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EFFECTIVENESS OF BIOLOGICS IN PATIENTS WITH RHEUMATOID ARTHRITIS – A SINGLE-CENTER EXPERIENCE

UČINKOVITOST BIOLOŠKIH LIJEKOVA U BOLESNIKA S REUMATOIDNIM ARTRITISOM – ISKUSTVA JEDNOG CENTRA

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Abstract

In the case of ineffectiveness of synthetic disease-modifying anti-rheumatic drugs (DMARDs) in the treatment of patients with active rheumatoid arthritis (RA), we can use one of the biological or biosimilar drugs according to the Croatian Society for Rheumatology guidelines from 2013. Despite the achieved remission and better disease control, according to literature data up to 60% of patients develop primary or secondary ineffectiveness of the drug.

In order to determine primary or secondary ineffectiveness of the drug in our patients, we retrospectively analyzed data from patients treated with biological drugs at the Division of Clinical Immunology, Allergology, and Rheumatology of the Department of Internal Medicine of the University of Zagreb School of Medicine, Clinical Hospital Dubrava, in the period 2008–2016.

The study included 88 patients, 25 men and 63 women. The activity of the disease was monitored using the DAS28(CRP) index.

In 39 patients (44%), 10 men and 29 women, the first biological drug was replaced with another. Out of these 39 patients, 30 (77%) achieved remission on the second line of treatment. Seven (18%) patients had to be given a third biological drug because of the ineffectiveness of the second drug, while two patients had to be given a fourth or fifth biological drug.

The most common cause of discontinuation of the drug was clinical ineffectiveness, which means that the high activity of the disease was maintained. We did not find a statistically significant difference in the titer of rheumatoid factor (RF) and/or anti-citrulatory peptide (anti-CCP) or smoking status in patients treated with a single biological agent and those in which two or more biological drugs had to be used.

Keywords: Arthritis, rheumatoid – drug therapy, immunology; Biological factors – therapeutic use; Antirheumatic agents – therapeutic use; Tumor necrosis factor-alpha – antagonists and inhibitors; Antibodies, monoclonal – immunology, therapeutic use; Severity of ilness index; Remission induction; Treatment outcome

Sažetak

Pri neučinkovitosti sintetskih lijekova koji modificiraju tijek bolesti (engl. *disease-modifying antirheumatic drugs* – DMARDs; u tekstu DMARD-i) u liječenju bolesnika s aktivnim reumatoidnim artritisom (RA) možemo primijeniti jedan od bioloških ili biosličnih lijekova prema smjernicama Hrvatskoga reumatološkog društva iz 2013. godine. Unatoč postignutoj remisiji i boljoj kontroli bolesti primarna ili sekundarna neučinkovitost lijeka razvije se, prema literaturnim podacima, čak u 60% bolesnika.

Radi utvrđivanja primarne odnosno sekundarne neučinkovitosti lijeka retrospektivno smo analizirali podatke bolesnika liječenih biološkim lijekovima u Zavodu za kliničku imunologiju, alergologiju i reumatologiju Klinike za unutarnje bolesti Medicinskog fakulteta Sveučilišta u Zagrebu, Kliničke bolnice Dubrava, od 2008. do 2016. god. Aktivnost bolesti praćena je indeksom DAS 28-CRP. U ispitivanje je bilo uključeno 88 bolesnika, 25 muškaraca i 63 žene.

U 39 bolesnika (44%), 10 muškaraca i 29 žena, prvi biološki lijek zamijenjen je drugime. Od 39 bolesnika, njih 30 (77%) postiglo je remisiju na primijenjeni drugi biološki lijek, a u sedam bolesnika (18%) zbog neučinkovitosti lijeka uveden je treći biološki lijek, dok je u dva bolesnika uveden i četvrti, odnosno peti lijek. Najčešći razlog prekida primjene lijeka bila je klinička neučinkovitost (visoka aktivnost bolesti). Nismo pronašli statistički značajnu razliku u titru reumatoidnog faktora, anticitrulinskih protutijela ni pušačkog statusa u bolesnika liječenih jednim biološkim lijekom i onih liječenih drugim, trećim ili većim brojem bioloških lijekova.

