at these clinics (Prof. Valentina Matijević, MD, PhD, Velimir Šušak, MD and Jelena Marunica Karšaj, MD). The Speech Therapy and Special Education (Rehabilitation) units (outpatient clinics) are also operating as specialist consultative healthcare units for children, and the experts working at these clinics also operate as members of the multidisciplinary team (in addition to the experts from the University Department and the Outpatient Clinic). A unit of the University Department, where activities related to the rehabilitation of cancer patients are carried out, is located at Ilica 197 (the experts working at this Unit are: specialists in



FIGURE 13. Physical Therapy – kinetec

SLIKA 13. Fizikalna terapija – kinetek



FIGURE 14. Physical therapy – lymphatic drainage of the hand

SLIKA 14. Fizikalna terapija – limfna drenaža ruke

diloartritise, s obzirom na to da Klinika kao Referentni centar Ministarstva zdravstva RH ima poseban interes za tu grupu upalnih reumatskih bolesti. U toj ambulanti rade prof. dr. sc. Simeon Grazio, doc. dr. sc. Frane Grubišić, dr. Hana Skala Kavanagh i dr. sc. Ines Doko Vajdić). U Ambulanti za elektromio(neuro)grafiju provodi se ta pretraga uz korištenje najsuvremenijeg nedavno nabavljenoga uređaja, a trenutno tu pretragu radi dvoje liječnika specijalista (prim. dr. sc. Tomislav Nemčić i prim. dr. sc. Diana Balen). Ambulanta za ultrazvuk lokomotornoga sustava uvelike olakšava dijagnosticiranje različitih bolesti i stanja, a osnaženi *doppler* pomaže u identificiranju pojačane prokrvljenosti napose izražene u upali. Pretragu na klinici trenutno radi četvero liječnika specijalista ili užih specijalista (prim. dr. sc. Tomislav Nemčić, dr. Hana Skala Kavanagh, dr. sc. Ines Doko Vajdić i prim. dr. sc. Diana Balen).

Fizijatrijske ambulante za djecu usmjerene su na dijagnosticiranje i indiciranje terapijsko-rehabilitacijskih metoda kod neurorazvojnih poremećaja, a u njima trenutno radi troje liječnika (prof. dr. sc. Valen-

Physiatry: Senija Brnić, MD and Vedran Brnić, MD). At this location, there is also an Outpatient Clinic for General Physiatry (Prof. Tihomir Žiger, MD, PhD is working at this unit). A unit of the University Department, where activities related to the rehabilitation of trauma patients are carried out, is located at Draškovićeve 19 (the experts working at this Unit are: physicians – specialists: Prim. Tatjana Nikolić, MD, Iva Rabić Popović, PhD, Gordana Tajsić, MD and Dubravka Sajković, MD). In addition to this unit, two Outpatient Clinics for Osteoporosis are also located at this site (the experts working there are Prim. Tatjana Nikolić, MD and Gordana Tajsić, MD), and at these clinics, the diagnostic test of bone densitometry can be performed on patients.

On an annual basis, approximately 1,200 patients are hospitalised at the University Department, and about a hundred of these patients are children up to the age of three and their mothers (as part of the “Mother and Child” programme). On an annual level, we have approximately 10,400 days of hospital stays, while treatment lasts about 8 days on average. An average of 1,300 patients visit the Outpatient Clinic annually. On an annual basis, approximately 50,000 patients are treated at the outpatient care and consultative healthcare units. Approximately 3,700 patients are diagnosed in the span of one year (electromyography, contrast-enhanced colour Doppler ultrasound and bone densitometry).

In pharmacological treatment, we apply the most modern drugs, both systemically and locally. In terms of locally administered drugs, glucocorticoids are used in most cases, while hyaluronan injections are used less often. Systemic treatment, in addition to symptomatic treatment, also includes biologic drugs and targeted synthetic antirheumatic drugs that change the course of the disease. These are mostly used for the most common inflammatory rheumatic diseases (rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis), and this is an area in which we are extremely experienced. According to the data from January 2020, our University Department was the third organisational unit in Croatia in terms of the number of patients with rheumatic diseases treated with biologic drugs, and the first organisational unit out of all organisational units in Croatia whose origin is primarily based on physiatry. Thus, we significantly improve the prognosis for patients with these disabling chronic inflammatory rheumatic diseases, we provide a better quality of life for them and prolong their survival.

One of the benefits of our University Department is that, along with the application of drug therapy, we use functional treatment methods. At all of the sites we carry out outpatient physical therapy, organised in ac-

tina Matijević, dr. Velimir Šušak i dr. Jelena Marunica Karšaj). U specijalističko-konzilijarnoj zaštiti za djecu još imamo ambulantu logopeda i ambulantu rehabilitatora, koji i u ovom segmentu, osim Odjela i Dnevne bolnice, djeluju kao članovi multidisciplinarnoga tima. Na lokaciji Ilica 197 nalazi se dio klinike koji se odnosi na rehabilitaciju onkoloških bolesnika (spec. fizijatri: dr. Senija Brnić i dr. Vedran Brnić), uz jednu opću fizijatrijsku ambulantu (prof. dr. sc. Tihomil Žiger). Na lokaciji Draškovićeve 19 nalazi se dio klinike koji se odnosi na rehabilitaciju traumatoloških bolesnika (liječnici – specijalisti: prim. dr. Tatjana Nikolić, dr. sc. Iva Rabić Popović, dr. Gordana Tajsić i dr. Dubravka Sajković), a tu su i dvije Ambulante za osteoporozi (prim. dr. Tatjana Nikolić i dr. Gordana Tajsić), s dijagnostičkom pretragom denzitometrijom skeleta.

Godišnje se na Klinici hospitalizira oko 1.200 bolesnika, od čega oko stotinjak djece do treće godine života sa svojim majkama u sklopu programa „Majka i dijete“. Na godišnjoj razini imamo oko 10.400 dana bolničkog liječenja, dok liječenje prosječno traje oko 8 dana. Kroz Dnevnu bolnicu prosječno prođe 1.300 bolesnika. U Polikliničko-konzilijarnoj zaštiti godišnje se liječi oko 50.000 bolesnika. Dijagnostički se godišnje obradi oko 3.700 bolesnika (elektromiografija, dijagnostički ultrazvuk i denzitometrija skeleta).

U farmakološkom liječenju primjenjujemo najsuvremenije lijekove sistemski i lokalno, a kao potonji se najčešće primjenjuju glukokortikoidi, rjeđe hijaluronani. Sistemsko liječenje uz ono simptomatsko uključuje i biološke lijekove i ciljane sintetske molekule antireumatika koji mijenjaju tijek bolesti i to za najčešće upalne reumatske bolesti (reumatoidni artritis, psorijatični artritis, ankilozantni spondilitis, neradiografski aksijalni spondiloartritis), u čemu imamo zavidno iskustvo. Naime, prema podacima iz siječnja 2020. Klinika je bila treća po redu organizacijska jedinica u Hrvatskoj po broju liječenih reumatoloških bolesnika biološkim lijekovima, a prva među svim organizacijskim jedinicama u Hrvatskoj temeljno fizijatrijske provenijencije. Tako bolesnicima s tim onesposobljavajućim kroničnim upalnim reumatskim bolestima znatno poboljšavamo prognozu i omogućujemo bolju kvalitetu života te im produžujemo preživljavanje.

