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LUNG DISEASES IN RHEUMATOID ARTHRITIS – EXPERIENCES OF A TERTIARY CENTRE

BOLESTI PLUĆA U REUMATOIDNOM ARTRITISU – ISKUSTVA TERCIJARNOG CENTRA

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Abstract

Introduction. Rheumatoid arthritis (RA) is a systemic autoimmune disease, and its most common extra-articular manifestation is involvement of the lung parenchyma and pleura. The most common pleuropulmonary manifestation of RA is interstitial lung disease (ILD). The aim of this study was to show the frequency and characteristics of pleuropulmonary manifestations in patients with RA who were treated at the University Hospital Centre Split. *Subjects and methods.* Patients treated with biological and targeted synthetic disease-modifying antirheumatic drugs (DMARDs) who were diagnosed with RA according to the 2010 EULAR/ACR classification criteria were included in the study. Data from the archive of medical records were analysed using the method of descriptive statistics. *Results.* A total of 188 patients with RA were analysed. There were 18 (9.6%) patients with pleuropulmonary manifestations of RA. The average age was 66.5 (range: 48–85), and 13 of these patients were women (72.2%). 6 patients were smokers (33.3%). 12 patients were diagnosed with seropositive RA (66.6%), and four of these patients were smokers (33.3%). Patients with seropositive RA and associated pleuropulmonary manifestations had the shortest disease duration (<10 years), and there were five of them (83.3%), with four of them being smokers (66.6%). Nodular lung disease was found in 12 patients (66.6%), and 9 of these patients had seropositive RA (75%). Bronchiectasis was found in 8 patients (44.4%) and pleural thickening in three patients (16,6%). ILD was radiologically diagnosed in 10 patients (55.5%), and 7 of them had seropositive RA (70%). The pattern of usual interstitial pneumonia (UIP) was present in 8 patients (80%), while the pattern of non-specific interstitial pneumonia (NSIP) was found in two patients (20%). *Conclusion.* Patients with seropositive RA have a higher risk of developing nodular lung disease and ILD than patients with seronegative RA. The most common radiologically determined pattern of ILD was UIP, which coincides with data available from the literature.

Key words: arthritis, rheumatoid, lung diseases, interstitial

Sažetak

Uvod. Reumatoidni artritis (RA) je sustavna autoimuna bolest čija je najčešća izvanzglobna manifestacija zahvaćanje plućnog parenhima i pleure. Najčešća pleuropulmonalna manifestacija RA je intersticijska bolest pluća (engl. interstitial lung disease, skr. ILD). Cilj istraživanja bio je prikazati učestalost i obilježja pleuropulmonalnih očitovanja u bolesnika s reumatoidnim artritisom liječenih u Kliničkom bolničkom centru Split. *Ispitanici i metode.* U istraživanje

su uključeni bolesnici na biološkoj i ciljanoj sintetskoj terapiji antireumaticima koji mijenjaju tijek bolesti (engl. disease-modifying antirheumatic drugs, skr. DMARDs) s dijagnozom RA prema EULAR/ACR klasifikacijskim kriterijima iz 2010. godine. Analizirani su podatci iz arhive medicinske dokumentacije metodom deskriptivne statistike. *Rezultati.* Ukupno je analizirano 188 bolesnika s RA-om. Broj bolesnika s pleuropulmonalnim očitovanjima RA bio je 18 (9,6%). Prosječna životna dob bila je 66,5 godina (raspon: 48 – 85), od toga je 13 bilo žena (72,2%). Među oboljelima, šest ispitanika bili su pušači (33,3%), od čega ih je četiri ženskoga spola (66,6%). U dvanaest bolesnika dijagnosticiran je seropozitivni RA (66,6%), od kojih je četvero bilo pušača (33,3%). Bolesnici sa seropozitivnim RA-om i pridruženim pleuropulmonalnim očitovanjima imali su najkraće trajanje bolesti (<10 godina), a bilo ih je petero (83,3%), od čega je četvero bilo pušača (66,6%). Nodularna bolest pluća bila je utvrđena u dvanaest bolesnika (66,6%), a devet ih je imalo seropozitivni RA (75%). Bronhiektazije su nađene u osam bolesnika (44,4%) te zadebljanje pleure u tri bolesnika (16,6%). U deset bolesnika (55,5%) radiološki je utvrđena ILD, od čega ih je sedam imalo seropozitivni RA (70%). Uzorak uobičajene intersticijske pneumonije (UIP) bio je zastupljen u osam bolesnika (80%), dok je uzorak nespecifične intersticijske pneumonije (NSIP) utvrđen u dva bolesnika (20%). *Zaključak.* U bolesnika sa seropozitivnim RA-om utvrđena je veća prevalencija nodularne te intersticijske bolesti pluća, nego u seronegativnih bolesnika. Najčešći radiološki utvrđen uzorak ILD-a bio je UIP, što se poklapa s podatcima dostupnim iz literature.