Ključne riječi: Reumatoidni artritis – farmakoterapija, imunologija; Biološki lijekovi – terapijska uporaba; Antireumatici – terapijska uporaba; Čimbenik tumorske nekroze alfa – antagonisti i inhibitori; Monoklonska protutijela – imunologija, terapijska uporaba; Ocjena težine bolesti; Indukcija remisije; Ishod liječenja

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic progressive autoimmune disease characterized by symmetrical polyarthritis affecting small joints on the hands and feet. In non-treated or inadequately treated patients, advanced disease leads to a significantly reduced quality of life, disability, and reduced lifespan. RA prevalence is around 1%, and women are affected more often than men (1). The etiology of RA is still unclear, although the disease seems to be caused by both environmental and genetic factors (2). Due to a better understanding of the pathophysiological processes in RA (3), the last 20 years have seen the development of medications directed at inhibiting the inflammatory process. The current approach to RA treatment requires early diagnosis (4, 5), so that the treatment may start as early as possible. The goal of the treatment is disease remission and preservation of the joint function and work capacity, or prevention of further progression of structural joint destruction (6). According to the 2013 Croatian Society for Rheumatology (HRD) recommendations (7), treatment with one of the DMARDs (methotrexate as the gold standard) should be introduced immediately after diagnosis. If remission is not achieved within six months of therapy with at least two DMARDs, the use of a biologic or biosimilar drug is indicated. Literature data indicate that, despite the improved remission rates with the use of biologics and/or biosimilars, ineffectiveness of the drug develops in up to 60% of the patients (8, 9).

The aim of our study was to determine the effectiveness of treatment with biologics or biosimilars in the group of patients with RA.

UVOD

Reumatoidni artritis (RA) sustavna je autoimunosna bolest progresivnog tijeka, koju označava simetrični poliartritis malih zglobova šaka i stopala. U neliječenih ili neadekvatno liječenih bolesnika uznapredovala bolest dovodi do znatno smanjene kvalitete života, invaliditeta i skraćenoga životnog vijeka. Prevalencija je RA oko 1%, a češće se javlja u žena (1). Etiologija RA i dalje je nejasna iako je poznato da je posljedica okolišnih i genskih čimbenika (2). Razumijevanjem patofizioloških procesa u RA (3) u posljednjih 20-ak godina proizvedeni su lijekovi kojima možemo usmjereno inhibirati upalni proces. Suvremeni pristup liječenju RA nalaže rano prepoznavanje bolesti (4, 5) radi što ranijeg započinjanja liječenja. Cilj liječenja, uz postizanje remisije, jest očuvanje funkcionalne, a time i radne sposobnosti sprječavanjem ili zaustavljanjem daljnje progresije strukturnih oštećenja zglobova (6). Prema preporukama Hrvatskoga reumatološkog društva (HRD) iz 2013. g. (7), liječenje treba započeti nakon postavljanja dijagnoze jednim od DMARD-a (metotreksat je zlatni standard). Ako se ne postigne remisija uz primjenu najmanje dvaju DMARD-a tijekom šest mjeseci od uvođenja lijekova, indicirana je primjena jednog od dostupnih bioloških ili biosličnih lijekova. Literaturni podatci upućuju na to da se unatoč boljem postizanju remisije primjenom bioloških i/ili biosličnih lijekova i u do 60% bolesnika razvije jedan od oblika neučinkovitosti na lijek (8, 9).

Cilj rada je bio istražiti učinkovitost liječenja biološkim i biosličnim lijekovima u grupi bolesnika s RA.

PATIENTS AND METHODS

We retrospectively analyzed the data of patients treated with biologics or biosimilars at the Division of Clinical Immunology, Allergology, and Rheumatology of the Department of Medicine of the University of Zagreb School of Medicine, University Hospital Dubrava, between 2008 and 2016, and followed up during 2017. Data were collected from the hospital information system and included age, sex, disease duration, smoking status, serological findings (rheumatoid factor [RF] and anti–cyclic citrullinated peptide [anti-CCP]), and time from diagnosis to introduction of the first biologic. All patients included in the analysis met the 2013 Croatian Society for Rheumatology criteria for the use of a biologic and/or biosimilar. The composite index Disease Activity Score in 28 joints with C-reactive protein (DAS28CRP) was used to assess the disease activity and thereby the effectiveness of the administered drug. DAS28 was recorded in 2016 and 2017 at the last two consecutive follow-up visits, irrespective of the time when the drug was introduced. We identified the patients who achieved a significant clinical improvement (reduction by ≥0.6 units DAS28, and DAS28 ≤5.1), patients achieving low activity of the disease (DAS28 ≤3.2), patients having achieved remission (DAS28 ≤2.6) at the last follow-up visit, those with positive RF and/or anti-CCP, and active smokers, as well as whether those parameters had any effect on the treatment outcome.

Statistical analysis

Normality of data distribution for numerical variables was tested by Shapiro-Wilk test. If distribution was not normal, the numerical variables were presented as median with interquartile range (IQR) and compared between groups using the Mann-Whitney U and Kruskal-Wallis ANOVA tests. Categorical variables were presented as ratios or percentages and compared between the groups using chi-square or Fisher's tests. At two timepoints the DAS28 values were compared using the Wilcoxon test for paired samples. In case of multiple comparisons, Bonferroni's correction was used. $P<0.05$ was considered statistically significant. Statistical analyses were performed with the MedCalc statistical program, version 17.9.6 (MedCalc Software bvba, Ostend, Belgium).

