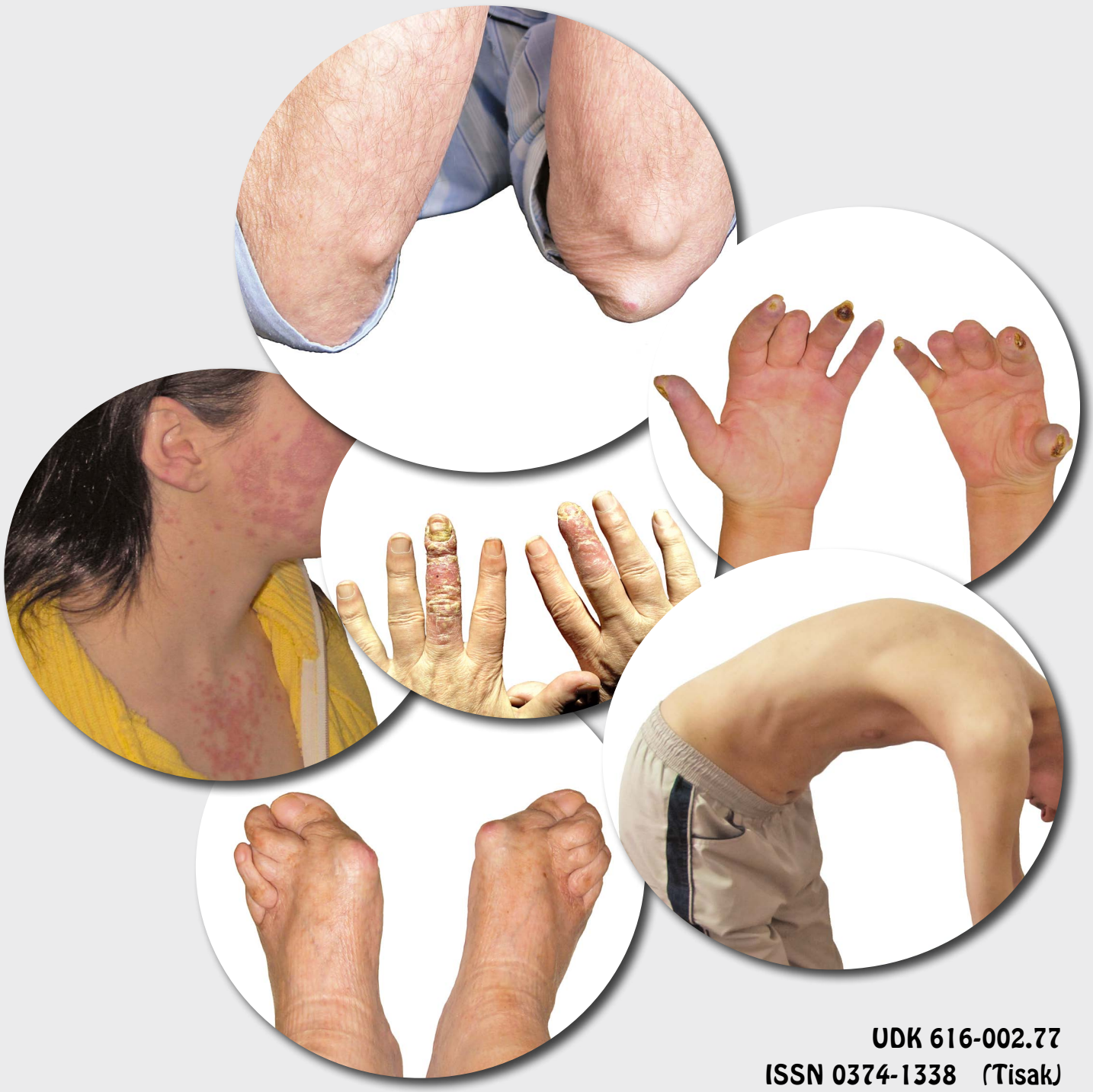
Časopis Hrvatskoga reumatološkog društva
Hrvatskoga liječničkog zbora

REUMATIZAM

Volumen 66 Broj 1 Godina 2019.



UDK 616-002.77
ISSN 0374-1338 (Tisak)
ISSN 2459-6159 (Online)

JUNE 2019
VOLUME 66 • NUMBER 1

REUMATIZAM

Journal of the Croatian Rheumatology Society of the CMA

Publisher
Hrvatsko reumatološko društvo HLZ-a, Zagreb

Editor-in-Chief
Simeon Grazio
glavni-urednik-reumatizam@reumatologija.org

Editor
Nadica Laktašić-Žerjavić
urednik-reumatizam@reumatologija.org

Secretary
Hana Skala-Kavanagh
tajnik-reumatizam@reumatologija.org

Scientific consultant
Armen Yuri Gasparyan

Educational and social media editor
Olena Zimba

Editors-in-Chief
Drago Čop (1954.–1963.)
Theodor Dürrigl (1963.–1990.)
Ivo Jajić (1991.–1998.)
Goran Ivanišević (1999.–2013.)
Simeon Grazio (2014.–)

Editorial address
REUMATIZAM
Klinika za reumatologiju, fizikalnu medicinu i rehabilitaciju,
KBC Sestre milosrdnice,
Vinogradska 29,
10000 Zagreb, Hrvatska

Croatian language editing
Branko Erdeljac

English language editing
Aleksandra Žmegač Horvat

Translation
Aleksandra Mišak

Front page design
Zvonimir Barišić

Graphic design and typesetting
Gredice, Zagreb

Printing
Printera, Sveta Nedelja

Circulation
400

Printed finished
June 2019

Reumatizam (Rheumatism) is the official peer-reviewed journal of the Croatian Society for Rheumatology of the Croatian Medical Association. The journal is published twice a year.

Reumatizam publishes editorials, scientific papers, professional papers, brief communications (reports), reviews, preliminary reports and case reports. It informs professionals in the field of rheumatology on developments that affect clinical and nonclinical aspect of their practices.

Periodically, supplements with abstracts or full-texts presented at the congresses or symposia are published. The journal brings relevant information on the evaluation of diagnostic and therapeutic procedures, as well as on comprehensive care for individuals with rheumatic diseases.

Papers are published in English and Croatian, provided they are not already published elsewhere.

Free On-line Access to Internet Edition
http://www.reumatologija.org/engCasopis.aspx
http://reumatizam.hlz.hr/
https://hrcak.srce.hr/reumatizam

LIPANJ 2019.
VOLUMEN 66 • BROJ 1

REUMATIZAM

Časopis Hrvatskoga reumatološkog društva HLZ-a

Izdavač
Hrvatsko reumatološko društvo HLZ-a, Zagreb

Glavni urednik
Simeon Grazio
glavni-urednik-reumatizam@reumatologija.org

Urednica
Nadica Laktašić-Žerjavić
urednik-reumatizam@reumatologija.org

Tajnica redakcije
Hana Skala-Kavanagh
tajnik-reumatizam@reumatologija.org

Savjetnik za znanost
Armen Yuri Gasparyan

Urednik za izobrazbu i društvene medije
Olena Zimba

Glavni urednici
Drago Čop (1954.–1963.)
Theodor Dürrigl (1963.–1990.)
Ivo Jajić (1991.–1998.)
Goran Ivanišević (1999.–2013.)
Simeon Grazio (2014.–)

Adresa uredništva
REUMATIZAM
Klinika za reumatologiju, fizikalnu medicinu i rehabilitaciju,
KBC Sestre milosrdnice,
Vinogradska 29,
10000 Zagreb, Hrvatska

Lektor za hrvatski jezik
Branko Erdeljac

Lektor za engleski jezik
Aleksandra Žmegač Horvat

Prijevod
Aleksandra Mišak

Rješenje naslovne stranice
Zvonimir Barišić

Grafički dizajn i slog
Gredice, Zagreb

Tisak
Printera, Sveta Nedelja

Naklada
400

Tiskanje dovršeno
Lipanj 2019.

Reumatizam, službeno glasilo Hrvatskoga reumatološkog društva Hrvatskoga liječničkog zbora, je recenzirani časopis, koji redovito izlazi dva puta godišnje.

Reumatizam objavljuje uvodnike, znanstvene radove, stručne radove, kratka priopćenja, pregledne radove, prethodna izvješća i prikaze bolesnika. Časopis obavještava reumatologe o novostima u kliničkom i nekliničkom djelokrugu rada.