Ključne riječi: artritis, reumatoidni, plućne bolesti, intersticijske

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disease whose prevalence is slightly less than 1% in developed countries (1). The most common extra-articular manifestation of RA is involvement of the lung parenchyma and pleura, primarily interstitial lung disease (ILD), with an estimated prevalence between 1.8% and 67% (2). In most patients, lung disease occurs within the period of nine years since RA diagnosis, although respiratory symptoms may precede the occurrence of joint disease in 2.3% to 10% of patients (3,4). Pleuropulmonary diseases in patients with RA include parenchymal lung diseases such as ILD and nodular lung disease, followed by airway diseases such as bronchiolitis, bronchiectasis, and chronic small airways obstruction, and pleural diseases such as pleurisy, pleural effusion, and pleural thickening. Chronic infections of the respiratory system can also be the cause of lung disease, particularly bronchiectasis. The impact of immunomodulators that increase the risk of developing infections, but can have a direct toxic effect on the lung parenchyma, is also important (4,5). Lung diseases present with symptoms such as exertion intolerance, chest pains and cough, but they can also be asymptomatic. Since pleuropulmonary diseases are responsible for 10–20% of mortality cases in patients with RA, clinical, functional and radiological monitoring is necessary in order to identify patients with progressive lung disease in the earliest possible stage (6,7). Factors that increase mortality include old age, male gender, history of smoking, low values of pulmonary function tests, pattern of usual interstitial pneumonia (UIP) shown on high-resolution computed tomography (HRCT), presence of emphysema, and acute exacerbation of ILD (8). Methotrexate (MTX) treatment is recommended as a first-line treatment for RA, as it effectively reduces disease activity, morbidity,

UVOD

Reumatoidni artritis (RA) je sustavna autoimuna bolest čija je prevalencija nešto manja od 1% u razvijenim zemljama (1). Najčešće izvanzglobno očitovanje RA jest zahvaćanje plućnog parenhima i pleure, ponajprije intersticijska bolest pluća (engl. interstitial lung disease, skr. ILD), s procijenjenom prevalencijom između 1,8% i 67% (2). U većine bolesnika bolest pluća javlja se unutar devet godina od postavljanja dijagnoze RA, iako respiratorni simptomi mogu prethoditi zglobnoj bolesti u 2,3% do 10% bolesnika (3,4). Pleuropulmonalni poremećaji u bolesnika s RA-om obuhvaćaju bolesti plućnog parenhima koje uključuju ILD te nodularnu bolest pluća, zatim bolesti dišnih putova koji uključuju bronhiolitis, bronhiektazije i kroničnu opstrukciju malih dišnih putova te bolesti pleure koje uključuju pleuritis, pleuralni izljev i zadebljanje pleure. Kronične infekcije dišnog sustava također mogu biti uzrok bolesti pluća, osobito bronhiektazija. Važan je i utjecaj imunomodulacijskih lijekova koji povećavaju rizik za razvoj infekcija, ali mogu imati izravni toksični učinak na plućni parenhim (4,5). Bolesti pluća prezentiraju se intolerancijom napora, bolovima u prsima te kašljem, međutim mogu biti i asimptomatske. Budući da su pleuropulmonalni poremećaji odgovorni za 10 – 20% smrtnosti u bolesnika s RA-om, neophodno je kliničko, funkcijsko i radiološko praćenje kako bismo što ranije prepoznali bolesnike s progresivnom bolešću pluća (6,7). Čimbenici koji povećavaju mortalitet uključuju stariju dob bolesnika, muški spol, anamnezu pušenja, snižene vrijednosti testova plućne funkcije, uzorak uobičajene intersticijske pneumonije (UIP) na kompjuteriziranoj tomografiji visoke rezolucije (engl. skr. HRCT), prisutnost emfizema te akutnu egzacerbaciju ILD-a (8). Liječenje metotreksatom (engl. skr. MTX) preporučuje se kao prva linija liječenja RA, budući da učinkovito smanjuje aktivnost bolesti, mor-

mortality, and the occurrence of RA-related ILD (RA-ILD) (9,10).