The study was performed according to the ethical standards and the Declaration of Helsinki, and approved by the Ethics Committee of the University Hospital Dubrava.

RESULTS

The study included a total of 88 patients treated with biologics or biosimilars (Table 1). Remission or low-

ISPITANICI I METODE

Retrospektivno smo analizirali podatke bolesnika koji su započeli liječenje biološkim ili biosličnim lijekovima u Zavodu za kliničku imunologiju, alergologiju i reumatologiju Klinike za unutarnje bolesti Medicinskog fakulteta Sveučilišta u Zagrebu, KB-a Dubrava, od 2008. do 2016. godine, a bili su na kontrolnim pregledima tijekom 2017. godine. Podatci su prikupljeni iz bolničkog informacijskog sustava (BIS). Evaluirani podatci uključili su dob, spol, trajanje bolesti, pušački status, serološke nalaze (RF, anti-CCP) i vrijeme između postavljanja dijagnoze do uvođenja prvoga biološkog lijeka. Svi bolesnici uključeni u ovo ispitivanje ispunjavali su kriterije za primjenu biološkog ili biosličnog lijeka prema smjernicama HRD-a iz 2013. godine. Radi procjene aktivnosti bolesti, a time i učinkovitosti primijenjenog lijeka upotrijebljen je kompozitni indeks DAS 28-CRP. Zabilježili smo njegovu vrijednost u 2016. i 2017. g., tijekom posljednje dvije uzastopne kontrole, neovisno o vremenu uvođenja lijeka. Utvrdili smo koliko je bolesnika postiglo signifikantno kliničko poboljšanje (smanjenje ≥ 0,6 jedinica DAS 28 i DAS 28 ≤ 5,1), koliko ih je postiglo nisku aktivnost bolesti (DAS 28 ≤ 3,2) i koliko ih je postiglo remisiju bolesti (DAS 28 ≤ 2,6) na posljednjem kontrolnom pregledu. Istražili smo koliko je bolesnika bilo s pozitivnim RF-om i/ili anti-CCP-om, koliko je bilo aktivnih pušača i utječu li ti parametri na ishod liječenja.

Statističke metode

Normalnost distribucije numeričkih varijabla analizirana je s pomoću Shapiro-Wilkova testa. Numeričke varijable nisu pratile normalnu distribuciju pa su prikazane kao medijani interkvartilni raspon (IKR) i uspoređene su između grupa Mann-Whitneyevim U-testom i Kruskal-Wallisovim ANOVA-testom. Kategorijske varijable prikazane su kao omjeri i postotci, a između skupina uspoređene su hi-kvadratnim testom (χ2-test) ili Fisherovim testom. Vrijednosti DAS 28 u dvije vremenske točke uspoređene su primjenom Wilcoxonova testa za uparene uzorke. P-vrijednosti niže od 0,05 smatrane su statistički značajnima. Pri više istodobnih usporedba upotrijebljena je Bonferronijeva korekcija. Za analize smo rabili statistički program *MedCalc*, verziju 17.9.6 (*MedCalc Software bvba*, Ostend, Belgija).

Istraživanje je provedeno u skladu s etičkim standardima Etičkog povjerenstva Kliničke bolnice Dubrava i Helsinškom deklaracijom iz 1975. godine, revidiranom 1983. godine.

REZULTATI

U istraživanje je uključeno ukupno 88 bolesnika od kojih je 49 održavalo remisiju ili nisku aktivnost bole-

Table 1. Characteristics of patients, according to number of drugs used, and overall.
*Tablica 1. Značajke bolesnika, prema broju primijenjenih lijekova i ukupno**

Number of biologic drugs used / Broj primijenjenih bioloških lijekova	1	2	≥ 3	Total / Svi	*P* value / P-vrijednost
Number of patients / Broj bolesnika	49	30	9	88	
Age (median, IQR; years) / Dob (medijan i IKR**, godine)	47 IKR (37 – 53)	45,5 IKR (39 – 54)	49 IKR (43 – 51)	46 IKR (38 – 54)	0.935
Sex / Spol					
Men / Muškarci	15/49 (30,6%)	6/30 (20%)	4/9 (44,4%)	25/88 (28,4%)	0.317
Women / Žene	34/49 (69,4%)	24/30 (80%)	5/9 (55,6%)	63/88 (71,6%)	
Smokers / Pušači	13/48 (27,1%)	5/29 (17,2%)	4/9 (44,4%)	22/86 (25,6%)	0.247
RF positive / RF-pozitivnost	36/46 (78,3%)	22/29 (75,9%)	9/9 (100%)	67/84 (79,8%)	0.270
Anti-CCP positive / Anti-CCP pozitivnost	31/43 (72,1%)	20/26 (76,9%)	7/9 (77,8%)	58/78 (74,4%)	0.878

**For some variables data were missing / Za neke varijable podatci nisu bili dostupni.*
Legend / Legenda: IQR/IKR – interquartile range / interkvartilni raspon; RF – rheumatoid factor / reumatoidni faktor; anti-CCP – anti–cyclic citrullinated peptide / anticiklički citrulinski peptid.