Prednost je naše Klinike u tome što uz lijekove provodimo funkcionalno liječenje. Na svim lokacijama provodi se ambulanta fizikalna terapija, organizirana prema najsuvremenijem integriranom modelu, dok se fizioterapijsko liječenje provodi i u drugim organizacijskim jedinicama klinike (Odjeli, Dnevne bolnice) pod vodstvom glavnog fizioterapeuta klinike Ivana Anzulovića i uz pomoć voditeljice fizioterapije Poliklinike Štefanije Opalin, s voditeljicama pridruženih jedi-

cordance with the most modern integrated model, while physiotherapy treatment is carried out in other organisational units of the Department as well (divisions, outpatient clinics) under the guidance of the chief physiotherapist of the University Department, Ivan Anzulović, the lead physiotherapist of the Outpatient Clinic, Štefanija Opalin, and the lead physiotherapists of the associated units, Renata Lončar Čigir and Mirna Crnković. In this sense, modern individual programmes of therapeutic exercises (kinesiotherapy) are carried out, along with various forms of physical therapy (thermotherapy, cryotherapy, electrotherapy, therapeutic ultrasound, electromagnetic therapy, light therapy, extracorporeal shock wave therapy (ESWT), etc.). Apart from our University Department, the activities related to the operation of the Outpatient Unit for Physiotherapy are also carried out in other units of the UHC. Work (occupational) therapy, practices of prescribing and education on the use of rehabilitation equipment are also part of the interventions that we carry out. In cancer patients, rehabilitation is part of a complex treatment process which is present in all stages of the disease, especially after surgery. It should be noted that, the comprehensiveness of the psychosocial and somatomotor areas of human life is perhaps most evident during this rehabilitation process. Therefore, in the case of these patients, as well as in the case of all chronic diseases and conditions, psychosocial support is applied (e.g., in cooperation with the Croatian League against Rheumatism, breast cancer awareness associations, the associations of laryngectomees, and the colostomy associations), which significantly contributes to a more favourable outcome. Complementary support therapy (e.g., music therapy) is sometimes used as well. In the comprehensive rehabilitation of trauma patients, the activities are focused on polytraumatised patients, burn injuries, spinal injuries, hand injuries, pelvic injuries, sports injuries, orthopaedic rehabilitation, etc. The work of speech therapists, educational rehabilitators, and clinical psychologists, that are a part of a multidisciplinary team, should be especially highlighted, as it is particularly important in the (re)habilitation of children with developmental disabilities.

The diagnosis and treatment of patients with inflammatory rheumatic diseases in which basically any organ or organ system can be affected (heart, lungs, liver, spleen, intestines, kidneys, central and peripheral nervous system, skin, eyes, etc.) are examples of cooperation with physicians and other health professionals of all departments and divisions within this UHC, and if need for that arises, outside of it. Collaboration and multidisciplinary approach are the only factors which are necessary in order to achieve the optimal quality of care of such patients. As part of our collaboration with

nica Renatom Lončar Čigir i Mirnom Crnković. U tom smislu primjenjuju se suvremeni individualni programi terapijskih vježba (kinezioterapija), uz provođenje različitih oblika fizikalne terapije (termoterapija, krio-terapija, elektroterapija, terapijski ultrazvuk, elektromagnetoterapija, svjetlosna terapija, terapija izvantjelesnim udarnim valovima – ESWT itd.). Rad fizioterapeutske klinike osim u našoj Klinici provodi se i u drugim klinikama KBC-a. Radna (okupacijska) terapija, propisivanje i edukacija o primjeni rehabilitacijskih pomagala također su dio naših intervencija. Kod onkoloških bolesnika rehabilitacija je dio kompleksnog liječenja prisutnog u svim stadijima bolesti, a napose nakon kirurškog zahvata. Inače, kod te rehabilitacije možda najviše dolazi do izražaja sveobuhvatnost psihosocijalnih i somatomotoričkih područja ljudskog života. Stoga se kod tih bolesnika, ali i svih kroničnih bolesti i stanja primjenjuje psihosocijalna potpora (npr. i u suradnji s Hrvatskom ligom protiv reumatizma, s udrugama žena liječenih zbog raka dojke, udrugom laringektomiranih osoba, udrugom osoba s koloileourostomom), što znatno pridonosi sveukupnomu povoljnijem ishodu. Katkad se primjenjuje i komplementarna suportivna terapija (npr. terapija glazbom). U sveobuhvatnoj rehabilitaciji traumatoloških bolesnika specifičnosti rada su politraumatizirani bolesnici, opekline ozljede, spinalne ozljede, ozljede šake, ozljede zdjelice, sportske ozljede, ortopedska rehabilitacija itd. Posebno valja istaknuti rad logopeda, rehabilitatora i kliničkog psihologa kao dijela multidisciplinarnog tima, što napose dolazi do izražaja u (re)habilitaciji djece s nerazvojnim smetnjama.

Primjeri suradnje s liječnicima i drugim zdravstvenim djelatnicima svih klinika i zavoda samog KBC-a, a prema potrebi i izvan njega, jesu obrada i liječenje bolesnika s upalnim reumatskim bolestima u kojih može biti zahvaćen praktički bilo koji organ ili organski sustav (srce, pluća, jetra, slezena, crijeva, bubrezi, središnji i periferni živčani sustav, koža, oči itd.). Samo se suradnjom i multidisciplinarnim pristupom postiže optimalna kvaliteta skrbi za te bolesnike. U sklopu suradnje s drugim strukama vrijedno je navesti suradnju s neurolozima – npr. bolesnici s bolestima i oštećenjima gornjeg i donjega motornog neurona kao što su vertebralni i vertebrogeni sindromi, stanja nakon cerebrovaskularnog infarkta, akutna i kronična bolna stanja itd.; kirurzima, traumatolozima, neurokirurzima i anesteziolozima – npr. akutna i kronična bolna stanja, stanja nakon traumatoloških, neurokirurških operacija i operacija probavnog trakta; ginekolozima i urolozima – npr. problemi inkontinencije, postoperativna stanja; ginekolozima – opstetričarima – npr. ocjena stanja i edukacije trudnica; pedijatrima – npr. neurorazvojni poremećaji, djeca s upalnim reumatskim bolestima, s

other professions, it is important to mention our collaboration with: neurologists (for example, in the case of patients with diseases and damage of the upper and lower motor neurons, such as vertebral and vertebro-genic syndromes, conditions following cerebrovascular accident, acute and chronic pain conditions, and similar conditions), surgeons, traumatologists, neurosurgeons and anaesthesiologists (for example, in the case of acute and chronic pain conditions, conditions following trauma surgery, neurosurgery or gastrointestinal surgery), gynaecologists and urologists (for example, in the case of incontinence problems, post-operative conditions, gynaecologists – obstetricians (for example, in the case of assessment of the condition and education of pregnant women), paediatricians (for example, in the case of neurodevelopmental disorders, children with inflammatory rheumatic diseases and tumours, premature babies), dermatologists (for example, in the case of psoriasis, scleroderma), oncologists (for example, in the case of women undergoing treatment after mastectomy or other surgical procedures), cardiologists (for example, in the case of complications following myocardial infarction), pulmonologists (for example, in the case of COPD and malignancies) endocrinologists (for example, in the case of osteoporosis and acromegaly), gastroenterologists (for example, in the case of percutaneous endoscopic colostomy and incontinence) and nephrologists (for example, in the case of haemodialysis patients). Collaboration with the Clinical Institute of Diagnostic and Interventional Radiology and the Clinical Institute of Chemistry is particularly valuable and useful in the diagnosis of the diseases and conditions of the locomotor system. The employees of the Outpatient Clinic dealing with the rehabilitation of trauma patients (located at Draškovićeveva 19) work closely with surgeons and other physicians of the University Hospital for Traumatology (including the Intensive Care Unit), while the employees dealing with the rehabilitation of cancer patients (the Outpatient Clinic located at Ilica 197) work closely with oncologists, surgeons, and other physicians who work at the University Hospital for Tumours.