The aim of our study was to present the clinical features of patients with pleuropulmonary manifestations as part of RA, in a sample of patients treated with biologics or targeted synthetic disease-modifying antirheumatic drugs (DMARDs).

SUBJECTS AND METHODS

This retrospective observational study was conducted during the course of 2022 on patients with RA, who were treated with biologics and targeted synthetic DMARDs, at the Division of Rheumatology, Allergy and Clinical Immunology of the University Hospital Centre Split. Data taken from the medical records archived at the outpatient clinic, inpatient unit and day-care hospital of the Division were used in the study. Moreover, the study included patients older than 18 years of age who met the 2010 EULAR/ACR classification criteria for RA, which was the inclusion criterion for the participation in the study. The exclusion criteria included the presence of another inflammatory rheumatic disease other than RA and known lung disease, the occurrence of which is not dependent on the presence of RA. Lung involvement was based on the findings of the high-resolution CT (HRCT) of the chest. Age and gender of the subjects, presence of rheumatoid factor (RF) and antibodies to anti-cyclic citrullinated peptide (anti-CCP), disease duration, history of smoking, pleuropulmonary manifestations and therapy were analysed.

Methods of descriptive statistics were used in the analysis of the results.

RESULTS

A total of 188 patients with RA who were treated with biologics and targeted synthetic DMARDs were included in the study. There were 18 (9.6%) patients with pleuropulmonary manifestations of RA, whose average age was 66.5 (range: 48–85), and 13 of these patients were women (72.2%). 6 patients were smokers (33.3%) and four of them were women (66.6%). 12 patients were diagnosed with seropositive RA (66.6%), and four of these patients were smokers (33.3%). According to disease duration, we divided the subjects into three groups (<10 years, 10–20 years, >20 years), with 6 patients in each group (33.3%). Patients with seropositive RA and associated pleuropulmonary manifestations had the shortest disease duration (<10 years), and there were five of them (83.3%), with four of them being smokers (66.6%). Nodular lung disease was found in 12 patients (66.6%), and 9 of these patients had seropositive RA (75%). Bronchiectasis was found in 8 patients (44.4%) and pleural thickening in three

biditet, mortalitet te pojavu ILD-a povezanog s RA-om (RA-ILD) (9,10).

Cilj našeg istraživanja bio je prikazati klinička obilježja bolesnika s pleuropulmonalnim očitovanjima u sklopu RA, u uzorku bolesnika liječenih biološkim ili ciljanim sintetskim antireumaticima koji mijenjaju tijek bolesti (engl. skr. DMARDs).

ISPITANICI I METODE

U ovo retrospektivno opservacijsko istraživanje uključeni su bolesnici s RA-om, koji su liječeni biološkom terapijom i ciljanim sintetskim DMARDs-ima, u Zavodu za reumatologiju, kliničku imunologiju i alergologiju Kliničkoga bolničkog centra Split tijekom 2022. godine. Korišteni su podatci iz medicinske dokumentacije u ambulanti, stacionaru i dnevnoj bolnici Zavoda. U istraživanje su uključeni bolesnici stariji od 18 godina koji su zadovoljavali klasifikacijske kriterije EULAR/ACR iz 2010. godine za RA, što je bio uključni kriterij. Isključni kriteriji bili su prisutnost druge upalne reumatske bolesti osim RA te poznata bolest pluća neovisno o RA-u. Zahvaćenost pluća temeljila se na rezultatima HRCT-a prsišta. Analizirani su dob i spol ispitanika, prisutnost reumatoidnog faktora (RF) i antitijela na ciklički citrulirani peptid (anti-CCP), trajanje bolesti, povijest pušenja, pleuropulmonalna očitovanja i terapija.

U analizi rezultata korištene su metode deskriptivne statistike.