Table 2. Average time of introduction of biologic/biosimilar drugs compared with the duration of disease and the average value of DAS28 index prior to treatment with biologic/biosimilar drugs.
Tablica 2. Prosječno vrijeme uvođenja biološkog/biosličnog lijeka u odnosu prema trajanju bolesti i prosječne vrijednosti indeksa DAS 28 prije početka liječenja biološkim/biosličnim lijekovima, u godinama

Parameter / Parametar	Number of biologic drugs used (median, interquartile range) / Broj primijenjenih bioloških lijekova (medijan, interkvartilni raspon)				*P* value / P-vrijednost
	1	2	≥ 3	total / svi	
DAS28 before the first biologic drug / DAS 28 prije uvođenja prvoga biološkog lijeka	5.7 (5.2–6.1)	5.4 (3.5–6.5)	5.3 (4.2–5.7)	5.5 (5.1–6.1)	0.532
Duration of disease (years) / Trajanje bolesti (godine)	10 (6–16)	13.5 (10–20.8)	11 (8–12)	11 (8–16.3)	0.134
Time from diagnosis to introduction of biologic drug (years) / Vrijeme od postavljanja dijagnoze do uvođenja biološkog lijeka (godine)	6 (3–9)	7 (4.5–10.3)	3 (2–5)	6 (3–9)	0.061

activity disease was maintained in 49 of 88 patients on the first biologic, whereas 33 of 88 patients achieved remission after the first biologic was replaced by another biologic or biosimilar. Nine of 88 patients received three or more different biologics. There were no statistically significant changes in baseline characteristics between patients who received one, two, three, or more biologic drugs. Age, sex, smoking, DAS28 index at the start of the biologic therapy, and a combination of RF and anti-CCP were not significantly associated with the need to switch drugs (P>0.05 for all comparisons, Table 1). The number of smokers was slightly, but not significantly, higher in the group of patients requiring three or more different biologics than in the other subgroups (Table 1).

We analyzed the average time that elapsed between the diagnosis and start of biologic therapy with respect to the number of biologics used (Table 2). Patients who

sti uz primjenu prvoga biološkog lijeka, a u njih 30 remisija je postignuta nakon zamjene prvoga biološkog lijeka drugime. Devetero bolesnika liječeno je trećim biološkim lijekom ili većim brojem njih. Osnovne značajke bolesnika prikazane su na tablici 1. Nismo našli statistički značajne razlike u osnovnim značajkama među bolesnicima koji su promijenili jedan, dva odnosno tri ili više bioloških lijekova. Dob, spol, pušenje, indeks DAS 28 pri uvođenju biološkog lijeka, RF, anti-CCP, kao ni kombinacija RF-a i anti-CCP-a nisu bili statistički značajno povezani s potrebom promjene lijeka (P > 0,05 za sve usporedbe; tablica 1.). Nešto veći udio pušača bio je u skupini bolesnika koji su trebali liječenje trećim biološkim lijekom ili većim brojem njih u odnosu prema ostalim skupinama, ali razlika nije bila statistički značajna (P = 0,247; tablica 1.). Na tablici 2. naveden je vremenski prosjek između postavljanja dijagnoze bolesti do uvođenja bioloških lijekova

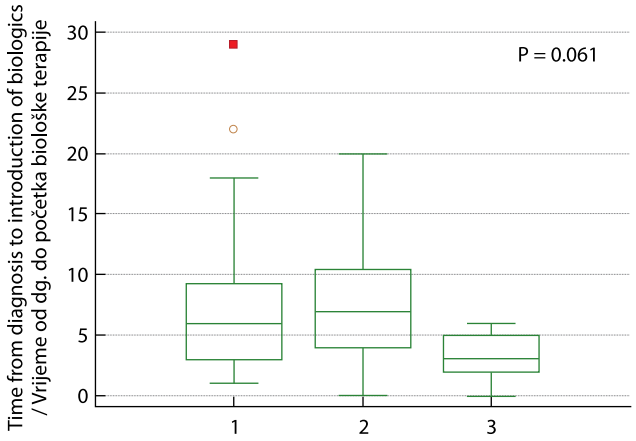

FIGURE 1 Time from diagnosis to introduction of biologics (in years), according to number of used biologics.
SLIKA 1. Vrijeme između postavljene dijagnoze i početka primjene biološkog lijeka (u godinama), prema broju primijenjenih bioloških lijekova