The specificity of this University Department is that it operates at three different locations, and some units of the University Department are located at four separate buildings at the main site (at Vinogradska), which, in some ways, complicates its operation. At the location at Vinogradska 29, the University Department is located on the first floor of building number 7 (this is where the outpatient clinics and outpatient clinic's unit for physical therapy for adults are located), on the fifth floor of building number 5 (this is where the outpatient clinics and outpatient clinic's Unit for Physical Therapy for Children are located), in building number 28 (this

tumorima, nedonošad; dermatolozi – npr. psorijaza, sklerodermija; onkolozi – npr. žene u tretmanu nakon mastektomije ili drugih kirurških zahvata; kardiolozi – npr. stanje nakon infarkta miokarda; pulmolozi – npr. KOPB, malignomi; endokrinolozi – npr. osteoporoza, akromegalija; gastroenterolozi – npr. perkutane stome, inkontinencija; nefrolozi – npr. bolesnici na hemodijalizi. U dijagnosticiranju bolesti i stanja lokomotornog sustava napose je vrijedna i korisna suradnja s Kliničkim zavodom za dijagnostičku i intervencijsku radiologiju i s Kliničkim zavodom za kemiju. Djelatnici Poliklinike koji se bave rehabilitacijom traumatoloških bolesnika (lokacija Draškovićeveva 19) usko surađuju s kirurzima i drugim liječnicima Klinike za traumatologiju (uključujući i jedinicu intenzivne skrbi), dok djelatnici koji se bave rehabilitacijom onkoloških bolesnika (lokacija Ilica 197) usko surađuju s onkolozima, kirurzima i drugim liječnicima Klinike za tumore.

Specifičnost je Klinike da radi na tri različite lokacije, a unutar glavne lokacije (Vinogradska ul.) dijelovi klinike su smješteni u četiri odvojene zgrade, što unekoliko usložnjava rad. Klinika je na lokaciji Vinogradska 29 smještena u prostorima I. kata zgrade br. 7 (ambulante i fizikalna terapija polikliničkog dijela za odrasle), na V. katu zgrade br. 5 (ambulante i fizikalna terapija polikliničkog dijela za djecu), u zgradi br. 28 (Odjel za reumatske bolesti, fizikalnu medicinu i rehabilitaciju, Odjel za rehabilitaciju djece i Dnevne bolnice za odrasle i za djecu) te u zgradi br. 24 (predstojnik, tajništvo, biblioteka, sobe liječnika, kabinet za praktičnu nastavu). Poliklinički dio klinike na lokaciji Ilica 197 smješten je u novom dijelu zgrade Klinike za tumore, dok je dio na lokaciji Draškovićeveva 19 smješten u prostorijama zgrade Klinike za traumatologiju.

Sedmero liječnika Klinike ima naziv primarijusa (D. Balen, S. Grazio, F. Grubišić, Z. Jajić, V. Matijević, T. Nemčić, T. Nikolić), a petoro liječnika uže specijalizacije iz reumatologije (S. Grazio od 2001., Z. Jajić od 2003., F. Grubišić od 2008., H. Skala Kavanagh od 2017. i I. Doko Vajdić od 2018.), što govori u prilog visokog stupnja stručnosti, kao i posebnoga interesa za reumatske bolesti, dok je deset doktora znanosti (D. Balen, I. Doko Vajdić, S. Grazio, F. Grubišić, Z. Jajić, V. Matijević, T. Nemčić, P. Kovačević, I. Rabić Popović, T. Žiger), što je pokazatelj znanstvenih aktivnosti i interesa liječnika klinike.

Uz nastavu na više visokoškolskih ustanova te aktivno sudjelovanje na brojnim kongresima, simpozijima i radionicama edukacijski karakter Klinike očituje se u činjenici da je Klinika centar obuke Europskog odbora za fizikalnu i rehabilitacijsku medicinu (EBPRM) i jedini je takav centar u Hrvatskoj, uz trenutno 15 ustanova u cijeloj Europi s tim prestižnim naslovom. Veza-

is where the Division of Rheumatic Diseases, Physical Medicine and Rehabilitation, the Division for the Rehabilitation of Children and the Outpatient Clinics for Adults and Children are located), and in building number 24 (this is where the office of the head of the organisational unit, secretariat, library, doctors' offices, and the laboratory for practical classes (laboratory exercises) are located). The Outpatient Unit of the University Department located at Ilica 197 is situated in the new part of the building that belongs to the University Hospital for Tumours, while the unit located at Draškovićeve 19 is located at the building that belongs to the University Hospital for Traumatology.

Seven physicians of the University Department have the title of Primarius (Prim). These physicians include: D. Balen, S. Grazio, F. Grubišić, Z. Jajić, V. Matijević, T. Nemčić, T. Nikolić. Moreover, five physicians of the University Department have the title of subspecialists in Rheumatology: S. Grazio (since 2001), Z. Jajić (since 2003), F. Grubišić (since 2008), H. Skala Kavanagh (since 2017), and I. Doko Vajdić (since 2018). The aforementioned facts speak in favour of the high degree of expertise of professionals working at our University Department, as well of the special interest of our physicians in rheumatic diseases. In addition to that, ten of our physicians have the title of Doctor of Philosophy (PhD): D. Balen, I. Doko Vajdić, S. Grazio, F. Grubišić, Z. Jajić, V. Matijević, T. Nemčić, P. Kovačević, I. Rabić Popović, and T. Žiger. This fact is an indicator of the scientific activities and interests of the physicians working at our University Department.

In addition to the teaching activities of employees, who teach classes at several institutions of higher education, and their active participation in numerous congresses, symposia and workshops, the educational character of the University Department is reflected in the fact that the University Department is the Training Centre of the European Board of Physical and Rehabilitation Medicine (EBPRM). It is the only such centre in Croatia, and it is one of the 15 institutions in Europe who have that prestigious title. In accordance with that, four physicians of our University Department have obtained the title of *Fellow of the European Board of Physical and Rehabilitation Medicine*, one of our physicians has obtained the title of *Senior Fellow of the European Board of Physical and Rehabilitation Medicine*, and all five of them have obtained the title of *Board Certified Trainer*, which was awarded to them by the EBPRM.