Reumatizam povremeno, kao suplement, objavljuje sažetke i/ili cjelovite radove s kongresa i simpozija. Časopis čitatelju daje bitne obavijesti u svezi evaluacije dijagnostičkih i terapijskih postupaka, odnosno pružanja sveobuhvatne skrbi osobama s reumatskim bolestima i stanjima.

Radovi se objavljuju na engleskom i hrvatskom jezikom uz uvjet da već nisu u istom obliku objavljeni drugdje.

Besplatan pristup internet izdanju časopisa
http://www.reumatologija.org/Casopis.aspx
http://reumatizam.hlz.hr/
https://hrcak.srce.hr/reumatizam

CONTENT / *SADRŽAJ*

Reumatizam 2019;66(1):1–9
https://doi.org/10.33004/reumatizam-66-1-1

PROFESSIONAL PAPER STRUČNI RAD

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

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

Marijana Šupe[1], Ana Gudelj Gračanin[2], Marko Lucijanić[3], Jadranka Morović-Vergles[2]

[1]General Hospital of Šibenik-Knin County, Šibenik, Croatia
/ Opća bolnica Šibensko-kninske županije, Šibenik, Hrvatska
[2]Division of Rheumatology, Allergology, and Clinical Immunology, Department of Internal Medicine, School of Medicine, University of Zagreb, University Hospital Dubrava, Zagreb, Croatia
/ Zavod za kliničku imunologiju, alergologiju i reumatologiju, Klinika za unutarnje bolesti Medicinskog fakulteta Sveučilišta u Zagrebu, Klinička bolnica Dubrava, Zagreb
[3]Division of Hematology, Department of Medicine, School of Medicine, University of Zagreb, University Hospital Dubrava, Zagreb, Croatia
/ Zavod za hematologiju, Klinika za unutarnje bolesti Medicinskog fakulteta Sveučilišta u Zagrebu, Klinička bolnica Dubrava, Zagreb

Corresponding author / Adresa autora za dopisivanje:
Marijana Šupe, dr. med.
General Hospital of Šibenik-Knin County / Opća bolnica Šibensko-kninske županije
Department of Internal Medicine / Odjel interne medicine
Ul. Stjepana Radića 83
22000 Šibenik, Croatia / Hrvatska
E-mail: supe.marijana@gmail.com

Received / Primljeno: July 3, 2018 / 3. 7. 2018.
Accepted / Prihvaćeno: October 11, 2018 / 11. 10. 2018.

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 Women / Žene	 15/49 (30,6%) 34/49 (69,4%)	 6/30 (20%) 24/30 (80%)	 4/9 (44,4%) 5/9 (55,6%)	 25/88 (28,4%) 63/88 (71,6%)	0.317
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

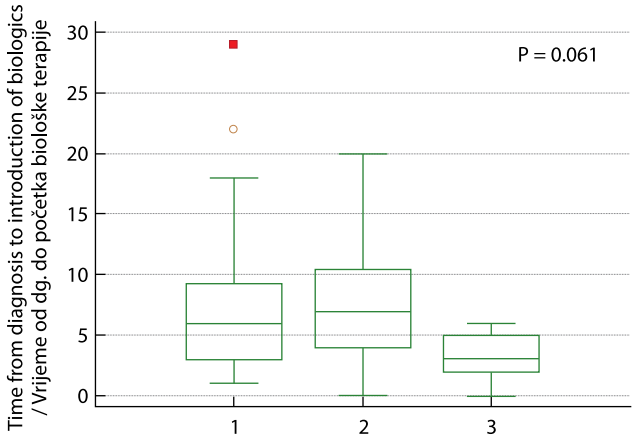


FIGURE 1 Time from diagnosis to introduction of biologics (in years), according to number of used biologics.
SLIKA 1. Vrijeme između postavljene dijagnoze i početka primjene biološkog lijeka (u godinama), prema broju primijenjenih bioloških lijekova

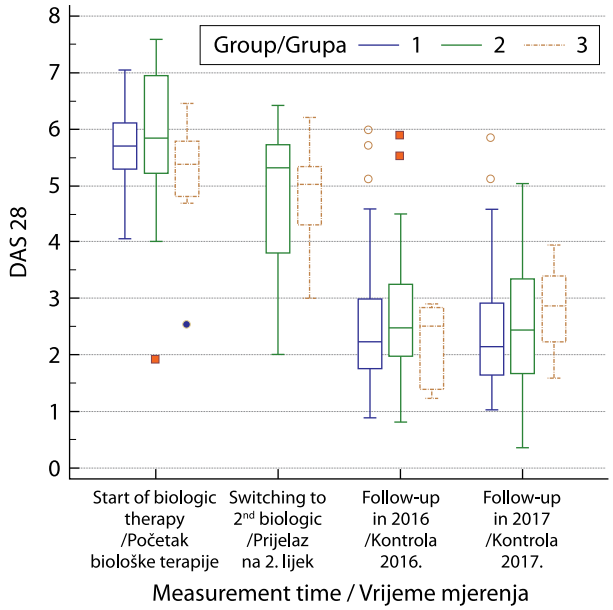


FIGURE 2 Dynamics of the DAS28 index in particular patient groups.
SLIKA 2. Dinamika kretanja indeksa DAS 28 u pojedinim grupama bolesnika

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 biosličnі 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.

REFERENCES / LITERATURA

1. Gabriel SE. The epidemiology of rheumatoid arthritis. Rheum Dis Clin North Am. 2001;27:269–81.
2. Angelotti F, Parma A, Cafaro G, Capecchi R, Alunno A, Puxeddu I. One year in review 2017: pathogenesis of RA. Clin Exp Rheumatol. 2017;35:368–78.
3. Furst DE, Emery P. Rheumatoid arthritis pathophysiology: update on emerging cytokine and cytokine-associated cell targets. Rheumatology (Oxford). 2014;53:1560–9.
4. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3. i sur. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis. 2010; 69:1580–8.
5. Van Steenbergen HW, Aletaha D, Beaart-van de Voorde LJ, Brouwer E, Codreanu C, Combe B i sur. EULAR definition of arthralgia suspicious for progression to rheumatoid arthritis. Ann Rheum Dis. 2017;76:491–6.
6. Smolen JS, Landewé R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M i sur. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis. 2017;76:960–77.
7. Ćurković B, Babić-Naglić Đ, Morović-Vergles J, Anić B, Grazio S, Martinović Kaliterna D i sur. Prijedlog primjene bioloških lijekova u reumatoidnom artritisu. Reumatizam. 2010;57(1): 29–35.
8. García-Lagunar MH, Gutiérrez-Cívicos MR, García-Simón MS, Conesa-Zamora P, Jimenez-Santos E, Cano-Vivar P i sur. Reasons for Discontinuation and Adverse Effects of TNFα Inhibitors in a Cohort of Patients With Rheumatoid Arthritis and Ankylosing Spondylitis. Ann Pharmacother. 2016;51(5): 388–93.
9. Aaltonen K, Ylikylä S, Tuulikki Joensuu J, Isomäki P, Pirilä L, Kauppi M i sur. Efficacy and effectiveness of tumour necrosis factor inhibitors in the treatment of rheumatoid arthritis in randomized controlled trials and routine clinical practice. Rheumatology (Oxford). 2017;56(5):725–35.
10. Mitrović J, Morović-Vergles J, Martinović Kaliterna D, Anić B, Babić-Naglić Đ, Grazio S i sur. Prijedlog preporuka Hrvatskoga reumatološkog društva za liječenje bolesnika s reumatoidnim artritisom biološkim i ciljanim sintetskim lijekovima, 2017. Reumatizam. 2017;64(2):65–70.
11. Kroot EJ, De Jong BA, van Leeuwen MA i sur. The prognostic value of anti-cyclic citrullinated peptide antibody in patients with recent-onset rheumatoid arthritis. Arthritis Rheum. 2000;43:1831–5.
12. Berglin E, Johansson T, Sundin U i sur. Radiological outcome in rheumatoid arthritis is predicted by presence of antibodies against cyclic citrullinated peptide before and at disease onset, and by IgA-RF at disease onset. Ann Rheum Dis. 2006;65: 453–8.
13. Padyukov L, Silva C, Stolt P, Alfredsson L, Klareskog L. A gene-environment interaction between smoking and shared epitope genes in HLA-DR provides a high risk of seropositive rheumatoid arthritis. Arthritis Rheum. 2004;50:3085–92.
14. Linn-Rasker SP, van der Helm-van Mil AHM, van Gaalen FA i sur. Smoking is a risk factor for anti-CCP antibodies only in rheumatoid arthritis patients who carry HLA-DRB1 shared epitope alleles. Ann Rheum Dis. 2006;65:366–71.
15. Tak PP. A personalized medicine approach to biologic treatment of rheumatoid arthritis: a preliminary treatment algorithm. Rheumatology (Oxford). 2012;51(4):600–9.
16. Ulfgren A, Gröndal L, Lindblad S i sur. Interindividual and intra-articular variation of proinflammatory cytokines in patients with rheumatoid arthritis: potential implications for treatment. Ann Rheum Dis. 2000;59:439–47.
17. Wolbink GJ, Vis M, Lems W i sur. Development of antiinfliximab antibodies and relationship to clinical response in patients with rheumatoid arthritis. Arthritis Rheum. 2006;54: 711–5.
18. Jamnitski A, Bartelds GM, Nurmohamed MT i sur. The presence or absence of antibodies to infliximab or adalimumab determines the outcome of switching to etanercept. Ann Rheum Dis. 2011;70(2):284–8.
19. Bartelds GM, Wijbrandts CA, Nurmohamed MT i sur. Anti-infliximab and anti-adalimumab antibodies in relation to response to adalimumab in infliximab switchers and anti-tumour necrosis factor naive patients: a cohort study. Ann Rheum Dis. 2010;69(5):817–21.
20. Specker C, Kellner H, Kästner P i sur. AB0396 Tocilizumab i.v. effectiveness in ra patients is independent of smoking status. Ann Rheum Dis. 2017;76:1187.
21. Pers YM, Fortunet C, Constant E i sur. Predictors of response and remission in a large cohort of rheumatoid arthritis patients treated with tocilizumab in clinical practice. Rheumatology (Oxford). 2014;53:76–84.
22. Hyrich KL, Watson KD, Silman AJ, Symmons DP; British Society for Rheumatology Biologics Register. Predictors of response to anti-TNF-α therapy among patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. Rheumatology (Oxford). 2006;45(12):1558–65.
23. Abhishek A, Butt S, Gadsby K, Zhang W, Deighton CM. Anti-TNF-alpha agents are less effective for the treatment of rheumatoid arthritis in current smokers. J Clin Rheumatol. 2010; 16(1):15–8.
24. Ramiro S, Landewé R, van der Heijde D i sur. Discontinuation rates of biologics in patients with rheumatoid arthritis: are TNF inhibitors different from non-TNF inhibitors? RMD Open. 2015;1(1):e000155.
25. Notario Ferreira I, Ferer González M, Morales Garrido P, González Utrilla A, García Sanchez A, Soto Pino MJ i sur. Two-year efficacy of tocilizumab in patients with active rheumatoid arthritis in clinical practice. Reumatol Clin. 2017;13(2):78–84.
26. Arora A, Mahajan A, Spurden D, Boyd H, Porter D. Long-Term Drug Survival of TNF Inhibitor Therapy in RA Patients: A Systematic Review of European National Drug Registers. Int J Rheum. 2013;2013:764518.
27. Kearsley-Fleet L, Davies R, De Cock D i sur.; BSRBR-RA Contributors Group. Biologic refractory disease in rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. Ann Rheum Dis. 2018;77(10):1405–12.