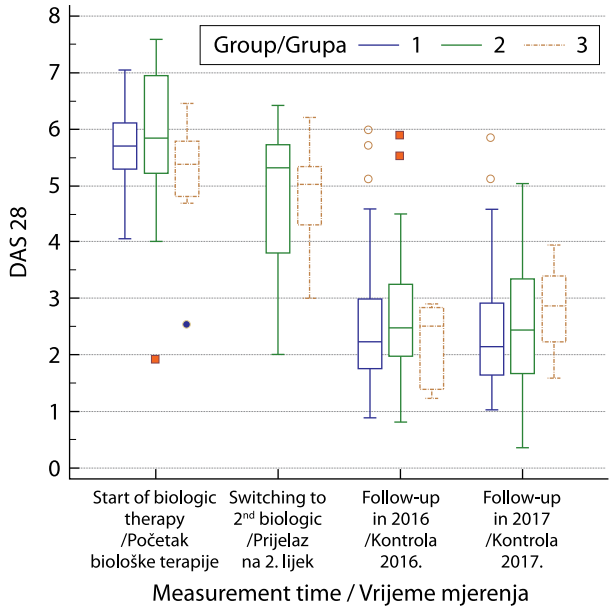

FIGURE 2 Dynamics of the DAS28 index in particular patient groups.
SLIKA 2. Dinamika kretanja indeksa DAS 28 u pojedinim grupama bolesnika

maintained a low-activity level or remission while on their first biologic started treatment within 6 months of RA diagnosis. In patients who had to switch to the second biologic due to ineffectiveness of the first one, the treatment started within seven years from RA diagnosis. In those switching to the third, fourth, or fifth biologic, treatment started within 3 years from the diagnosis (P=0.061). In patients who changed three or more biologic drugs, the time period between the diagnosis and the start of treatment was shorter than in the other groups (P=0.022, not significant according to 3 concomitant comparisons; Figure 1). We analyzed DAS28 changes in the period from the time of diagnosis to the follow-up visits in 2016 and 2017 (Figure 2). The patients who received different numbers of biologics did not differ in DAS28 index values at the start of biologic therapy (P=0.532; Table 2). No difference in DAS28 index values determined one year apart was found between the patients treated with different numbers of biologics (Table 3). Biologics or biosimilars used as first-line treatment in 88 patients included adalimumab (24 patients), etanercept (22 patients), tocilizumab (15 patients), infliximab (11 patients), biosimilar infliximab – Inflectra (5 patients), golimumab (4 patients), rituximab (4 patients), biosimilar infliximab – Remsima (2 patients), and certolizumab (1 patient). The median duration of exposure to the first biologic or biosimilar was 3 years (IQR, 3–4) and showed no statistically significant difference between the groups (P=0.123). Biologics or biosimilars used as second-line treatment in 39 patients included tocilizumab (13 patients), etanercept (12 patients), adalimumab (9 patients), golimumab (2 patients), rituximab (2 patients), and biosimilar infliximab Remsima (1 patient). Biologics or biosimilars used as third-line treatment in 9 patients included tocilizumab (8 patients) and rituxu odnosu prema broju primijenjenih lijekova. Bolesnici koji su održavali nisku aktivnost bolesti ili remisiju na prvome biološkom lijeku u prosjeku su počeli liječenje u šest godina nakon postavljanja dijagnoze RA. Bolesnici kojima je prvi biološki lijek zbog neučinkovitosti zamijenjen drugim počeli su liječenje prosječno u sedam godina od postavljanja dijagnoze, dok su oni kojima je uveden treći biološki lijek ili više njih počeli liječenje u prosjeku tri godine nakon postavljanja dijagnoze bolesti, a rezultat nije bio statistički značajan (ukupni P = 0,061). Bolesnici kojima su promijenjena tri ili više bioloških lijekova najprije su počeli liječenje biološkim lijekom od postavljanja dijagnoze u odnosu prema ostalim skupinama (P = 0,022; rezultat nije zna-

TABLE 3. DAS28 index in two follow-up measurements during one year.
TABLICA 3. Indeks DAS 28 u dva kontrolna mjerenja u razmaku od jedne godine

Number of drugs administered / Broj primijenjenih lijekova	Year of measurement 2016 (median, IQR*) / Mjerenje 2016. (medijan i IKR*)	Year of measurement 2017 (median, IQR*) / Mjerenje 2017. (medijan i IKR)	*P* value / P-vrijednost
1	2,2 IKR (1,7 – 2,9)	2,2 IKR (1,6 – 2,9)	0.734
2	2,5 IKR (1,9 – 3,2)	2,3 IKR (1,6 – 3,3)	0.458
≥ 3	2,5 IKR (1,4 – 2,8)	2,8 IKR (2,0 – 3,4)	0.250