REZULTATI

Ukupno je uključeno 188 bolesnika s RA-om koji su liječeni biološkim i ciljanim sintetskim DMARDs-ima. Broj bolesnika s pleuropulmonalnim očitovanjima u sklopu RA bio je 18 (9,6%), a njihova prosječna životna dob bila je 66,5 godina (raspon: 48 – 85 godina), od čega je bilo 13 žena (72,2%). Među oboljelima, šest ispitanika su bili pušači (33,3%), od čega ih je četiri žene (66,6%). U dvanaest bolesnika dijagnosticiran je seropozitivni RA (66,6%), od kojih je četvero bilo pušača (33,3%). Prema trajanju bolesti, ispitanike smo podijelili u tri skupine (<10 godina, 10 – 20 godina, >20 godina) te smo dobili po šest bolesnika u svakoj skupini (33,3%). Bolesnici sa seropozitivnim RA-om i pridruženim pleuropulmonalnim očitovanjima imali su najkraće trajanje bolesti (<10 godina), a njih je bilo petero (83,3%), od čega je četvero bilo pušača (66,6%). Nodularna bolest pluća bila je zastupljena u dvanaest bolesnika (66,6%), od čega je njih devet imalo seropozitivni RA (75%). Bronhiektazije su nađene u osam bolesnika (44,4%) a zadebljanje pleure u tri bolesnika (16,6%). U deset bolesnika (55,5%) radiološki je utvrđena ILD, od čega ih je sedam imalo seropozitivni RA (70%). Uzorak uobičajene intersticijske pneumonije (UIP) bio je zastupljen u osam bolesnika (80%), dok je

Table 1 Pulmonary diseases in patients with rheumatoid arthritis
Tablica 1. Pleuropulmonalna očitovanja u bolesnika s reumatoidnim artritisom

	Year of birth / Godina rođenja	Gender/Spol	Disease duration in years / Trajanje bolesti u godinama	RF / anti-CCP	ILD /IBP	Nodular lung disease / Nodularna bolest pluća	Bronchiectasis / Bronhiektazije	Pleural thickening / Zadebljanje pleure	Smoking / Pušenje
1	1954.	Man/Muškarac		–	–	+	+	+	+
2	1964.	Woman/Žena		+	+	–	+	–	+
3	1959.	Woman/Žena	<10	+	+	+	–	+	–
4	1963.	Woman/Žena		+	+	+	–	–	+
5	1959.	Man/Muškarac		+	–	–	+	–	+
6	1953.	Man/Muškarac		+	–	+	–	–	–
7	1967.	Woman/Žena		+	–	+	–	–	–
8	1954.	Woman/Žena		+	–	+	–	–	–
9	1974.	Woman/Žena	10–20	–	+	–	–	–	–
10	1957.	Woman/Žena		+	+	+	+	–	–
11	1949.	Woman/Žena		–	+	–	+	–	–
12	1959.	Woman/Žena		–	+	–	+	–	+
13	1951.	Man/Muškarac		–	–	+	–	–	–
14	1957.	Woman/Žena		+	+	+	+	–	–
15	1937.	Woman/Žena	>30	+	+	+	–	–	+
16	1948.	Woman/Žena		+	–	+	–	+	–
17	1952.	Woman/Žena		+	+	–	+	–	–
18	1953.	Man/Muškarac		–	–	+	–	–	–

Legend / Legenda: RF – Rheumatoid factor / reumatoidni faktor, anti-CCP – Anti-Cyclic Citrullinated Peptide Antibody / antitijela na ciklički citrulirani peptid, ILD/IBP – interstitial lung disease / intersticijska bolest pluća

patients (16,6%). ILD was radiologically diagnosed in 10 patients (55.5%), and 7 of them had seropositive RA (70%). The pattern of usual interstitial pneumonia (UIP) was present in 8 patients (80%), while the pattern of non-specific interstitial pneumonia (NSIP) was found in two patients (20%) (Table 1). 8 patients (44.4%) were treated with rituximab, while four patients were treated with TNF-α and IL-6 inhibitors (22.2% in both cases), and two patients were treated with Janus kinase (JAK) inhibitors (11.1%). 10 patients (55.5%) were treated with concomitant therapy with methotrexate (MTX).