Reumatizam 2019;66(1):10–25
https://doi.org/10.33004/reumatizam-66-1-2

PROFESSIONAL PAPER STRUČNI RAD

BIOLOGIC THERAPY AND PREGNANCY – A TERTIARY CENTER EXPERIENCE

BIOLOŠKA TERAPIJA I TRUDNOĆA – ISKUSTVO TERCIJARNOG CENTRA

Marija Bakula, Paula Kilić, Mislav Cerovec, Miroslav Mayer, Branimir Anić

Division of Clinical Immunology and Rheumatology, Department of Internal Medicine, University of Zagreb School of Medicine, Universitiy Hospital Center Zagreb, Croatia / Zavod za kliničku imunologiju i reumatologiju, Klinika za unutarnje bolesti, Klinički bolnički centar Zagreb, Zagreb, Hrvatska

Corresponding author / Adresa autora za dopisivanje:
Marija Bakula, dr. med.
Division of Clinical Immunology and Rheumatology / Zavod za kliničku imunologiju i reumatologiju
Department of Internal Medicine / Klinika za unutarnje bolesti
University of Zagreb School of Medicine / Medicinski fakultet Sveučilišta u Zagrebu
Universitiy Hospital Center Zagreb / Klinički bolnički centar Zagreb
Kišpatićeva 12, Zagreb
Tel: 01 2388 330, Fax: 01 2388 335
E-mail: marijaandrassy@gmail.com

Received/Primljeno: September 17, 2018 / 17. 9. 2018.
Accepted/Prihvaćeno: February 10, 2019 / 10. 2. 2019.

Abstract

Treatment of inflammatory rheumatic diseases and control of disease activity have considerably improved after the introduction of biologic therapy over a decade ago. The safety profile of biologic therapy in the preconception period as well as during pregnancy and lactation is neccessary to consider when planning the treatment of young female patients.

Neither the Food and Drug Administration Agency nor the European Medicines Agency have declared biologic therapy safe during pregnancy. Both the European League Against Rheumatism and the British Society for Rheumatology proposed guidelines for the treatment of female rheumatology patients during pregnancy and lactation, and the American College of Rheumatology is currently developing guidelines for the therapeutic approach during pregnancy. On the other hand, there are numerous publications of pregnancy outcomes in patients treated with biologic therapy, with a small number of adverse effects.

We analyzed the modalities of biologic therapy and pregnancy outcomes in patients treated at our Department, during planned and unplanned pregnancies. Our results do not differ from the literature published to date. Among the patients described here, 15 were treated with an inhibitor of tumor necrosis factor-α and one with an IL-6 inhibitor during or just before pregnancy. Only 2 patients stopped biologic therapy in compliance with the guidelines. Of the 16 aforementioned patients, 3 had to undergo medically-induced abortion; one patient because of a severe fetal malformation and the other two patients because they had been treated with conventional disease-modifying antirheumatic drugs, which are contraindicated during pregnancy.

Keywords: Rheumatic diseases – drug therapy; Pregnancy complications – drug therapy; Antirheumatic agents – therapeutic use; Biological products – therapeutic use; Tumor necrosis factor-alpha – antagonists and inhibitors; Antibodies, monoclonal, humanized – therapeutic use; Pregnancy outcome

Sažetak

Biološka se terapija primjenjuje u liječenju upalnih reumatskih bolesti posljednjih desetak godina čime se znatno unaprijedila kontrola aktivnosti bolesti. Sigurnost primjene biološke terapije u pretkoncepcijskom razdoblju te tijekom trudnoće i laktacije veoma je važna pri planiranju liječenja mladih bolesnica.

Ni Američka agencija za hranu i lijekove ni Europska agencija za lijekove do danas nisu nijedan biološki lijek proglasile sigurnim u trudnoći. Europska liga protiv reumatizma i Britansko reumatološko društvo predložili su

smjernice za liječenje reumatoloških bolesnica tijekom trudnoće i laktacije, dok Američko reumatološko društvo trenutačno izrađuje smjernice za terapijski pristup u trudnoći. S druge strane, objavljeni su mnogi radovi o ishodima trudnoća u bolesnica liječenih inhibitorima faktora tumorske nekroze i drugom biološkom terapijom, s malim brojem neželjenih ishoda.

Cilj je ovog rada bila analiza primjene biološke terapije u bolesnica koje su planirano ili neplanirano zanijele za vrijeme liječenja u našoj ustanovi te ishoda tih trudnoća. Naši se rezultati ne razlikuju od dosad objavljene literature. Petnaest prikazanih bolesnica primalo je jedan od blokatora tumorske nekroze-α, a jedna bolesnica blokator interleukina-6 tijekom trudnoće ili neposredno prije začeća. Samo su dvije bolesnice poštovale preporučeni minimalni period od obustave terapije do začeća. Od navedenih 16 bolesnica 3 su imale medicinski indiciran prekid trudnoće: jedna zbog teške malformacije ploda, a dvije zbog terapije konvencionalnim lijekovima koji modificiraju bolest, a kontraindicirani su u trudnoći.

Ključne riječi: Reumatske bolesti – farmakoterapija; Komplikacije u trudnoći – farmakoterapija; Antireumatici – terapijska uporaba; Biološki lijekovi – terapijska uporaba; Čimbenik tumorske nekroze alfa – antagonisti i inhibitori; Humanizirana monoklonksa protutijela – terapijska uporaba; Ishod trudnoće

INTRODUCTION

During the last 20 years, advances in molecular biology, pharmacology, and understanding of the immune system have yielded novel therapies targeted against specific factors involved in the pathogenic mechanisms of autoimmune diseases. Biologic therapy has given a new perspective to a large number of patients and has significantly improved disease control. Physicians introduce biologic therapy after an inadequate effect of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs).