** IQR/IKR – interquartile range / interkvartilni raspon*

Table 4. Reason for discontinuation of therapy.
Tablica 4. Razlog prekida primjene lijeka

	Number (%) of patients / Broj i postotak (%) bolesnika N=38
High disease activity (%)* / Visoka aktivnost bolesti (%)*	29 (76%)
Erythema at the administration site (%) / Eritem na mjestu primjene (%)	2 (0.05%)
Anaphylaxis (%) / Anafilaksija (%)	1 (0.03%)
Psychotic episode (%) / Psihotični napadaj (%)	1 (0.03%)
Malignant disease (%) / Maligna bolest (%)	1 (0.03%)
Radiological progression (%)** / Radiološka progresija (%)**	3 (0.07%)
Myalgia (%) / Mialgije (%)	1(0,03%)

** DAS 28 (CRP) index >5.1.;*
***as shown by ultrasound, magnetic resonance imaging, or computed tomography / promjene na ultrazvuk, magnetska rezonancija ili kompjuterizirana tomografija*

imab (1 patient). A revision performed in 2017 showed that of 48 patients in the first group, 23 were in remission, 17 had low-activity disease, and 7 had achieved significant clinical improvement. Of 30 patients who had to receive a second biologic/biosimilar drug, 11 had achieved remission, 10 had low-activity disease, and 9 showed significant clinical improvement. In the third group of 9 patients, 2 patients were in remission, 4 had low-activity disease, and 3 had achieved a significant clinical improvement. The most common reason for discontinuation was persistent high-activity disease, i.e., DAS28>5.1. Three patients showed radiological progression of the disease, and the treatment was discontinued in a few patients due to pronounced local reactions at the administration site or myalgia (Table 4).

DISCUSSION

The retrospective analysis included RA patients treated with biologics or biosimilars between 2008 and 2016. Treatment was performed in accordance with the Croatian Society for Rheumatology 2013 guidelines, which recommend introducing biologic or biosimilar therapy after a patient has been treated with a minimum of 2 synthetic DMARDs including metotrexate, during 6 months in full dosage. The first biologic or biosimilar must be a TNF-alpha inhibitor. The assessment of treatment effectiveness was performed every 3 months in order to achieve remission according to the "treat to target" principle after 6 months from treatment onset. In case that one of the biologics was ineffective, switching to another drug from the same or a different class was recommended, and therapy

čajan s obzirom na 3 istodobne usporedbe; slika 1.). Analizirali smo dinamiku kretanja DAS 28 od trenutka postavljanja dijagnoze i za vrijeme kontrolnih pregleda u sve tri skupine tijekom 2016. i 2017. godine (slika 2.). Na tablici 2. vidi se da se bolesnici koji su promijenili jedan, dva, tri ili više bioloških lijekova nisu razlikovali u vrijednostima DAS 28 pri početku liječenja biološkim lijekom (P = 0,532). Nije bilo razlike u vrijednostima DAS 28 tijekom razmaka od godine dana u pojedinim grupama bolesnika liječenih različitim brojem lijekova u pojedinim kategorijama bolesnika (tablica 3.). Primjenjivani biološki ili biosličnи lijekovi u prvoj liniji bili su: adalimumab u 24/88 (27,3%) bolesnika, etanercept u njih 22/88 (25%), tocilizumab u 15/88 (17%), infliksimab u 11/88 (12,5%), biosličan infliksimab – Inflectra u 5/88 (5,7%), golimumab u 4/88 (4,5%), rituksimab u 4/88 (4,5%), biosličan infliksimab – Remsima u 2/88 (2,3%) i certolizumab u 1/88 (1,1%) bolesnika. Medijan razdoblja izloženosti prvom lijeku bio je 3 godine, interkvartilni raspon (IKR) (3 – 4) i nije se statistički značajno razlikovao između skupina bolesnika (P = 0,123). Primjenjivani biološki lijekovi u drugoj liniji bili su: tocilizumab u 13 od 39 (33,3%) bolesnika, etanercept u njih 12 od 39 (30,8%), adalimumab u 9 od 39 (23,1%), golimumab u 2 od 39 (5,1%), rituksimab u 2 od 39 (5,1%) i biosličan infliksimab – Remsima u jednog od 39 (2,6%) bolesnika. U trećoj su liniji primjenjivani tocilizumab u 8 od 9 (88,9%) bolesnika i rituksimab u jednog od njih 9 (11,1%). Pri reviziji učinjenoj 2017. g. u prvoj skupini bolesnika njih 23/48 (48%) bilo je u remisiji bolesti, 17/48 (35%) imalo je nisku aktivnost bolesti, a 7/48 (15%) postiglo je znatno kliničko poboljšanje. Od 30 bolesnika koji su morali primiti drugi lijek, njih 11 (37%) postiglo je remisiju, 10 (33%) imalo je nisku aktivnost bolesti, a kod 9 (30%) postiglo se znatno kliničko poboljšanje. U trećoj skupini bolesnika 2/9 (22%) bilo je u remisiji, 4/9 (44%) imalo je nisku aktivnost bolesti, a 3/9 (33%) postiglo je znatno kliničko poboljšanje. Najčešći razlog prekida primjene lijeka bila je i dalje visoka aktivnost bolesti, tj. DAS 28 > 5,1. U troje bolesnika utvrđena je radiološka progresija bolesti, a kod nekoliko njih liječenje je prekinuto zbog izraženih reakcija na mjestu aplikacije lijeka ili mialgija (tablica 4.).