DISCUSSION

Pleuropulmonary diseases occur in 30–40% of patients with RA and are the second main cause of mortality, right after cardiovascular diseases (11). There are several factors associated with the development of lung disease in RA. It has been confirmed that lung disorders are associated with the male gender, seropositive RA, smoking and mucin-5B (MUC-5B) gene mutation. The MUC-5B polymorphism leads to inefficient removal of inhaled particles and pathogens in the respiratory system, increasing the risk for RA-ILD (3,4,12,13). The most common patterns on HRCT of the thorax in patients with RA-ILD are usual interstitial pneumonia (UIP), non-specific interstitial pneumonia (NSIP), lymphocytic interstitial pneumonia (LIP), organizing pneumonia (OP),

uzorak nespecifične intersticijske pneumonije (NSIP) utvrđen u dva bolesnika (20%) (tablica 1). Broj bolesnika liječenih rituksimabom bio je osam (44,4%), dok je po četvero bolesnika liječeno TNFα i IL-6 inhibitorima (oboje po 22,2%), a dvoje bolesnika inhibitorima Janus kinaze (JAK) (11,1%). Na konkomitantnoj terapiji s MTX-om bilo je deset bolesnika (55,5%).

RASPRAVA

Pleuropulmonalni poremećaji javljaju se u 30 – 40% bolesnika s RA-om i drugi su glavni uzrok smrtnosti, odmah iza kardiovaskularnih bolesti (11). Postoji više čimbenika povezanih s nastankom bolesti pluća u RA. Potvrđena je povezanost plućnih poremećaja s muškim spolom, seropozitivnim RA-om, pušenjem te mutacijom gena za mucin 5B (MUC5B). Polimorfizam MUC5B dovodi do neučinkovitog uklanjanja inhaliranih čestica i patogena u sluznici dišnog sustava, povećavajući rizik za nastanak RA-ILD-a (3,4,12,13). Najčešći uzorci na HRCT-u toraksa u bolesnika s RA-ILD-om su uobičajena intersticijska pneumonija (UIP), nespecifična intersticijska pneumonija (NSIP), limfocitna intersticijska pneumonija (LIP), organizirana pneumonija (OP),

spiratory mucosa, thus increasing the risk of RA-ILD development (3,4,12,13). The most common patterns found on chest HRCT in patients with RA-ILD are usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia (NSIP), lymphocytic interstitial pneumonia (LIP), organizing pneumonia (OP), acute interstitial pneumonia (AIP), and desquamative interstitial pneumonia (DIP) (6).

In our study, the proportion of patients with pleuropulmonary disorders in RA was 9.6%, with an average age of 66.5, which is in accordance with data from the literature. The subjects were predominantly female (72.2%), while in some studies, male predominance was established (3–5,7).

Smoking was present in 6 patients (33.3%), which is slightly less than in the researched literature, where smokers comprised more than 50% of subjects, especially with RA-ILD pattern found on chest HRCT (3, 4). In our study, the majority of smokers were female (66.6%), while in the multicentre study conducted by Kelly et al., a larger proportion of smokers were male (3). The RA-ILD pattern found on chest HRCT was present in all subjects who used tobacco products, in contrast to the aforementioned study conducted by Kelly and colleagues, which did not establish that smoking is a risk factor for the development of RA-ILD in women (3). The mentioned deviation may be a consequence of the smaller number of subjects in our study. It is believed that smoking induces the formation of enzymes that promote the modification of peptides in the lung parenchyma, that is, the conversion of arginine into citrulline, which binds to human leukocyte antigen II (HLA II) on antigen-presenting cells (the so-called "common epitope" HLA-DRB1). This type of a more immunogenic, citrullinated peptide is presented to T lymphocytes and leads to the formation of anti-CCP antibodies, activation of cytokines and growth factors (vascular endothelial growth factor — VEGF, platelet-derived growth factor — PDGF) that contribute to fibroblast proliferation (5,11,13,14).

Patients with RA have elevated values of circulating RF and anti-CCP antibodies, which can be present in the serum several years before the clinical onset of the disease. Both antibodies may be associated with the development of lung disease in RA, especially anti-CCP which is primarily associated with the development of RA-ILD (5,13). In our study, 12 patients were diagnosed with seropositive RA (66.6%), which is in accordance with data from the literature (3, 4). However, we found that in the case of 5 patients (83.3%) with seropositive RA there was a significantly shorter period until the diagnosis of lung disease (<10 years) and that four of them were smokers (66.6%). This data shows that seropositivity and smoking lead to an earlier onset of pulmonary manifestations in patients with RA.

akutna intersticijska pneumonija (AIP) i deskvamativna intersticijska pneumonija (DIP) (6).