The incidence of inflammatory rheumatic diseases is high in women of reproductive age. The safety profile of biologic therapy in the preconception period, as well as during pregnancy and lactation, is highly important and an ongoing concern during treatment planning for young female patients.

As yet, neither the Food and Drug Administration (FDA) nor the European Medicines Agency (EMA) have confirmed biologic therapy as safe during pregnancy. Tumor necrosis factor alpha inhibitors (TNFis), the interleukin (IL)-1 receptor antagonist (anakinra), and the IL-12 blocker (ustekinumab) have been labeled as risk category B by the FDA; animal reproduction studies have failed to demonstrate a risk to the fetus, but there are no controlled human studies. The IL-6 inhibitor (tocilizumab, TCZ), anti-CD20 monoclonal antibody (rituximab, RTX), lymphocyte T stimulation modulator (abatacept), as well as the B-cell activating factor inhibitor (belimumab) have been labeled as risk category C drugs; animal reproduction studies have shown adverse effects as well as increased rates of miscarriage and neonatal death after administration of higher doses.

Resarch and data on the safety profile of the aforementioned therapeutics in pregnant patients are too scarce to yield valid conclusions. Randomized clinical trials cannot be designed or carried out due to ethical issues. Therefore, observations are based on various

UVOD

Tijekom posljednjih dvadeset godina napretci u molekularnoj biologiji, farmakologiji i razumijevanju imunosnog sustava pridonijeli su razvoju nove terapije usmjerene na čimbenike uključene u patogenetski mehanizam autoimunosnih bolesti. Biološka terapija pružila je novu perspektivu mnogim bolesnicima i znatno unaprijedila kontrolu bolesti. Liječnici ju uvode nakon nezadovoljavajućeg učinka konvencionalnih lijekova koji modificiraju tijek bolesti (engl. *Conventional synthetic disease-modifying antirheumatic drug* – csDMARD).

Incidencija upalnih reumatskih bolesti velika je u žena reproduktivne dobi. Zbog toga je sigurnost primjene biološke terapije u pretkoncepcijskom razdoblju te tijekom trudnoće i dojenja veoma važna i aktualno je pitanje pri planiranju liječenja mladih bolesnica.

Ni Američka agencija za hranu i lijekove (engl. *Food and Drug Administration* – FDA) ni Europska agencija za lijekove (engl. *European Medicines Agency* – EMA) još nisu proglasile nijedan biološki lijek sigurnim u trudnoći. FDA je klasificirala inhibitore faktora tumorske nekroze-α (TNFi), antagonist receptora interleukina (IL) 1 (anakinra) te blokator IL-12 (ustekinumab) u skupinu kategorije rizika „B". To znači da testiranja na životinjama nisu dokazala njihovu štetnost u trudnoći, dok kontroliranih ispitivanja u ljudi nema. Inhibitor IL-6 (tocilizumab), monoklonsko protutijelo anti-CD20 (rituksimab), modulator stimulacije limfocita T (abatacept) te inhibitor faktora aktivacije limfocita B (belimumab) svrstani su u kategoriju „C", što znači da su provedena ispitivanja na životinjskim modelima pokazala povećanu učestalost pobačaja i smrti novookoćene mladunčadi nakon izloženosti visokim dozama.

Podatci i istraživanja o sigurnosti primjene navedenih lijekova u trudnica nisu dovoljni da bi se mogao donijeti valjan zaključak. Randomizirani klinički pokusi ne mogu biti ustrojeni ni provedeni zbog etičkih razloga. Podatci se stoga dobivaju iz retrospektivnih

retrospective studies which have been performed since the introduction of biologic therapy. So far, there has been a substantial amount of published research on pregnancy outcomes in patients treated with TNFi, with only a small number of adverse events (1–5).

The aim of our research was to analyze the application of biologic therapy in patients with planned or unplanned pregnancy treated at our Clinic and the outcomes of these pregnancies.

PATIENTS AND METHODS

This research was designed as a retrospective observational non-interventional study.

Data on female patients born after 1962 were extracted from the list of patients treated with biologic therapy from January 1, 2003 to September 30, 2017 (520 patients in total). After analyzing the patient records, we found a total of 18 female patients who were on biologic therapy just before or during pregnancy. The biologics had been introduced because of rheumatoid arthritis (RA; n=9), ankylosing spondylitis (AS, n=2), seronegative spondiloarthropathy (SnSA, n=2), psoriatic arthritis (PsA, n=2), juvenile idiopathic arthritis (JIA, n=1), adult-onset Still's disease (n=1), and Castleman disease (n=1).

The patients included in this study were treated with TNFis (infliximab (IFX), etanercept (ETA), adalimumab (ADA), golimumab (GOL)) and the IL-6 blocker TCZ. All patients were treated with generic biologic therapy and not with biosimilars.

According to the period of therapy cessation, the patients were divided into three groups (Table 1): 1. two patients discontinued biologic therapy 6 months before conceiving; 2. five patients discontinued biologics just before conceiving; 3. eleven patients were on biologic therapy during pregnancy.

It is worth noting that all information on patient compliance and regularity of medication taking as well as on the discontinuation of therapy (not just biologics, but also conventional therapy and glucocorticoids) was based on patient reports with the assumption that they were correct.

RESULTS

Patients who discontinued biologic therapy according to treatment guidelines

Two patients stopped taking biologic therapy 6 months before conceiving. Both of them were treated with GOL for AS.

A patient born in 1987 had been treated for HLA-B27 positive AS with radiologic signs of sacroileitis since age 13. She was on csDMARDs (sulphasalzine (SSZ), chloroqine) along with glucocorticoids (GC) and nonsteroidal anti-inflammatory drugs (NSAIDs)

ispitivanja koja se provode od uvođenja bioloških lijekova u kliničku praksu. Objavljeni su mnogi radovi o ishodima trudnoća u bolesnica liječenih TNFi-jem, s malim brojem štetnih događaja (1 – 5).

Cilj je ovog rada bio utvrditi udio i opisati bolesnice koje su planirano ili neplanirano zanijele za vrijeme liječenja biološkom terapijom u našoj ustanovi te ishode tih trudnoća.

BOLESNICE I METODE

Ovo je ispitivanje ustrojeno kao retrospektivno, opservacijsko, neintervencijsko ispitivanje.

Iz popisa bolesnika koji su primali biološku terapiju u razdoblju od 1. siječnja 2003. godine do 30. rujna 2017. godine (ukupno 520 bolesnika) prikupljeni su podatci o bolesnicama rođenima 1962. godine i poslije. Uvidom u povijesti bolesti izdvojeno je 18 bolesnica koje su primale biološku terapiju neposredno prije ili tijekom trudnoće radi liječenja reumatoidnog artritisa (RA, n = 9), ankilozantnog spondilitisa (AS, n = 2), seronegativne spondiloartropatije (SnSA, n = 2), psorijatičnog artritisa (PsA, n = 2), juvenilnog idiopatskog artritisa (JIA, n = 1), Stillove bolesti u odrasloj dobi (n = 1) i Castlemanove bolesti (n = 1).

Bolesnice uključene u ispitivanje liječene su TNFi-jevima (infliksimab (IFX), etanercept (ETA), adalimumab (ADA), golimumab (GOL)) i blokatorom IL-6 (TCZ). Sve su bolesnice liječene izvornim lijekovima, a ne njihovim biološki sličnim inačicama.

S obzirom na vrijeme prekida biološke terapije, bolesnice su podijeljene u tri skupine (tablica 1.). Prvu skupinu činile su dvije bolesnice koje su zbog planiranja trudnoće biološku terapiju prekinule 6 mjeseci prije začeća prema smjernicama za biološke lijekove. U drugoj skupini bilo je pet bolesnica koje su terapiju prekinule neposredno prije začeća, dok je u trećoj skupini bilo jedanaest bolesnica koje su primale biološku terapiju u vrijeme začeća i tijekom trudnoće.

Informacije o redovitom uzimanju lijekova prema uputama, kao i o prestanku njihova uzimanja (bioloških lijekova, konvencionalne terapije i glukokortikosteroida) prikupljene su iz iskaza bolesnica s pretpostavkom da su točne.