And, last but not least, it is important to note that our hard-working and long-time secretary, Marijana Bregni, deals with almost all of the activities that are carried out at our University Department. She performs all of her tasks diligently, meticulously, and with great professionalism and enthusiasm, often sacrificing

no s tim četiri liječnika klinike imaju naslov *Fellow of the European Board of Physical and Rehabilitation Medicine*, a jedan naslov *Senior Fellow of the European Board of Physical and Rehabilitation Medicine*, dok svih pet imaju naslov certificiranog trenera od strane navedenoga odbora (*Board Certified Trainer*).

Naposljetku, ne i najmanje važno jest da gotovo sve aktivnosti na Klinici prolaze kroz vrijedne ruke naše dugogodišnje tajnice Marijane Bregni, koja sve svoje zadatke obavlja marljivo, stručno, pedantno i s velikim entuzijazmom, često za Kliniku žrtvujući svoje slobodno vrijeme.

BUDUĆNOST KLINIKE

Klinika za reumatologiju, fizikalnu medicinu i rehabilitaciju jedna je od vrhunskih ustanova u područjima svog djelovanja. Budućnost klinike je u daljnjem razvijanju i napretku svih djelatnosti koje provodi, a temelj toga su kvalitetni kadrovi svih profila. U tom smislu izbor djelatnika, povećanje njihovoga broja, a napose onih za kojima je najveća potreba (npr. reumatologa), te edukacija postojećih i novozaposlenih djelatnika jamac je visoke razine kliničkoga rada. Druga je važna sastavnica suvremena oprema, koju Klinika kao vodeća ustanova u Hrvatskoj treba imati, a da bismo mogli pratiti struku i trendove te istovremeno odgovarajuće educirati kako naše djelatnike tako i ostale koji nam dolaze na usavršavanje. Uz navedeno i dostupnost naj-suvremenije farmakološke terapije (uključivo npr. biološke lijekove i ciljane sintetske molekule za liječenje bolesnika s upalnim reumatskim bolestima) povezana je s dodatnim materijalnim izdancima, koje, međutim, treba prihvatiti kao ulaganje, jer je dugoročno i ekonomski opravdano glede budućih direktnih i indirektnih troškova te napose kvalitete života naših bolesnika. Sljedeća važna sastavnica rada jesu prostorni uvjeti, koji su u određenoj mjeri poboljšani, a kapaciteti i prošireni (na lokaciji Vinogradska 29 te novi prostori na lokaciji Ilica 197). U potresima 2020. godine dio zgrada Klinike je zadobio značajna oštećenja, što zahtijeva dodatna ulaganja u njihovu sanaciju. Optimalno rješenje bila bi izgradnja novih prostora Klinike, gdje bi sve djelatnosti bile funkcionalno objedinjene, čime bi se postigla najbolja kvaliteta naših sveukupnih aktivnosti. Informatička i programska podrška također je važna sastavnica optimalnog rada, na čemu treba ustrajati.

Potrebno je poticati i dalje razvijati nastavno/edukativne aktivnosti, kako sudjelovanjem u nastavi visokoškolskih ustanova, prvenstveno fakulteta, tako i u organizaciji i aktivnom sudjelovanju u drugim oblicima edukacije kao što su tečajevi, radionice i slično. Klinika ima značajnu tradiciju i kao znanstvena ustanova te je u tom smislu potrebno nastojati aktivno sudjelovati u

her free, leisure time in order to carry out the tasks that are important for the operation of the University Department.

THE FUTURE OF THE DEPARTMENT

The Department of Rheumatology, Physical and Rehabilitation Medicine is one of the top institutions in its fields of activity. The future of the Department lies in the further development and progress of all the activities it carries out, and the basis of this achievement is the quality personnel of all profiles. In this sense, the selection of employees, the increase in the number of employees (especially those who are needed the most, e.g., rheumatologists), and the education and training of existing and newly employed staff is a guarantee of a high quality of clinical work. Another important component is modern equipment, which is a prerequisite for the operation of our Department as a leading institution in Croatia. This is also important because it enables us to follow the course and trends of our profession and simultaneously and adequately educate both our employees and the employees of other institutions who are trained at our Department. In addition to the aforementioned, it is also important to mention another crucial component: the availability of state-of-the-art pharmacological therapy (including, for example, biologic drugs and targeted synthetic drugs for the treatment of patients with inflammatory rheumatic diseases). This component is associated with additional material costs, but it should be considered an investment which shall bring long-term success in the future, and which is justified from an economic standpoint in terms of future direct and indirect costs, and especially the quality of life of our patients. The next important component of the operation of our Department are the working conditions, which have been improved to a certain extent. In addition to that, the capacities of the Department have also been expanded (with new facilities at our site at Vinogradska 29 and new work premises at our site at Ilica 197). Some of the buildings of the Department were extremely damaged in the 2020 earthquakes, and additional investments need to be made in order for them to be restored. The optimal solution would be the construction of new premises of the Department, at which all of the activities of the Department would be functionally unified, and which would enable us to achieve the best quality of our overall activities. IT and software support is also an important component which contributes to the achievement of optimal work quality which we should always strive for.

It is also necessary to encourage and further develop our teaching/educational activities, both by participating in the teaching activities of institutions of higher education, primarily universities/faculties, and in the organisation and active participation in other forms of

znanstvenim projektima i programima, a napose u onima koji su podržani od relevantnih hrvatskih i inozemnih institucija i međunarodnih organizacija, uključivo i suradnju s drugim ustanovama i institucijama. Rezultati vlastitih istraživanja prezentirat će se na kongresima, simpozijima ili konferencijama, kao i objavljivati radove, preferabilno u časopisima s neovisnom (međunarodnom) recenzijom i u onima što višeg čimbenika odjeka.

Sveukupno, Klinika za reumatologiju, fizikalnu medicinu i rehabilitaciju KBC-a Sestre milosrdnice u Zagrebu dala je izuzetno velik doprinos hrvatskoj reumatologiji i fizikalnoj medicini i rehabilitaciji te vjerujem da će tu, jednu od vodećih uloga, zadržati i nadalje.

U Zagrebu, 1. travnja 2021.

education such as courses, workshops and the like. The Department also has a long tradition as a scientific institution, and in this sense, it is necessary to try to actively participate in scientific projects and programmes, especially those supported by relevant Croatian and foreign institutions and international organisations, which also includes cooperation with other organisations and institutions. The results of research studies conducted by employees of our Department will be presented at congresses, symposia or conferences, their research papers will be published, preferably in journals with independent (international) review and in journals with the highest possible impact factor.

Overall, the Department of Rheumatology, Physical and Rehabilitation Medicine of the Sestre milosrdnice UHC in Zagreb has made an extremely large contribution to the field of rheumatology and physical and rehabilitation medicine in Croatia, and I strongly believe that it will continue to play this leading role in the future.

In Zagreb, 1 April 2021

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Svi se radovi provjeravaju na originalnost i plagiranje, umnažanje, dupliciranje i prekomjernu prijavu/publikaciju i teksta i slikovnih prikaza iz drugih izvora (pomoću, na primjer, programa DupliChecker, Plagiarism Checker, Plagium, PlagScan). Plagirani ili na bilo koji drugi neetički način objavljeni radovi bit će povučeni u skladu s COPE-ovim Uputama o povlačenju radova (COPE – *Retraction Guidelines*; <https://publicationethics.org/files/retraction%20guidelines.pdf>).