U našem istraživanju, udio bolesnika s pleuropulmonalnim poremećajima u RA-u bio je 9,6%, s prosječnom dobi 66,5 godina, što je u skladu s podatcima iz literature. Prevladavale su osobe ženskog spola (72,2%), dok je u nekim istraživanjima utvrđena predominacija muškog spola (3–5,7).

Pušenje je bilo zastupljeno u šest bolesnika (33,3%), što je nešto manje nego u pretraženoj literaturi, gdje su pušači obuhvaćali više od 50% ispitanika, osobito s uzorkom RA-ILD-a na HRCT-u toraksa (3,4). U našem istraživanju većina pušača bile su osobe ženskog spola (66,6%), dok je u multicentričnom istraživanju Kellyja i suradnika veći udio pušača bio muškoga spola (3). Uzorak RA-ILD-a na HRCT-u toraksa bio je zastupljen u svih ispitanica koje su koristile duhanske proizvode, za razliku od navedenog istraživanja Kellyja i suradnika koje nije utvrdilo da je pušenje rizični čimbenik za razvoj RA-ILD-a u žena (3). Spomenuto odstupanje moguće je posljedica manjeg broja ispitanika u našem istraživanju. Smatra se da pušenje inducira nastanak enzima koji potiču modifikaciju peptida u plućnom parenhimu, odnosno konverziju arginina u citrulin koji se veže za humani leukocitni antigen II (HLA II) na antigen-predočnim stanicama (tzv. „zajednički epitop" HLA-DRB1). Takav imunogeničniji, citrulirani peptid predočuje se T-limfocitima te dovodi do stvaranja anti-CCP antitijela, aktivacije citokina i čimbenika rasta (čimbenik rasta vaskularnog endotela – VEGF, čimbenik rasta podrijetlom iz trombocita – PDGF) koji pridonose proliferaciji fibroblasta (5,11,13,14).

Bolesnici s RA-om imaju povišene vrijednosti cirkulirajućih antitijela RF i anti-CCP, koja mogu biti prisutna u serumu i nekoliko godina prije kliničke pojave bolesti. Oba antitijela mogu biti povezana s nastankom bolesti pluća u RA, osobito anti-CCP koji je povezan ponajprije s razvojem RA-ILD-a (5,13). U našem istraživanju, u dvanaest bolesnika dijagnosticiran je seropozitivni RA (66,6%), što je u skladu s podatcima iz literature (3,4). Ipak, utvrdili smo da je pet bolesnika (83,3%) sa seropozitivnim RA-om imalo značajno kraće vrijeme do postavljanja dijagnoze bolesti pluća (<10 godina) te da ih je četvero bilo pušača (66,6%). Ovaj podatak pokazuje da seropozitivitet i pušenje dovode do ranije pojave plućnih očitovanja u bolesnika s RA-om.

U našem istraživanju najzastupljenija bolest plućnog parenhima bila je nodularna bolest pluća u dvanaest bolesnika (66,6%), što je nešto više nego u dostupnoj literaturi u kojoj je prevalencija iznosila između 1% i 32% (4,15–17). Ovo odstupanje u našim rezultatima može biti povezano s manjim brojem ispitanika. Druga po zastupljenosti bila je RA-ILD u deset ispitanika (55,5%), od kojih ih je sedam (70%) imalo seropozitivni RA. Prema dostupnoj literaturi, vjerojatnost da će bole-