REZULTATI

Bolesnice koje su prekinule biološku terapiju prije začeća prema smjernicama za liječenje

Dvije bolesnice prekinule su terapiju biološkim lijekom 6 mjeseci prije začeća, obje boluju od AS-a i obje su primale Simponi (GOL).

Prva bolesnica, rođena 1987. godine, boluje od AS-a pozitivnog na HLA-B27 s radiološkim znakovima sakroileitisa od 13. godine. Tijekom 11 godina bila je na terapiji DMARD-ima (sulfasalazinom (SSZ) i klo-

Table 1. Patients treated with biologic therapy before and/or during pregnancy
Tablica 1. Bolesnice liječene biološkom terapijom prije i/ili u vrijeme trudnoće

No. R.br.	Year of birth Godina rođenja	Diagnosis Dijagnoza	Year of pregnancy Godina trudnoće	Age during pregnancy Dob u vrijeme trudnoće	Biologic therapy Biološka terapija	Start of biologic therapy Početak biološke terapije	Disease activity Aktivnost bolesti	Pregnancy number R.br. trudnoće	Pregnancy outcomes and comments Ishodi trudnoće i napomene
1) Planned therapy cessation 6 months before pregnancy / Planirani prekid biološke terapije 6 mjeseci prije trudnoće									
1	1987.	AS	2017.	30	Simponi (GOL)	2014.	BASDAI 1,6	1	Healthy child born full term Zdravo dijete u terminu
2	1977.	AS	2013.	36	Simponi (GOL)	2011.	BASDAI 4,6	1	No data Nema podataka
2) Last administration of biologic therapy shortly (less than a month) before pregnancy / Posljednja doza biološkog lijeka primjenjena neposredno pred začeće									
3	1981.	RA	2010.	26	Remicade (IFX)	2003.	/	1	Twins born full term, one died of sepsis at 2 weeks, the other healthy Blizanci u terminu, jedan u 2. tj života preminuo zbog sepse, 2. blizanac zdrav
4	1972.	RA	2013.	41	Enbrel (ETA)	2009.	DAS28-SE 3,65	2	Healthy child born full term Zdravo dijete u terminu
5	1979.	RA	2010.	31	Enbrel (ETA)	2006.	DAS28-SE 1,64	1	Healthy child born full term Zdravo dijete u terminu
6	1972.	RA	2012.	40	Enbrel (ETA)	2011.	/	1	Healthy child born full term Zdravo dijete u terminu
7	1989.	PsA, SpA	2017.	32	Simponi (GOL)	2015.	BASDAI 4,4	1	Healthy child born full term Zdravo dijete u terminu
8	1974.	RA	2012.	38	Remicade (IFX)	2012.	DAS28-SE 2,84	1	Healthy child born full term Zdravo dijete u terminu
3) Biologic therapy given during pregnancy / Biološka terapija tijekom trudnoće									
9	1995.	PsA	2014.	19	Remicade (IFX)	2010.	/	1	Medically-induced abortion (at 10 w.) Medicinski opravdan pobačaj u 10. tj
10	1993.	JIA	2008.	16	Enbrel (ETA)	2007.	/	1	Healthy child born full term Zdravo dijete u terminu
11	1988.	M. Castelmann	2017.	29	RoActemra (TCZ)	2016.	/	4	Healthy child born full term Zdravo dijete u terminu Habitual abortions (3 times), conceived by IVF Habitualni pobačaji (3x), zanijela metodom IVF
12	1989.	Still adultorum	2015.	27	RoActemra (TCZ)	2011.	DAS28-SE 0,5	1	Healthy child born full term Zdravo dijete u terminu
13	1986.	RA	2017.	31	Enbrel (ETA)	2016.	BASDAI 3.1	1	Healthy child born full term Zdravo dijete u terminu
14	1980.	RA	2016.	36	Remicade (IFX)	2014.	DAS28-SE 2,13	1	Healthy child born full term Zdravo dijete u terminu
15	1995.	RA, HLA B27+	2016.	22	Enbrel (ETA)	2015.	BASDAI 1,1 DAS28-SE 1,13	1	Healthy child born full term Zdravo dijete u terminu
16	1987.	RA, SpA	1. 2015. 2. 2017.	1. 28 2. 30	1. Remicade (IFX) 2. Enbrel (ETA)	2014.	1. DAS28-SE 4,46 2. DAS28-SE 3,2	1 2	1. Abortion (spina bifida) 1. Pobačaj (spina bifida) 2. Healthy child born full term 2. Zdravo dijete u terminu
17	1983.	RA	2016.	33	RoActemra (TCZ)	2014.	DAS28-SE 1,53	1	Spontaneous abortion (at 7 w.) Spontani pobačaj u 7. tj
18	1988.	PsA	2014.	26	Humira (ADA)	2009.	DAPSA 22,4	1	Medically-induced abortion (at 7 w.) Medicinski opravdan pobačaj u 7. tj

for 11 years. Treatment with GOL started after clinical impairment with a BASDAI score of 7.9, and as the disease soon went into persistent remission (BASDAI 0.9 in 12/2011), there was no need for analgesic therapy. The patient started planning pregnancy in 2016 and therefore was advised to discontinue biologic therapy.

rokinom), uz glukokortikoide (GK) i nesteroidne antireumatike (NSAR). Zbog pogoršanja kliničke slike (BASDAI 7,9) započeto je liječenje Simponijem uz znatno poboljšanje nakon druge primjene lijeka (u prosincu 2011., BASDAI 0,9) te perzistentnu remisiju, bez potrebe za analgeticima. Bolesnica je 2016. počela

Six months later, she conceived. The AS reactivated during pregnancy, with a maximum BASDAI score of 6.2. The pregnancy proceeded without complications, delivery was on term, and the baby was healthy and had a normal neonatal development.

A patient born in 1977 was diagnosed with AS when she was 27. GOL was introduced due to persistent active disease. After a year on biologic therapy, the AS went into remission and the patient started planning pregnancy. She conceived 6 months after discontinuing biologic therapy, in 4/2013. The last follow-up at our Clinic was in 1/2014, in the 39th gestational week. The patient was scheduled for a cesarean section because of the underlying disease. Afterwards, we lost contact with the patient and there is no available medical data, neither on the course of the delivery nor on the further disease development.

Patients who discontinued biologic therapy just before pregnancy

There were five patients who stopped taking biologic therapy just before conception.

A patient born in 1981 had had seropositive RA since she was 10. Treatment with IFX started 10 years after the disease was diagnosed and the patient had been on biologic therapy during the following 7 years, along with methotrexate (MTX) and GC permanently. In 4/2010 the last dose of IFX was administered and right afterwards the patient conceived twins. During pregnancy she was on GC 6 mg daily along with paracetamol and folic acid, but the RA mildly exacerbated. The pregnancy went without complications and delivery was on term in 1/2011. Unfortunately, one child died of sepsis 2 weeks after. The other twin was helathy, with no signs of infection or other complications.

A patient born in 1972 had had persistent active RA since she was 34. After 3 years of therapy with leflunomide (LEF) and GC, ETA was introduced and csDMARD continued. Several months later the disease was well controlled with a DAS 28-ESR score of 4.41 and remained stable during the next 3 years. An unplanned pregnancy was discovered in 1/2014, in the same month the patient received the last dose of ETA. Since the patient had not been taking LEF for a longer period of time, a termination of pregnancy was not considered. The patient delivered a healthy baby on term. ETA was reintroduced one year later, after the patient stopped breastfeeding.

A patient born in 1979 had been treated for RA since age 23. In the first year of the disease she was treated with MTX and GC, but ADA was soon introduced. Despite the therapy, disease activity remained high. Therefore, three years later the patient was started on ETA, and better disease control was achieved. In 2010 the therapy with ETA and MTX was discontinued be-

planirati trudnoću te joj je savjetovano da prekine terapiju. Zanijela je šest mjeseci nakon prekida primjene Simponija. Tijekom trudnoće bolest se počela pogoršavati, s maksimalnim rezultatom BASDAI-ja od 6,2. Sama trudnoća protekla je bez komplikacija i bolesnica je u terminu rodila zdravo dijete koje se normalno razvijalo u novorođenačkom razdoblju.

Druga bolesnica, rođena 1977. g., boluje od AS-a od 27. godine. Zbog perzistirajuće aktivne bolesti bolesnica je započela terapiju Simponijem. Nakon godinu dana biološke terapije i zadovoljavajuće remisije bolesti prekinuta je primjena Simponija zbog planiranja trudnoće. Bolesnica je zanijela 6 mjeseci nakon prekida terapije, u travnju 2013. godine. Na posljednjoj kontroli, u siječnju 2014., bolesnica je bila u 39. tjednu uredne trudnoće, koja se planirala dovršiti carskim rezom zbog osnovne bolesti. Poslije se bolesnica nije javljala na kontrolu niti postoji nama dostupna medicinska dokumentacija o porođaju i daljnjem tijeku bolesti.