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Reumatizam objavljuje ove vrste radova kod kojih je potrebna recenzija : kliničke smjernice, uvodnike, originalne znanstvene radove, pregledne radove, stručne radove, kratka/preliminarna priopćenja, pregledne radove i dobro dokumentirane prikaze bolesti (s pregledom literature).

Uvodnik (*Editorial*): maksimalno 1200 riječi; do 1 slike ili tablice; do 20 referencija; 3 – 6 MeSH ključnih riječi; nestrukturirani sažetak do 300 riječi (ako je primjenjivo).

Practice Guidelines, Review and Expert Opinion articles: 6,000 words maximum; up to 5 figures and 5 tables; unlimited number of references; 3 – 6 keywords; structured abstract up to 300 words (except for articles on the history of medicine that may have an unstructured abstract).

Letters (Short or Preliminary Communication, Brief Report): 1,500 words maximum; up to 3 figures or tables; up to 15 references; 3 – 6 keywords.

Case Report (Case Based Review): 6,000 words maximum; up to 5 figures or tables; unlimited number of references; 3–6 keywords; unstructured abstract up to 300 words.

Erratum: enables correction of errors made in writing, printing, or publication process of an article. To be sent to: *Reumatizam*, Uredništvo, Klinika za reumatologiju, fizikalnu medicinu i rehabilitaciju, Klinički bolnički centar Sestre milosrdnice, Vinogradska 29, 10000 Zagreb, Croatia, or via email: glavni-urednik-reumatizam@reumatologija.org and urednik-reumatizam@reumatologija.org.

ARTICLE / MANUSCRIPT PREPARATION

Reumatizam publishes articles in Croatian, including the title, abstract, keywords, and table and figure titles and legends in English, or articles in English (American standard), including the title, abstract, keywords, and table and figure titles and legends in Croatian. The writing style should be clear and concise. Articles should be structured following the EQUATOR Network principles (<http://www.equator-network.org>).

The text should be typed in 12-point font, on white A4 paper (210 x 297 mm), double-spaced, with a maximum of 30 lines per page, including the title page, abstract, text, acknowledgments, conflict of interest statement, references, tables, and legends. The left margin should be 35 mm, and the right, top and bottom margins 25 mm each. All the pages, including the title page, should be numbered in the bottom right corner.

Measurements, if needed, should be reported using the International System of Units (SI). Names that can be abbreviated should be spelled out in full followed by the abbreviation in parentheses at the first mention, and referred to only in the abbreviated form further in the text. Latin names should be italicized, with the full name at the first mention, and only the abbreviated form further in the text. Drugs should be referred to by their generic names, and trade names, if necessary, may follow in parentheses, with the manufacturer's name. Manufacturers of specific instruments or reagents (name and location) should be given in parentheses.

Except for reviews and letters to the editor, manuscripts should include the following: a title page (on a separate page), abstract and keywords (on a separate page), the main text (with the following sections: introduction, participants and methods, results, discussion, and conclusion), acknowledgments, funding, conflict of interest statement, references, list of tables, list of figures, tables and figures.

Title page

The title page should include the article title (concise, clear, and informative) both in Croatian and in English, and the full name of each author, followed by the full name of the author's affiliation, with full postal address (street, city, and country) of the institution. If the article was prepared by several authors of various affiliations, all authors should be linked to their corresponding affiliation(s) using superscript numerals after their respective names, and preceding the institution name.

This should be followed by the name, surname, and full contact address of the corresponding author responsible for the correspondence related to the article, with his/her telephone and fax numbers, and e-mail address.

Abstract and keywords

The second page should include the abstract, both in English and Croatian, of up to 300 words, providing the purpose of the study/research, materials (participants) and methods, results, and conclusions.

Originalni rad (*Original Research Article*): maksimalno 6500 riječi; do 6 slika i 6 tablica; neograničeni broj referencija; 3 – 6 ključnih riječi; strukturirani sažetak do 300 riječi (izuzetak su radovi iz povijesti medicine koji mogu imati nestrukturirani sažetak).

Kliničke smjernice (*Practical Guidelines*), pregledni radovi (*Review*) i radovi temeljeni na mišljenju eksperata (*Expert Opinion Articles*): maksimalno 6 000 riječi; 5 slika i 5 tablica; neograničeni broj referencija; 3–6 ključnih riječi, strukturirani sažetak sa do 300 riječi (izuzetak su radovi iz povijesti medicine koji mogu imati nestrukturirani sažetak).

Kratko priopćenje (*Short Communication, Brief Report*): maksimalno 1500 riječi; do 3 slike ili tablice; do 15 referencija; 3 – 6 ključnih riječi.

Prikaz bolesnika (*Case Based Review*) maksimalno 6000 riječi; do 5 slika ili tablica; neograničeni broj referencija; 3 – 6 ključnih riječi; nestrukturirani sažetak do 300 riječi.

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U časopisu *Reumatizam* objavljuju se članci na hrvatskom jeziku, s naslovom, sažetkom, ključnim riječima te s naslovom i legendom tablica i slika na engleskom jeziku ili članci na engleskom jeziku (*UK spelling*), s naslovom, sažetkom, ključnim riječima te s naslovom i legendom tablica i slika na hrvatskom jeziku. Stil pisanja treba biti jasan i jezgrovit. Radovi trebaju biti strukturirani sukladno principima EQUATOR Networka (<http://www.equator-network.org>).

Tekst treba biti napisan slovima veličine 12 točaka na bijelom papiru formata A4 (210 × 297 mm) s dvostrukim proredom, s najviše 30 redaka po stranici, uključujući i naslovnu stranicu, sažetak, tekst, zahvale, izjavu o sukobu interesa, referencije, tablice i legende. Lijeva margina treba biti široka 35 mm, a desna margina te gornji i donji rub 25 mm. Sve stranice, uključujući naslovnu, trebaju imati redni broj u donjem desnom kutu.

Pri potrebi izražavanja podataka rabe se SI mjerne jedinice. Kod naziva koji se mogu pisati kraticom pri prvom je pojavljivanju potrebno napisati puni naziv, s kraticom, a u daljnjem tekstu samo kraticu. Latinski nazivi pišu se načinom *Italic*, i to puni naziv kod prvog pojavljivanja u tekstu, a u daljnjem tekstu navodi se kratica. Lijekovi se navode generičkim imenom, a ako je nužno, može se u zagradi navesti tvorničko ime, s imenom proizvođača. Proizvođače specifičnih instrumenata ili reagensa (naziv i lokacija) treba navesti u zagradi.

Izuzet preglednih radova i pisama uredniku radovi trebaju imati sljedeće elemente: naslovna stranica (posebna stranica), sažetak i ključne riječi (posebna stranica), glavni tekst rada (s dijelovima: uvod, ispitanici i metode, rezultati, rasprava i zaključak), zahvale, financiranje, izjava o sukobu interesa, literatura, popis tablica i slika te tablice i slike.

Naslovna stranica

Na naslovnoj stranici trebaju biti naslov rada (sažet, jasan i informativan) na hrvatskom i engleskom jeziku te puno ime svakog od autora. U sljedećem retku treba navesti puni naziv ustanove, ulicu i broj, grad i državu. Ako su u izradi rada sudjelovali autori iz različitih ustanova, za svakog od njih poslije imena i prezimena te prije navoda ustanove treba napisati odgovarajući broj u superskriptu.