RASPRAVA

U ovom je radu provedena retrospektivna analiza podataka bolesnika liječenih biološkim ili biosličnim lijekom u razdoblju od 2008. do 2016. g., kojima je terapija uvedena u skladu s tada vrijedećim smjernicama HRD-a iz 2013. g., a prema kojima liječenje biološkim ili biosličnim lijekovima započinje nakon što je bolesnik liječen minimalno s 2 sintetska DMARD-a tijekom šest mjeseci u punoj dozi, od kojih je jedan obvezatno MTX. Prvi biološki ili biosličan lijek mora biti

py was adjusted individually for each patient. According to the current 2018 Croatian Society for Rheumatology guidelines for biologic therapy, first-line treatment includes all TNF-alpha inhbitors (original and biosimilar), tocilizumab, rituximab, and JAK-inhibitors as monotherapy or in combination with other synthetic DMARDs. This may have a large impact on future study results (10). Currently, there are no known biological markers to predict the effectiveness of individual biologics in individual patients. Patients seropositive for RA are known to have a more progressive clinical course of the disease with a more pronounced destruction of bones and joints (11, 12). Also, smoking was shown to have a poor effect on the disease outcome (13, 14). If a biosimilar or biologic is not effective, it should be determined if the ineffectiveness is primary or secondary. Primary ineffectiveness is defined by the lack of clinical response within the first 6–12 weeks from the start of therapy (15), whereas secondary ineffectiveness means the loss of effect of the drug over time. The mechanisms of development of ineffectiveness are not completely elucidated. Different cytokines and their dominant role in the inflammatory process in individual patients are a possible cause of primary inefficiency (16). Secondary inefficiency may partly be explained by the production of neutralizing antibodies against the drug (17). Clinical studies and clinical experience indicate that administration of a second drug with the same mechanism of action may elicit a satisfactory response in RA patients. Jamnitski et al. (18) found that patients treated with adalimumab or infliximab in whom antibodies were detected achieved a similar clinical response after switching to etanercept as patients who were treated with etanercept as first-line therapy (18). Similar results were obtained in patients treated with infliximab who were switched to adalimumab irrespective of the presence of anti-drug antibodies (19). In everyday clinical practice, anti-drug antibodies are not routinely determined. In case of inefficiency, the plasma concentration of the drug may be measured. Several studies found that smoking, an independent predictor of a more progressive course of the disease, did not affect the effectiveness of tocilizumab therapy (20, 21), but nevertheless led to a poorer clinical response in smokers than in non-smokers (22). Smoking induces an immune response, immunosuppression, secretion of numerous proinflammatory cytokines, and DNA damage. The mechanism of poor response to TNF-alpha inhibitors is partly explained by the increased production of TNF-alpha and TNF-alpha receptors in smokers, which leads to a faster degradation of the circulating drug in plasma (23). Although our study did not include a large number of patients, switching to three or more biologic drugs was recorded more frequently in smokers.