Bolesnice koje su posljednju dozu biološke terapije primile neposredno prije začeća

U ovoj je skupini pet bolesnica u kojih je biološka terapija prekinuta neposredno prije začeća.

Treća bolesnica, rođena 1981. godine, boluje od seropozitivnog RA od 10. godine. Primjena Remicadea (IFX) započela je 10 godina nakon postavljene dijagnoze te ga je bolesnica uzimala tijekom idućih 7 godina, uz metotreksat (MTX) i GK trajno. U travnju 2010. primijenjena je posljednja doza biološkog lijeka, nakon čega je bolesnica neposredno zanijela blizance. Tijekom trudnoće uzimala je GK u dozi od 6 mg na dan uz paracetamol i folnu kiselinu; pratila se blaga egzacerbacija bolesti. Trudnoća je protekla uredno i dovršena je u terminu, u siječnju 2011. Jedno je novorođenče preminulo 2 tjedna nakon rođenja zbog sepse, a drugo je dijete zdravo, bez težih infekcija i drugih komplikacija u razvoju.

Četvrta bolesnica, rođena 1972., boluje od perzistirajućeg aktivnog RA od 34. godine. Nakon 3 godine terapije leflunomidom (LEF) i GK-om uvedena je i primjena Enbrela (ETA). Nekoliko mjeseci poslije bolest je bila u zadovoljavajućoj kontroli (DAS 28-SE 4,41), uz postupno poboljšanje tijekom iduće 3 godine. U siječnju 2014. bolesnica je neplanirano zanijela, mjesec dana nakon posljednje doze Enbrela. Budući da bolesnica već dulje vrijeme nije uzimala LEF, prekid trudnoće nije bio razmatran. Bolesnica je rodila zdravog dječaka u terminu. Terapija Enbrelom nastavljena je godinu dana poslije, nakon prestanka dojenja.

Peta bolesnica, rođena 1979., započela je liječenje RA u 23. godini. Prvih godinu dana primala je MTX i GK kojima je zatim pridodana Humira (ADA), no bez većeg učinka na aktivnost bolesti. Tri godine poslije u

cause the patient started planning pregnancy. Nevertheless, a minimum safety period from therapy cessation to pregnancy had not been reached because the patient conceived within a month. The pregnancy proceeded without complications and disease activity remained low with GC 10 mg daily. Delivery was on term and the baby was healthy. In 4/2011, because of RA relapse, ETA was reintroduced.

A patient born in 1972 was diagnosed with high-activity RA when she was 27 and soon ETA was introduced. According to the medical records, she stopped taking biologic therapy just before conceiving, in 3/2012. The pregnancy was without complications. During the whole pregnancy the patient was on GC 10 mg daily and the RA was in remission. She underwent cesarean section in term and a healthy child was born. Postpartum recovery and neonatal development were without complications.

A patient born in 1989 was diagnosed with SnSA when she was 25. A year later, GOL was introduced and the disease went into stable remission. Two years after, biologic therapy was discontinued because of planned in-vitro fertilization. Two months later (in 1/2017) the patient conceived. The pregnancy was without complications and the patient delivered by cesarean section in the 35th gestational week. The child was healthy (Apgar 10/10) and further neonatal development was normal.

Patients who were on biologic therapy at the time of conception and during pregnancy

The last patient group comprised 11 patients who were on biologic therapy during pregnancy, with two of them also taking csDMARDs (MTX and LEF).

A patient born in 1974, with a history of addiction, had been treated for RA since she was 23. During 2009 she was on methadone and concomitant therapy with ribavirin and pegilated interferon due to hepatitis C, which soon went into remission. For a long period of time she was on csDMARDs, first SSZ and then MTX, and GC permanently. The patient received the first dose of IFX 15 years after RA was established. It was later discovered that she had been taking only 5 mg of MTX weekly instead of the prescribed 15 mg weekly. The biologic therapy induced substantial clinical improvement (DAS28-ESR score 2.84) and the patient was on IFX every 8 weeks, following a standard protocol. At every biologic therapy application, a thorough clinical examination was conducted and every time the patient reported regular menstrual cycles. In 2/2013, before the 9th aplication of IFX, the attending physician suspected pregnancy. The patient was promptly referred to a gynecologist who confirmed a pregnancy of 31 weeks. Fetal ultrasound did not reveal any malformations. The biologic therapy, as well as MTX, was interapiju je uveden Enbrel kojim je postignuta bolja kontrola bolesti. Terapija Enbrelom i MT-om prekinuta je 2010. zbog planiranja trudnoće, no nije ispunjen uvjet sigurnog razdoblja stanke od terapije: bolesnica je zanijela isti mjesec. Trudnoća je protekla bez komplikacija, s niskom aktivnosti bolesti uz terapiju GK-om u dozi od 10 mg na dan. Bolesnica je rodila zdravo dijete u terminu. U travnju 2011. nastavljena je terapija Enbrelom zbog relapsa RA.

Šesta bolesnica, rođena 1972., boluje od RA visoke aktivnosti od 27. godine, zbog čega je uvedena terapija Enbrelom. U medicinskoj dokumentaciji zabilježeno je da je prekinula biološku terapiju neposredno prije začeća, u ožujku 2012. Trudnoća je protekla uredno. Tijekom cijele trudnoće bolesnica je uzimala terapiju GK u dozi od 10 mg na dan i bolest je bila u remisiji. Carskim rezom rodila je zdravo dijete u terminu. Poslijeporođajni tijek i razvoj djeteta bili su uredni.

Sedmoj bolesnici, rođenoj 1989., postavljena je dijagnoza SnSA u 25. godini, a godinu dana poslije započeto je liječenje Simponijem. Uz terapiju je bolest bila u stabilnoj remisiji. Dvije godine poslije liječenje Simponijem obustavljeno je radi planiranog postupka potpomognute oplodnje te je bolesnica nakon dva mjeseca, u siječnju 2017., zanijela. Trudnoća je protekla bez komplikacija i carskim je rezom u 35. tjednu rođeno zdravo dijete (Apgarina indeksa 10/10) koje je uredno napredovalo.

Bolesnice koje su uzimale biološku terapiju u vrijeme začeća i tijekom trudnoće

U posljednju skupinu spada jedanaest bolesnica koje su primale biološku terapiju u vrijeme začeća i tijekom trudnoće, a dvije od njih uzimale su i DMARD (MTX i LEF).

Osma bolesnica, s anamnezom ovisnosti, rođena 1974. g., liječi se zbog RA od 23. godine. Tijekom 2009. liječena je metadonom te ribavirinom i pegiliranim interferonom zbog hepatitisa C koji je otad u remisiji. Niz godina bolesnica je liječena primjenom DMARD-a, prvo SSZ-a, a zatim MTX-a uz GK trajno. Bolesnica je primila prvu dozu Remicadea 15 godina nakon postavljene dijagnoze RA. Naknadno se saznaje da je bolesnica, umjesto propisanih 15 mg na tjedan, uzimala MTX u dozi od 5 mg na tjedan. Uz biološku terapiju došlo je do jasnoga kliničkog poboljšanja (DAS 28-SE 2,84) te je Remicade primjenjivan prema standardnom protokolu svakih 8 tjedana. Tijekom cijelog perioda liječenja bolesnica je navodila da ima redovite menstrualne cikluse. Pri kliničkom pregledu u veljači 2013., prije 9. primjene lijeka, pregledom trbuha postavljena je sumnja na trudnoću. Hitnim ginekološkim pregledom u Klinici za ženske bolesti i porode potvrđena je trudnoća u 31. tjednu. Ultrazvučni pregled nije otkrio nikakve malformacije ploda. Odmah su prekinute bio-

stantly discontinued and the patient was on GC throughout the rest of the pregnancy. The patient delivered in 4/2013, at home, in the 36th gestational week. The newborn was healthy and with no complications in the further neonatal development. After ablactation in 5/2013, IFX was reintroduced, along with MTX and GC. Nevertheless, the patient was soon lost to follow-up.