Slijede ime i prezime te puna adresa autora za dopisivanje u vezi s radom, njegov/njezin telefonski broj, broj faksa i e-mail adresa.

The abstract should emphasize new and important aspects of the study, or observations. Below the abstract, three to six keywords or short terms should be listed, both in Croatian and in English, to help index the article. The keywords may be published with the abstract. Terms from the Medical Subject Headings (MeSH) list of the National Library of Medicine of US should be used for the keywords. General and plural terms, and multiple concepts (e.g., using "and", "or") should be avoided. The abstract should not include references.

Introduction

The introduction provides a brief outline of the context/background of the topic, as well as the purpose and rationale for conducting the study/research. It is recommended to cite only relevant references, which should be well-balanced and recent (not older than 10 years, if possible). At the end, the objective(s) of the study/research should be stated clearly and precisely. No data from the paper or conclusions should be given in the introduction.

Materials and methods

This section provides details about how the study/research was conducted: the place and time, as well as the eligibility criteria for selecting the experimental or observational participants (or laboratory animals), with all their important characteristics. The author(s) should provide a detailed outline of the study (e.g., a randomized-controlled study, an observational study, a prospective/retrospective study, etc.), the data collection methods applied, the meaning of the descriptors, and explain and identify the methods, devices (including the manufacturer's name in parentheses), and procedures, sufficiently detailed to enable others to reproduce the results. References should be given for established methods, and new or substantially modified methods should be described in detail, stating the reasons for using them, and evaluating their limitations.

Generic names should be used for drugs and chemicals. All measurements should be given in SI units. In Croatian texts a decimal comma should be used, and in texts in English a decimal point.

Ethics / Ethical standards

Studies involving human subjects or animals should have received the approval of the respective ethics committee. The work described should have been carried out in accordance with the ethical standards of an institutional or national committee responsible for experiments involving human subjects, as well as with The Code of Ethics of the World Medical Association (Declaration of Helsinki 1964 and its revisions) for experiments involving humans <http://www.wma.net/en/30publications/10policies/b3/index.html>; EU Directive 2010/63/EU and for animal experiments http://ec.europa.eu/environment/chemicals/lab_animals/legislation_en.htm. Also, it should be stated explicitly that informed consent was obtained from all participating adult subjects or from parents or legal guardians for minors or incapacitated adults, together with the manner in which informed consent was obtained (i.e., oral or written).

Participants' names and/or surnames should not appear, particularly in figurative/illustrative materials.

Statistics

Statistical methods should be described in detail, to enable a knowledgeable reader with access to the original data to verify the reported results. Where possible, findings should be quantified and presented with appropriate indicators of measurement error or uncertainty. The statistical software used should be specified.

Results

Results should be presented in a logical sequence in the text, tables, and figures. In this section, the results are not interpreted nor are their implications discussed. In addition to absolute numbers

Sažetak i ključne riječi

Druga stranica treba sadržavati sažetak na engleskom i hrvatskom jeziku (do 300 riječi) u kojem su navedeni cilj studije/istraživanja, materijal (ispitanici) i metode, rezultati i zaključci.

U sažetku valja naglasiti nove i važne aspekte studije ili opservacije. Ispod sažetka autori trebaju navesti tri do šest ključnih riječi ili kratkih pojmova na hrvatskom i engleskom jeziku koji će pomoći pri indeksiranju članka. Ključne riječi se mogu objaviti uz sažetak. Za ključne riječi treba se koristiti pojmovima iz popisa *Medical Subject Headings* (MeSH) Indexa Medicusa. Općenite, množine i mnogostruke koncepte (primjerice uz uporabu „i“, „ili“) treba izbjegavati. Sažetak ne smije sadržavati navode referencija.

Uvod

U uvodu se ukratko navode kontekst/pozadinsko znanje o temi, svrha i razlog provođenja studije/istraživanja. Preporučuje se navesti samo relevantne referencije, koje trebaju biti uravnotežene i recentne (po mogućnosti ne starije od 10 godina). Na kraju treba jasno i točno navesti cilj/-eve studije/istraživanja. U uvodu se ne navode podatci iz rada niti zaključci.

Materijal i metode

Navode se detalji provedbe studije/istraživanja: gdje i kad je provedena, na koji je način učinjen odabir i sve važne karakteristike ispitanika (ili laboratorijskih životinja) koje su studirane ili opservirane. Treba detaljno specificirati nacrt studije (npr., randomizirana-kontrolirana studija, opservacijska studija, prospektivna/retrospektivna itd.), način prikupljanja podataka, značenje deskriptora te objasniti, identificirati metode, aparate (s nazivom proizvođača u zagradi) i postupke, dovoljno detaljno kako bi se rezultati mogli reproducirati. Za poznate metode treba navesti referencije, a nove metode ili metode koje su znatnije modificirane detaljno opisati, navodeći razlog njihove primjene i procjene njihovih ograničenja.

Za lijekove i kemikalije moraju se rabiti generička imena. Sve veličine trebaju biti izražene u SI jedinicama. U tekstovima na hrvatskom jeziku rabi se decimalni zarez, a u tekstovima na engleskom decimalna točka.

Etika / Etički standardi

Radovi koji uključuju ljude ili životinje trebaju imati odobrenje od odgovarajućeg etičkog povjerenstva. Takav rad treba biti proveden sukladno etičkim standardima institucije ili nacionalnom povjerenstvu odgovornom za eksperimente koji uključuju ljude i s Etičkim kodeksom udruge World Medical Association (Helsinška deklaracija iz 1964. i njezine kasnije inačice) za istraživanja koja uključuju ljude <http://www.wma.net/en/30publications/10policies/b3/index.html>; EU Direktiva 2010/63/EU I za istraživanja na životinjama http://ec.europa.eu/environment/chemicals/lab_animals/legislation_en.htm. Također, treba jasno navesti da je dobiven informirani pristanak od strane svih odraslih ispitanika ili od strane roditelja ili zakonskih skrbnika za maloljetne ispitanike ili nesposobne odrasle osobe, kao i način na koji je taj pristanak dobiven (npr. usmeno ili pismeno).

Imena i /ili prezimena ispitanika ne smiju biti obznanjena, naročito u grafičkim/slikovnim materijalima.

Statistika

Treba iscrpno opisati statističke metode kako bi se obrazovanom čitatelju koji ima pristup originalnim podacima omogućilo da potvrdi navedene rezultate. Gdje god je to moguće zaključke treba kvantificirati i prezentirati odgovarajućim indikatorima pogreške ili odstupanja od mjerenja. Treba navesti upotrijebljeni računalni program.

Rezultati

Rezultati se izlažu logičnim slijedom u tekstu, tablicama i slikama. U ovom se dijelu rezultati ne tumače niti se raspravljaju o njima.

and percentages, it is necessary to include the results of statistical analysis, by stating, for example, P values or other parameters. All the data from the tables or figures should not be repeated in the text, but rather only the most important observations should be emphasized or summarized. Redundant tables and figures (e.g., presenting the same data in different formats) should be avoided, as should the use of figures and tables when it is better to include the data in the textual part (e.g., when there is insufficient data for tables or figures).