In our study, the most common disease of the lung parenchyma was nodular lung disease, which was found in 12 patients (66.6%), which is slightly more than in the available literature, where the prevalence was between 1% and 32% (4,15–17). This deviation in our results may be related to a smaller number of subjects in our study. The second most common disease of the lung parenchyma was RA-ILD, which was found in 10 subjects (55.5%), and 7 of them (70%) had seropositive RA. According to the available literature, the probability that patients with RA will develop ILD is nine times higher than in the general population, and the prevalence of RA-ILD in other studies was as high as 67% (2,4–6,15–17). In our study, the most common RA-ILD pattern found on chest HRCT was the UIP pattern (80%), which is slightly higher than in the available studies, which could be a consequence of late diagnosis of pulmonary manifestations (4,15,17). Bronchiectasis was the most common manifestation of respiratory diseases and was present in 8 patients (44.4%), four of whom were smokers (50%). In other studies, the prevalence of bronchiectasis was somewhat lower and was up to 30% (5,15–17). More frequent bronchiectasis are probably caused by smoking and chronic inflammation. The most common manifestation of pleural involvement was pleural thickening, which was present in 3 subjects (16.6%). All subjects with involvement of the pleura also had nodular lung disease. In other studies, a slightly lower frequency of involvement of the pleura was demonstrated, approximately between 3 and 5%, and this primarily includes pleural effusions (5,15–17). It should be noted that it was difficult to make an estimation of prevalence due to the great heterogeneity among studies and the imaging methods used for the purpose of making a diagnosis. Given that malignant diseases can present with symptoms that are similar to those of nodular lung disease, the importance of multidisciplinary collaboration with pulmonologists should be highlighted.

In patients with RA, it is important to immediately evaluate the presence of pulmonary manifestations, the severity of the disease, and identify patients with progressive disease through further monitoring. Factors suggestive of progressive disease are worsening symptoms, low values of pulmonary function tests (PFTs), and/or radiological progression. It is recommended to perform pulmonary function tests in all patients who are newly diagnosed with RA. In asymptomatic patients, pulmonary function tests should be performed once a year, and in the case of RA-ILD confirmed through HRCT, they should be repeated every 6 months (18). Disease severity and progression are two major factors to consider when deciding on immunomodulatory treatment in patients with RA-ILD. Among other things, it is necessary to consider other

snici s RA-om razviti ILD devet je puta veća u odnosu na opću populaciju te je prevalencija RA-ILD-a u drugim istraživanjima iznosila i do 67% (2,4–6,15–17). U našem istraživanju najzastupljeniji uzorak RA-ILD-a na HRCT-u toraksa bio je uzorak UIP-a (80%), što je nešto više nego u dostupnim istraživanjima, što bi moglo biti posljedica kasnijeg dijagnosticiranja plućnih promjena (4,6,15,17). Bronhiektazije su bile najčešća očitovanja bolesti dišnih putova te su bile zastupljene u osam bolesnika (44,4%), a njih četvero je bilo pušača (50%). U drugim istraživanjima prevalencija bronhiektazija bila je nešto manja te je iznosila do 30% (5,15–17). U podlozi učestalijih bronhiektazija vjerojatno su pušenje i kronična upala. Najčešća manifestacija zahvaćenosti plućne ovojnice bilo je zadebljanje pleure, što je bilo prisutno u tri ispitanika (16,6%). Svi su ispitanici sa zahvaćenom pleurom imali i nodularnu bolest pluća. U drugim istraživanjima dokazana je nešto manja učestalost zahvaćanja pleure, otprilike između 3% i 5%, i to ponajprije pleuralni izljevi (5,15–17). Potrebno je napomenuti da je procjena prevalencije bila otežana zbog velike heterogenosti među studijama i slikovnih metoda korištenih za postavljanje dijagnoze. Budući da se i maligne bolesti mogu prezentirati slično nodularnoj bolesti pluća, valja istaknuti važnost multidisciplinarne suradnje sa specijalistima pulmologije.

U bolesnika s RA-om važno je odmah u početku procijeniti prisutnost plućnih manifestacija i težinu bolesti te daljnjim praćenjem prepoznati bolesnike s progresivnom bolešću. Čimbenici koji upućuju na progresivnu bolest jesu pogoršanje simptoma, smanjenje testova plućne funkcije (PFT) i/ili radiološka progresija. Preporučljivo je obaviti testove plućne funkcije u svih novodijagnosticiranih bolesnika s RA-om. U asimptomatskih bolesnika testovi plućne funkcije trebali bi se kontrolirati jednom godišnje, a u slučaju HRCT-om utvrđene RA-ILD potrebno ih je ponavljati svakih šest mjeseci (18). Ozbiljnost i progresija bolesti dva su glavna čimbenika koja treba uzeti u obzir pri odlučivanju o imunomodulacijskom liječenju u bolesnika s RA-ILD-om. Među ostalim, potrebno je razmotriti i druge čimbenike, poput dobi i komorbiditeta kao i želje bolesnika kod donošenja terapijskih odluka (15,18). U našem istraživanju deset bolesnika bilo je na konkomitantnom liječenju metotreksatom (55,5%). Juge i suradnici su također u svom istraživanju naveli slične podatke koji su uključivali između 55,3% i 66,7% ispitanika liječenih metotreksatom te su dokazali smanjenu pojavnost RA-ILD-a u tih bolesnika (10). Osim konvencionalne terapije, osam ispitanika u našem istraživanju liječeno je rituksimabom (44,4%), po četvero je liječeno inhibitorima TNF-α i IL-6 (oboje po 22,2%) te dvoje ispitanika inhibitorima JAK (11,1%). U kohortnoj studiji provedenoj u Ujedinjenom Kraljevstvu rituksimab je pokazao zadovoljavajući sigurnosni profil u bolesni-