A patient born in 1995 was diagnosed with PsA when she was 15. Shortly after PsA was established, she was started on IFX in another (pediatric) institution. She had been receiving biologic therapy for 4 years without pause. Throughout that time she had also been on LEF. At the first visit to our Clinic, within transition to adult rheumatology, pregnancy was suspected and confirmed by ultrasound. Application of IFX and LEF was instantly discontinued. Even though it was an unplanned pregnancy at a very early stage (less than 10 weeks) which started while the patient was on therapy with LEF, termination of pregnancy was medically indicated. In 6/2014 biologic therapy with IFX was continued.

A patient born in 1993 was diagnosed with JIA when she was 3. Medical records from a pediatric rheumatology clinic showed that she had been on MTX until 2008 and that the last dose of ETA was administered in 7/2009. The same month the patient delivered a healthy baby, after a normal pregnancy, without complications. Since 2009 she has been in follow-up at our Clinic and in 2/2010 ETA was reintroduced.

A patient born in 1988 had been in hematologic follow-up for multicentric Castleman disease. The disease was well controlled with low doses of GC. According to the medical documentation, high titres of anticardiolipin IgM antibodies were permanently present in patient's serum and, despite prophylactic therapy with low-molecular-weight heparin, she had three habitual abortions in the first trimester of pregnancy (2nd and 3rd weeks). In 1/2017, a consultation at our Clinic was held to consider treatment options in a potential pregnancy. TCZ was introduced as induction therapy during the IVF procedure and then discontinued in the first trimester of pregnancy. The patient was 21 weeks pregnant when this paper was finished and by that time no complications in the fetal development had been described.

A patient born in 1989 was diagnosed with adult Still's disease when she was 21. She was treated with TCZ during the following 4 years. The last dose was administered in 9/2015, when the patient was 4 weeks pregnant. The pregnancy proceeded without complications and the patient delivered a healthy baby in 6/2016. Further postpartal recovery as well as neonatal development was normal.

A patient born in 1986 was diagnosed with SnSA when she was 29. After 9 months of therapy with ADA,

loška terapija i terapija MTX-om, a liječenje je nastavljeno samo primjenom GK i analgeticima. Početkom travnja 2013. g. bolesnica je u 36. tjednu trudnoće kod kuće rodila zdravo dijete koje se normalno razvijalo, bez komplikacija. U bolesnice je u svibnju 2013., nakon ablaktacije, nastavljena primjena Remicadea, MTX-a i GK, no nedugo zatim izgubljena je iz praćenja.

Deveta bolesnica, rođena 1995., boluje od PsA od 15. godine. Odmah nakon postavljene dijagnoze započeta je terapija Remicadeom u drugoj (pedijatrijskoj) ustanovi. Terapiju je primala četiri godine bez stanke. Uz to je redovito uzimala i LEF. Pri prvom pregledu u našoj Klinici, u sklopu tranzicijske ambulante i potrebe prelaska na adultnu reumatologiju, postavljena je sumnja na trudnoću koja je i potvrđena ultrazvučnim pregledom. Primjena Remicadea i LEF-a odmah je prekinuta. Budući da je bila riječ o ranoj i neplaniranoj trudnoći (manje od 10 tjedana) te da je do začeća došlo uz terapiju LEF-om, medicinski je bio indiciran prekid trudnoće. U lipnju 2014. nastavljena je primjena Remicadea.

Deseta bolesnica, rođena 1993., započela je liječenje JIA u 3. godini. Iz povijesti bolesti pedijatrijske reumatološke klinike vidljivo je da je MTX prestala uzimati 2008., a posljednja doza Enbrela primijenjena je u srpnju 2009. Isti je mjesec bolesnica rodila zdravo dijete, a trudnoća je protekla uredno. Od 2009. kontrolira se u našoj Klinici. Enbrel je ponovo uveden u terapiju u veljači 2010.

Jedanaesta bolesnica, rođena 1988., pod redovitom je kontrolom hematologa zbog multicentričnog oblika Castlemanove bolesti. Bolest je bila dobro kontrolirana niskim dozama GK. U medicinskoj dokumentaciji bilježe se trajno pozitivna antikardiolipinska protutijela razreda IgM u visokom titru te habitualni pobačaji (tri zaredom) u prvom tromjesečju trudnoće (2. i 3. tjedan) usprkos profilaktičkoj terapiji niskomolekularnim heparinom. U siječnju 2017. zatražen je konzilijarni pregled reumatologa zbog pitanja terapije u trudnoći. Uvedena je RoActemra (TCZ) kao indukcijska terapija za pripremu trudnoće i predviđenog postupka potpomognute oplodnje. Primjena TCZ-a prekinuta je u prvom tromjesečju. U vrijeme pisanja ovog rada bolesnica je bila u 21. tjednu trudnoće, koja je dotad protjecala bez komplikacija u razvoju ploda.

Dvanaesta bolesnica, rođena 1989. g., boluje od Stillove bolesti od 21. godine. Liječena je RoActemrom tijekom četiri godine. Posljednja primjena lijeka bila je u rujnu 2015., kada je terapija obustavljena zbog otkrivene trudnoće od četiri tjedna. U lipnju 2016., nakon uredna tijeka trudnoće, u terminu je rođeno zdravo dijete, a poslijeporođajni tijek bio je bez komplikacija i u djeteta i u majke.

Trinaesta bolesnica, rođena 1986. g., boluje od SnSA od 29. godine. Nakon 9 mjeseci terapije Humirom pri-

a pregnancy of 4 weeks was discovered and biologic therapy discontinued. The patient delivered a healthy baby on term and there were no complications in the further neonatal development. Since there were no signs of disease activity, biologic therapy was not reintroduced.

A patient born in 1980 was diagnosed with RA and treated with IFX. Because of disease remission a year after the introduction of biologic therapy, MTX was stopped. During a regular follow-up in 1/2016, a pregnancy of 4 weeks was discovered and IFX discontinued. A healthy baby was born in term, after a normal pregnancy without complications. There was no need for reintroducing biologic therapy, since the RA remained in remission.

A patient born in 1995 was diagnosed with RA and was HLA-B27 positive. She was treated with ETA. The last dose of biologic therapy was administered in the 8th week of gestation, in 12/2016. The patient delivered a helathy baby in term (39th week) after a short hospitalization due to premature rupture of membranes. The labor was induced but there were no postpartum complications.

A patient born in 1987 started receiving IFX 10 years after she was diagnosed with RA. The last dose of biologic therapy was administered in 4/2015 and the same month the patient conceived. Unfortunately, in the 28th week of gestation an abortion had to be induced, because of spina bifida and severe brain malformation in the fetus. A month later, IFX was reintroduced. Due to high disease activity, after 3 months the patient was switched to GOL, and 6 months later she was switched to ETA. The patient conceived again in 2/2017 and therapy with ETA was continued until the end of the 1st trimester. In 10/2017 the patient delivered a healthy baby by cesarean section.

A patient born in 1983 was diagnosed with RA and treated with IFX. After the 5th application of therapy, in 6/2016, treatment was temporarily stopped because of a Bartholin gland inflammation. At follow-up at the gynecologist 2 weeks later, a pregnancy of 6 weeks was discovered. Unfortunately, the patient had a spontaneous miscarriage the next week. She then conceived in 4/2017 and delivered a healthy baby by cesarean section in term.

A patient born in 1988 was diagnosed with PsA. Seven years later, biologic therapy was introduced. The patient was started on ADA. Because of persistent infections, a switch to IFX had been attempted, but soon discontinued due to primary inefficiency. ETA was then introduced, but the patient soon developed cutaneous side-effects. In 2014 ADA was reintroduced and three months later a pregnancy was discovered. Since the patient had been on MTX permanently during the prior 2 years, an abortion was medically advised. Since 1/2015 the patient has been treated with ustekinumab.

mjena tog lijeka obustavljena je zbog novootkrivene trudnoće od četiri tjedna. Trudnoća je protekla uredno i bolesnica je rodila zdravo dijete u terminu. U bolesnice nije došlo do aktivacije bolesti nakon trudnoće pa biološka terapija nije nastavljena.

Četrnaesta bolesnica, rođena 1980. g., boluje od RA i liječena je Remicadeom. Zbog dobre kontrole bolesti prekinut je MTX godinu dana nakon uvođenja biološke terapije. Pri redovitoj kontroli u siječnju 2016. utvrđena je trudnoća u trajanju od četiri tjedna, zbog čega je obustavljena primjena Remicadea. Trudnoća je protekla bez komplikacija i bolesnica je rodila zdravo dijete u terminu. Nakon porođaja biološka terapija nije nastavljena.