Discussion

Most of this section is the interpretation of results. New and important aspects of the study, and its implications, should be emphasized. It is not recommended to repeat in detail data or any other material given in the Introduction or in the Results section. Own findings should be compared with the findings of other studies/research, showing the similarities and differences. It is also important to explain the significance of the results obtained, their limitations, and implications for future research, avoiding, however, making statements and drawing conclusions not completely confirmed by the obtained data. When necessary, new hypotheses may be given, but clearly labelled as such.

Conclusions

The main conclusions are drawn based on the author's or authors' own results (3 – 5 sentences maximum).

Abbreviations

Only standard abbreviations should be used. The spelled-out abbreviation followed by the abbreviation in parentheses should be used at the first mention unless the abbreviation is a standard unit of measurement. Abbreviations should be avoided in the manuscript title.

Symbols

Symbols used in the text should be explained. A detailed list of symbols may be given in an appendix.

Tables

Tables should be presented on a separate page. They should not be submitted as images/photographs. Each table should have a title and be numbered consecutively in the order it appears in the text. Tables should be self-explanatory and as simple as possible. Table legends should be given below the table, and may include a reference to data in the table indicated by a superscript figure or letter. Results presented elsewhere in the article (e.g., in an illustration), should not be repeated in the table. If a table originating from other sources is used, permission for such publication should be obtained from the respective publisher/author.

Figures / Illustrations

All figures should be professionally drawn or photographed. Letters, numbers, and symbols on figures should be clear enough to remain legible when the figure is reduced for publication. Figure titles and descriptions are considered to be a part of the text, and not part of the figure/illustration. Each figure/illustration should be numbered consecutively according to the order in which it appears in the text, and have a clear mark showing which is the upper side. Figures/illustrations should appear in a quality appropriate for print publication. Photocopied images or photographs are not suitable for reproduction. If submitted in electronic format, figures/illustrations should be in a high resolution TIFF or JPEG file format, a minimum of 1,500 pixels wide. Figures/illustrations submitted in other formats may be accepted only with the prior consent of the editorial board. The editorial board reserves the right not to publish any figures/illustrations that fail to meet the above require-

vim implikacijama. Uz apsolutne brojeve i postotke potrebno je uključiti rezultate statističke analize, navođenjem obično p-vrijednosti ili drugog parametra. U tekstu se ne ponavljaju svi podatci iz tablica ili slika, već se naglašavaju ili sažimaju samo bitna opažanja. Potrebno je izbjegavati suvišne tablice i slike (npr. prikaz istih podataka u različitim formatima) ili uporabu slika i tablica u slučaju kada je informacije bolje uključiti u tekstualni dio (npr. kada nema dovoljno podataka za tablice ili slike).

Rasprava

Većina ovog dijela odnosi se na interpretaciju rezultata. Potrebno je naglasiti nove i bitne aspekte studije te implikacije koje iz nje proistječu. Ne preporučuje se detaljno ponavljati podatke ni bilo koje druge materijale koji su navedeni u uvodnom dijelu ili u dijelu s rezultatima. U dijelu za raspravu treba usporediti vlastite rezultate s rezultatima iz drugih studija/istraživanja te navesti sličnosti i razlike. Također, važno je objasniti značenje dobivenih rezultata, njihova ograničenja i implikacije vezane uz buduća istraživanja, ali uz izbjegavanje izjava i zaključaka koji nisu potpuno potvrđeni dobivenim podacima. Kad je potrebno, mogu se navesti nove hipoteze uz jasno naglašavanje da su nove.

Zaključci

Na osnovi vlastitih rezultata izvode se glavni zaključci (maksimalno 3 – 5 rečenica).

Kratice

Treba rabiti samo standardne kratice. Puni pojam za koji se rabi kratica mora biti naveden pri prvoj uporabi kratice u tekstu, osim ako je riječ o standardnim kraticama mjernih jedinica. Kratice treba izbjegavati u naslovu rada.

Simboli

U tekstu se simboli moraju objasniti. U dodatku se može navesti iscrpan popis simbola.

Tablice

Tablice se pišu na posebnoj stranici. Ne smiju se slati kao slike/fotografije. Svaka tablica mora imati naslov i redni broj prema redoslijedu pojavljivanja u tekstu. Tablica mora biti pregledna i jednostavna. Legende tablica trebaju biti napisane ispod tablice, uz oznaku u tablici u superskriptu. Tablice ne bi trebale ponavljati rezultate koji su prezentirani bilo gdje drugdje u radu (npr. u slici). Tablice preuzete iz drugih izvora treba popratiti dopuštenjem za objavu njihovih izdavača/autora.

Slike / Ilustracije

Sve slike trebaju biti profesionalno nacrtane ili snimljene. Slova, brojevi i simboli moraju biti čitki i u smanjenom obliku u kojem će se objaviti. Svaka slika mora imati broj prema redoslijedu pojavljivanja u tekstu, ime autora i označenu gornju stranu. Svaki crtež mora imati broj prema redoslijedu pojavljivanja u tekstu i označenu gornju stranu. Crteži trebaju biti dovoljno kvalitetno izrađeni za objavu u tisku. Fotokopije slika ili fotografija nisu pogodne za reprodukciju. Ako se dostavljaju u elektroničkom obliku, slike/ilustracije moraju biti u formatu TIFF ili JPEG visoke kvalitete, najmanje širine 1500 piksela. Slike/ilustracije u ostalim formatima mogu biti prihvaćene samo uz prethodni dogovor s uredništvom. Uredništvo pridržava pravo ne objaviti slike/ilustracije koje ne zadovoljavaju ove uvjete. Fotografije osoba mogu se objavljivati samo uz pismeno dopuštenje osobe na fotografiji (ili skrbnika) ili osoba mora biti neprepoznatljiva (prekrivanje očiju, lica i sl.). Slike preuzete iz drugih izvora treba popratiti dopuštenjem za objavu njihova izdavača/autora.

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Acknowledgments

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References

Comprehensive and systematic searches through Scopus, Web of Science, PubMed, Directory of Open Access Journals (DOAJ), and specialist bibliographic databases are strongly encouraged to cite highly relevant, updated, and evidence-based items. The following relevant recommendations could be consulted at <https://rdcu.be/bVOOt> and <https://bit.ly/2PxEGDz>.

References should be presented using the Vancouver style, a numeric citation style as recommended by the US National Library of Medicine. The most frequent examples can be consulted in the following recommendations: ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals: Samples of Formatted References for Authors of Journal Articles (https://www.nlm.nih.gov/bsd/uniform_requirements.html). Detailed instructions can be found in the following book: Citing Medicine (<https://www.ncbi.nlm.nih.gov/books/NBK7256>).

References in the text, tables, and legends should be numbered in Arabic numerals, in parentheses, consecutively in the order of appearance in the text. When more than one reference is given, these should be separated by a comma.

In the list of references, **authors** and/or **editors** are cited with the surname(s) and followed by the initial(s) of the name(s). Initials do not end with a full stop, unless the initial comes immediately before the title. For several authors/editors, their names are separated by a comma. For more than six authors/editors, the first six should be listed with surnames and initials followed by "et al.", and the others omitted. In **titles**, only the first word is capitalized, and any other words that are usually written with a capital. In pagination, repeated identical initial digits for page numbers are omitted (for example: 123-125 becomes 123-5). Each reference should end with a full stop.