onaj iz skupine inhibitora TNF-alfa. Procjena učinkovitosti liječenja provodila se svaka 3 mjeseca, radi postizanja remisije prema principu *treat-to-target*, 6 mjeseci nakon početka liječenja. Pri neučinkovitosti jednog od bioloških lijekova preporučen je prelazak na drugi lijek iz iste ili druge skupine, individualnom prilagodbom terapije prema bolesniku. Prema danas dostupnim smjernicama HRD-a za uvođenje biološke terapije iz 2018. g., prva linija liječenja uključuje sve inhibitore TNF-alfa (originalne i biosličnе), tocilizumab, rituksimab i inhibitore JAK-a kao monoterapiju ili u kombinaciji s drugim sintetskim DMARD-om, što će uvelike utjecati na rezultate budućih studija (10). Zasad ne raspolažemo biološkim biljezima koji bi predvidjeli učinkovitost djelovanja pojedinoga biološkog lijeka u pojedinca. Poznato je da bolesnici sa seropozitivnim RA imaju progresivniji klinički tijek bolesti s izraženijom destrukcijom koštano-zglobnih struktura (11, 12). Također, utvrđeno je da pušenje, posebice kod nositelja gena HLA-DRB1, zbog promjene u citrulinaciji proteina utječe na lošiji ishod bolesti (13, 14). Ako primijenjeni biološki ili biosličnи lijek nije učinkovit, moramo utvrditi radi li se o primarnoj ili sekundarnoj neučinkovitosti. Primarna neučinkovitost definirana je izostankom kliničkog odgovora u prvih 12 – 16 tjedana od početka primjene lijeka (15), a sekundarna kao gubitak učinkovitosti lijeka tijekom vremena. Mehanizmi nastanka neučinkovitosti lijeka nisu potpuno razjašnjeni. Različiti ključni citokini i njihova dominantnost pri upalnom procesu u pojedinog bolesnika moguć su razlog primarne neučinkovitosti (16). Sekundarna neučinkovitost može se dijelom objasniti stvaranjem protutijela koja neutraliziraju lijek (17). Klinička ispitivanja, kao i kliničko iskustvo upućuju na to da se primjenom drugog lijeka istog mehanizma djelovanja može u bolesnika s RA postići zadovoljavajući odgovor. Anna Jamnitski i suradnici pokazali su da su bolesnici liječeni adalimumabom ili infliksimabom, a kod kojih su detektirana protutijela, nakon što su bili „prebačeni" (engl. *cycling*) na etanercept postigli sličan klinički odgovor poput skupine bolesnika liječenih etanerceptom kao prvim biološkim lijekom (18). Slični rezultati dobiveni su kod bolesnika liječenih infliksimabom koji su „prebačeni" na adalimumab, bez obzira na to jesu li bila prisutna protutijela na lijek ili nisu (19). U svakodnevnoj kliničkoj praksi određivanje protutijela na lijek nije rutinska metoda. Pri neučinkovitosti možemo određivati i koncentraciju lijeka u plazmi. Veći broj istraživanja utvrdio je da je pušački status, kao posebni prediktivni čimbenik za progresivniji tijek bolesti, iako nije utjecao na učinkovitost liječenja tocilizumabom (20, 21), ipak dovodio do lošijega kliničkog odgovora nego što je zabilježeno u nepušača (22). Pušenje dovodi do indukcije imunosnog odgovora, imunosupresije, izlučivanja brojnih proupalnih

Although biologics were introduced relative late in the treatment (on average, after 11 years from diagnosis), the treatment efficiency rate was satisfactory. Almost half of our patients had to be switched to another biologic drug, which is in line with other studies (24, 25) and meta-analyses (26, 27).

CONCLUSION

Our retrospective study included middle-aged and elderly patients with long-term RA lasting 11 years on average, who were first treated with biologic or biosimilar therapy after more than 6 years from diagnosis. The study limitations were a relatively small sample size and a heterogeneous patient population. We could not identify any factors predictive of poor response to therapy. Early diagnosis and early introduction of biologic therapy will result in a better treatment response, as well as in the identification of factors predictive of treatment response.

Conflict of interest statement: Authors declare no conflict of interest.

citokina i oštećenja DNK. Mehanizam lošijeg odgovora na inhibitore TNF-alfa dijelom se objašnjava pojačanim stvaranjem citokina TNF-alfa, kao i receptora TNF-alfa kod pušača, što dovodi do brže razgradnje cirkulirajućeg lijeka u plazmi (23). U našem istraživanju koje nije uključivalo velik broj ispitanika utvrdili smo da je promjena lijeka na treći ili veći broj bioloških lijekova zabilježena češće u bolesnika koji su bili pušači. Nadalje, unatoč relativno kasnom uvođenju bioloških lijekova u naših bolesnika (u prosjeku 11 godina) od početka bolesti stopa učinkovitosti liječenja bila je zadovoljavajuća. Naime, 45% bolesnika iziskivalo je promjenu lijeka, što se podudara s rezultatima istraživanja drugih autora (24, 25) i rezultatima metaanaliza (26, 27).

ZAKLJUČAK

Rezultati našega retrospektivnog istraživanja, ograničenog malenim brojem bolesnika i heterogenim uzorkom, upućuju na to da je riječ o bolesnicima srednje do starije dobi, s dugogodišnjim RA prosječnog trajanja bolesti oko 11 godina, a koji su prvim biološkim ili biosličnim lijekom liječeni u prosjeku nakon više od 6 godina od postavljanja dijagnoze. Nismo utvrdili koji su prediktivni čimbenici lošeg odgovora na lijek. Rano postavljanje dijagnoze i ranije uvođenje biološkog lijeka, kao i prepoznavanje prediktivnih čimbenika odgovora na lijek zasigurno će polučiti bolji odgovor na primijenjenu terapiju.

Izjava o sukobu interesa: Autori izjavljuju da nisu u sukobu interesa.

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