factors, such as age and comorbidities, as well as the patient's wishes when it comes to making decisions regarding treatment (15,18). In our study, 10 patients received concomitant treatment with methotrexate (55.5%). In their study, Juge et al also reported similar data, which included between 55.3% and 66.7% of subjects treated with methotrexate, and they proved a reduced incidence of RA-ILD in these patients (10). In addition to conventional therapy, 8 subjects in our study were treated with rituximab (44.4%), four of them were treated with TNF-α and IL-6 inhibitors (22.2% in both cases) and two subjects were treated with JAK inhibitors (11.1%). In a UK cohort study, rituximab showed a satisfactory safety profile in patients with RA-ILD, with stable or improved lung function over a 10-year follow-up period, which is similar to the results of a smaller study conducted by Fui et al (19,20). A study conducted by Detorakis et al. which included 82 subjects with RA, showed an effective and favourable safety profile of TNF-α inhibitors in these patients. Therefore, no new ILDs or exacerbations of already existing ILDs were found in the studied population (21). Treatment with tocilizumab has also shown a potential role in the stabilization of lung disease (6,22). In a retrospective cohort study conducted by Baker et al. RA patients treated with a JAK inhibitor had the lowest incidence of ILD compared to patients treated with biologics (23). Therefore, JAK inhibitors are introduced as the drug of choice in patients with ILD as part of RA.

CONCLUSION

In our sample of patients with RA who were treated with biologics or targeted synthetic DMARDs, a higher prevalence of nodular and interstitial lung diseases was found in seropositive patients than in seronegative patients. Therefore, it is necessary to conduct more intensive clinical, functional and radiological monitoring of patients with seropositive RA, especially smokers, in order to prevent the progression of lung disease. The most common radiological pattern of RA-ILD was usual interstitial pneumonia (UIP).

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ka s RA-ILD-om, uz stabilnu ili poboljšanu plućnu funkciju tijekom desetogodišnjeg razdoblja praćenja, slično kao i istraživanje Fui i suradnika s manjim brojem ispitanika (19,20). Istraživanje Detorakisa i suradnika koje je uključivalo 82 ispitanika s RA-om pokazalo je učinkovit i povoljan sigurnosni profil inhibitora TNF-α u ovih bolesnika. Dakle, nisu utvrđene novonastale ILD ili egzacerbacija već postojećih ILD-a u ispitivanoj populaciji (21). Liječenje tocilizumabom također je pokazalo potencijalnu ulogu u stabilizaciji plućne bolesti (6,22). U retrospektivnom kohortnom istraživanju Bakera i suradnika bolesnici s RA-om liječeni inhibitorom JAK imali su najmanju incidenciju ILD-a u usporedbi s bolesnicima liječenim biološkom terapijom (23). Stoga se inhibitori JAK nameću kao lijek izbora u bolesnika s ILD-om u sklopu RA.

ZAKLJUČAK

U našem uzorku bolesnika s RA-om liječenih biološkim ili ciljanim sintetskim DMARDs-ima, u seropozitivnih bolesnika utvrđena je veća prevalencija nodularne te intersticijske bolesti pluća nego u seronegativnih bolesnika. Stoga je bolesnike sa seropozitivnim RA-om, posebice pušače, neophodno intenzivnije klinički, funkcijski i radiološki nadzirati radi sprječavanja progresije bolesti pluća. Najčešći radiološki uzorak RA-ILD-a bio je UIP.

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