For articles in **English**, it is recommended that titles of references published in other languages are cited in English (if available), or an English translation of the title provided (placed in square brackets), with an indication of the language of the original placed at the end.

Zahvale

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[Example] *Journal article, more than six authors:*

1. Ćurković B, Babić-Naglić Đ, Morović-Vergles J, et al. Proposal for biologic drugs therapy in rheumatoid arthritis. *Reumatizam*. 2010;57(1):29–35. Croatian.

[Example] *Journal article, continuous pagination:*

2. Ritchlin CT. From skin to bone: translational perspectives on psoriatic disease. *J Rheumatol*. 2008;35:1434–7.

[Example] *Supplement article:*

3. Gladman DD, Antoni C, Mease P, Clegg DO, Nash P. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. *Ann Rheum Dis*. 2005;64(Suppl 2):ii14–7.

Books

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[Example] *Book (authors):*

4. Walker JM, Helewa A. Physical rehabilitation in arthritis. 2nd ed. St. Louis: Saunders; 2004.

[Example] *Book (editors):*

5. Isenberg DA, Maddison PJ, Woo P, Glass D, Breedveld FC, editors. *Oxford textbook of rheumatology*. 3rd ed. New York: Oxford University Press; 2004.

[Example] *Chapter in a book:*

6. Vasey FB, Espinoza LR. Psoriatic arthritis. In: Calin A, editor. *Spondyloarthropathies*. Orlando: Grune and Stratton; 1984. pp. 151–85.

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[Example] *Papers presented at meetings, published in a supplement:*

7. Matucci Cerinic M, Pignone A. The early diagnosis of rheumatoid arthritis (RA). *Reumatizam*. 1997;44(Suppl):1.

[Example] *Papers presented at meetings, published in a book:*

8. Babić-Naglić Đ. Fizička aktivnost i vježbe [Physical activities and exercises]. In: Ivanišević G, editor. *Talasoterapija, kineziterapija i aromaterapija u Hrvatskoj* [Thalassotherapy, kineziterapija and aromatherapy in Croatia]. Proceedings of the 14th Lošinj School of Natural Remedies; 2013 Sep 6–7; Veli Lošinj, Croatia. Zagreb: Hrvatski liječnički zbor; 2013, pp. 49–55. Croatian.

[Example] *Conference proceedings (book):*

9. Gordon DA, editor. Immune reactions and experimental models in rheumatic diseases. *Proceedings of the Fourth Ca-*

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1. Ćurković B, Babić-Naglić Đ, Morović-Vergles J i sur. Prijedlog primjene bioloških lijekova u reumatoidnom artritisu. *Reumatizam*. 2010;57(1):29–35.

[Primjer] *Članak iz časopisa, kontinuirana paginacija:*

2. Ritchlin CT. From skin to bone: translational perspectives on psoriatic disease. *J Rheumatol*. 2008;35:1434–7.

[Primjer] *Članak iz suplementa:*

3. Gladman DD, Antoni C, Mease P, Clegg DO, Nash P. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. *Ann Rheum Dis*. 2005;64(Supl 2):ii14–7.

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4. Walker JM, Helewa A. Physical rehabilitation in arthritis. 2. izd. St. Louis: Saunders; 2004.

[Primjer] *Knjiga (urednici):*

5. Isenberg DA, Maddison PJ, Woo P, Glass D, Breedveld FC (ur.). *Oxford textbook of rheumatology*. 3. izd. New York: Oxford University Press; 2004.

[Primjer] *Poglavlje u knjizi:*

6. Vasey FB, Espinoza LR. Psoriatic arthritis. U: Calin A (ur.). *Spondyloarthropathies*. Orlando: Grune and Stratton; 1984., str. 151–85.

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7. Matucci Cerinic M, Pignone A. The early diagnosis of rheumatoid arthritis (RA). *Reumatizam*. 1997;44(Supl):1.

[Primjer] *Izlaganje na znanstvenom skupu, objavljeno u knjizi:*

8. Babić-Naglić Đ. Fizička aktivnost i vježbe. U: Ivanišević G (ur.). *Talasoterapija, kineziterapija i aromaterapija u Hrvatskoj*. Zbornik izlaganja na 14. lošinskoj školi prirodnih ljekovitih činitelja; 2013 Ruj 6–7; Veli Lošinj, Hrvatska. Zagreb: Hrvatski liječnički zbor; 2013., str. 49–55.

[Primjer] *Zbornik izlaganja na znanstvenom skupu (knjiga):*

9. Gordon DA (ur.). Immune reactions and experimental models in rheumatic diseases. Zbornik izlaganja na četvrtoj kanadskoj konferenciji o istraživanju reumatskih bolesti; 1970 Lis 15–17; Toronto, Kanada. Toronto: University of Toronto Press; 1972.

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10. Mak A, Kow NY. The pathology of T cells in systemic lupus erythematosus. *J Immunol Res* [Internet]. 2014;2014:419029. Dostupno na: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4017881>. [Pristupljeno: 25. 5. 2014.].

[Primjer] *Članak iz časopisa na internetu, sadržava DOI:*

11. Vivar N, Van Vollenhoven RF. Advances in the treatment of rheumatoid arthritis. *F1000Prime Rep*. 2014 Svi 6;6:31. doi: 10.12703/P6-31. PubMed PMID: 24860653; PubMed Central PMCID: PMC4017904.

nadian Conference on Research in Rheumatic Diseases; 1970 Oct 15–17; Toronto, Canada. Toronto: University of Toronto Press; 1972.

Web publications

References for web publications should include the URL and date of access, unless it is a publication with a DOI.

[Example] *Journal article on the Internet:*

10. Mak A, Kow NY. The pathology of T cells in systemic lupus erythematosus. *J Immunol Res* [Internet]. 2014;2014:419029. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4017881>. [cited: 2014 May 25].

[Example] *Journal article on the Internet, with a DOI:*

11. Vivar N, Van Vollenhoven RF. Advances in the treatment of rheumatoid arthritis. *F1000Prime Rep*. 2014 May 6;6:31. doi: 10.12703/P6-31. PubMed PMID: 24860653; PubMed Central PMCID: PMC4017904.

[Example] *Book/monograph on the Internet:*

12. Chen Q, editor. Osteoarthritis – diagnosis, treatment and surgery [Internet]. Rijeka: InTech; 2012. Available from: <http://www.intechopen.com/books/osteoarthritis-diagnosis-treatment-and-surgery>. [2013 Oct 8].

[Example] *Web page:*

13. Hrvatsko reumatološko društvo [Internet]. Zagreb: Croatian Society for Rheumatology of the CMA; c2014. Available from: <http://www.reumatologija.org/Pocetna.aspx>. [cited: 2014 Apr 1].

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12. Chen Q (ur.). Osteoarthritis – diagnosis, treatment and surgery [Internet]. Rijeka: InTech; 2012. Dostupno na: <http://www.intechopen.com/books/osteoarthritis-diagnosis-treatment-and-surgery>. [Pristupljeno: 8. 10. 2013.].

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13. Hrvatsko reumatološko društvo [Internet]. Zagreb: Hrvatsko reumatološko društvo HLZ-a; c2014. Dostupno na: <http://www.reumatologija.org/Pocetna.aspx>. [Pristupljeno: 1. 4. 2014.].

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