Petnaesta bolesnica, rođena 1995. g., liječila se Enbrelom zbog RA uz pozitivan HLA-B27. Primjena lijeka prekinuta je u 8. tjednu trudnoće, u prosincu 2016. U 39. tjednu trudnoće bolesnica je hospitalizirana zbog otjecanja plodne vode, induciran je porođaj te je rođeno zdravo dijete. Poslijeporođajni tijek i u majke i djeteta bio je uredan.

Šesnaesta bolesnica, rođena 1987. g., počela je primati Remicade 10 godina nakon postavljene dijagnoze RA. Posljednju dozu biološkog lijeka primila je u travnju 2015. i isti je mjesec zanijela. U 28. tjednu trudnoće učinjen je medicinski indiciran prekid trudnoće zbog spine bifide i teške nerazvijenosti mozga ploda. Mjesec dana poslije nastavljena je terapija Remicadeom. Nakon tri mjeseca, zbog visokoaktivne bolesti, bolesnica je prebačena na Simponi, a zatim je 6 mjeseci poslije, ponovo zbog neučinkovitosti, u bolesnice terapija promijenjena u Enbrel. Bolesnica je ponovo zanijela u veljači 2017., a terapija Enbrelom nastavljena je do kraja prvog tromjesečja. U listopadu 2017. bolesnica je rodila zdravog dječaka carskim rezom.

Sedamnaesta bolesnica, rođena 1983. g., liječena je Remicadeom zbog RA. Nakon pete primjene lijeka, u lipnju 2016., lijek je privremeno obustavljen zbog upale Bartholinove žlijezde. Na kontrolnome ginekološkom pregledu 2 tjedna poslije utvrđena je trudnoća u trajanju od šest tjedana, no već je u sedmom tjednu trudnoća završila spontanim pobačajem. Bolesnica je ponovo zanijela u travnju 2017., a carskim je rezom u terminu rodila zdravo dijete.

Osamnaesta bolesnica, rođena 1988. g., boluje od PsA. Sedam godina nakon dijagnoze započeta je primjena biološke terapije. Prvotno je terapijski uvedena Humira, a zbog stalno prisutnih infekcija pokušao se uvesti Remicade koji se pokazao primarno nedjelotvoran. Zatim je uveden Enbrel, ali bolesnica je ubrzo dobila kožne nuspojave. Terapija Humirom ponovo je uvedena 2014., a tri mjeseca poslije ustanovljena je trudnoća. Budući da je bolesnica tijekom prethodne dvije godine trajno uzimala MTX, savjetovan je medicinski opravdan prekid trudnoće. Od siječnja 2015. bolesnica prima ustekinumab.

DISCUSSION

There are numerous publications describing the effects of biologic therapy and csDMARDs on the course and outcomes of pregnancy. To date, the FDA and EMA have not declared biologic agents safe during pregnancy or lactation (6–11). The pharmaceutical industry recommends avoiding biologic therapy during this period. Nevertheless, there are many reports and literature reviews with results showing no greater incidence of adverse effects of such a therapy in pregnant patients. (1–5, 12–17) Systematic literature reviews highlight the effects of other factors on pregnancy outcomes, such as disease activity and patients' comorbidities, which have not yet been thoroughly reviewed. (18, 19) Given that among biologic agents today TNFis have been in the longest use for the treatment of autoimmune diseases, the experience with TNFi application in pregnancy is also the greatest. Most of the reports on TNFi therapy during pregnancy have not associated the treatment with adverse effects. Some publications raise questions about the association of this therapy with higher incidences of congenital malformations such as the VACTERL syndrome (*vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, renal anomalies, limb abnormalities*), (20, 21) but the aforementioned analyses are doubious due to methodological errors. (21, 22)

The patients described here have been treated with TNFis (ETA, IFX, GOL, ADA) and the IL-6 blocker (TCZ) during or just before pregnancy.

TNFis exist as monoclonal antibodies (IFX, ADA, GOL, certolizumab-pegol (CZP)) or as fusion proteins (ETA). Monoclonal antibodies consist of human immunogloblin G1 Fc fragments (except for CZP) and Fab fragments, which bind to the TNF-α molecule. Depending on the type of Fab fragment, monoclonal antibodies used today can be chimeric (e.g., IFX, RTX), humanized (e.g., TCZ), or human (e.g., GOL, ADA). It is well-known that only the IgG antibody significantly crosses the human placenta. During the first two trimesters, fetal concentrations of IgG molecules are low in the umbilical cord, while their transfer through the placenta rapidly increases in the third trimester of pregnancy. (23) The IgG1 subclass of immunoglobulins is transferred most efficiently across the placenta. (24) Although according to the FDA all TNFis belong to the risk category B, the minimum recommended time for treatment cessation before pregnancy differs from one TNFi to the other. Therefore, for GOL and IFX the recommended period is 6 months, for ADA 5 months, and for ETA 3 weeks. (7–11) Nevertheless, according to the recommendations of the European League Against Rheumatism (EULAR), treatment with IFX, ADA, and GOL should be discontinued around the 20th gestational week, while therapy with

RASPRAVA

U mnogim su radovima opisani učinci biološke terapije, kao i terapije temeljnim antireumaticima na tijek i ishod trudnoće. FDA i EMA nisu proglasile nijedan biološki lijek sigurnim u vrijeme trudnoće i laktacije (6 – 11). Proizvođači bioloških lijekova preporučuju izbjegavanje takve terapije u tom razdoblju. Ipak, mnogi izvještaji i pregledi literature ne pronalaze veću incidenciju neželjenih događaja u trudnoći u bolesnica na biološkoj terapiji (1 – 5, 12 – 16). U sistematskim pregledima literature napominje se da ishod trudnoće ovisi i o drugim faktorima, pogotovo o aktivnosti osnovne bolesti i komorbiditetima trudnice, te da njihov utjecaj na tijek trudnoće često nije dovoljno razmotren (17, 18). Među danas dostupnom biološkom terapijom TNFi se najdulje primjenjuje u liječenju autoimunosnih bolesti pa stoga i postoji najviše iskustva u njegovoj primjeni tijekom trudnoće. Neki radovi upozoravaju na moguću povezanost ove terapije s većom incidencijom kongenitalnih malformacija kao što je sindrom VACTERL (engl. *vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities*) (19, 20), no navedena su istraživanja dovedena u pitanje zbog metodoloških pogrešaka (20, 21).

Prikazane su bolesnice tijekom trudnoće ili neposredno prije začeća liječene primjenom TNFi-ja (ETA, IFX, GOL, ADA) te blokatorom IL-6 (TCZ).

Lijekovi koji blokiraju TNF-α proizvode se kao monoklonska protutijela (infliksimab, golimumab, adalimumab, certolizumab-pegol (CZP)) ili kao fuzijski proteini (etanercept). Monoklonska protutijela sastoje se od Fc-regije (izuzev CZP-a) ljudskog imunoglobulina G1 (IgG1) te Fab-dijela koji veže molekulu TNF-α. Ovisno o načinu proizvodnje Fab-dijela, monoklonska protutijela koja se danas rabe u reumatologiji mogu biti kimerična (npr., infliksimab, rituksimab), humanizirana (kao blokator IL-6 (TCZ)) ili humana (npr., golimumab, adalimumab). Poznato je da jedino protutijelo IgG prolazi kroz uteroplacentalnu barijeru. U prva dva tromjesečja trudnoće fetalne su koncentracije molekula IgG u pupkovini niske, dok se u trećem tromjesečju njihov transport kroz placentu naglo povećava (22). Upravo je podskupina imunoglobulina IgG1 ta koja se najbolje transportira kroz posteljicu (23). Iako je čitava skupina TNFi-ja svrstana u kategoriju rizika „B" prema FDA, minimalno preporučeno razdoblje od prestanka uzimanja lijeka do začeća razlikuje se za pojedine lijekove. Tako je to razdoblje za golimumab i infliksimab 6 mjeseci, za etanercept 3 tjedna, a za adalimumab 5 mjeseci (7 – 11). Prema preporukama Europske lige protiv reumatizma (EULAR), pak, terapiju IFX-om, ADA-om i GOL-om valja obustaviti oko 20. tjedna gestacije, dok se primjena ETA može nastaviti do 32. tjedna (18). Ovdje je potrebno izdvojiti CZP, po-

ETA can be continued up to the 32nd week of gestation. (19) The last approved TNFi, CZP, used for the treatment of RA (2009), AS, and PsA (2013), has to be singled out. This humanized monoclonal antibody differs from other TNFis in its pegilated Fab fragment and absence of the Fc region. Pegilation enhances the solubility of CZP, prolongs its half-life, and reduces its immunogenicity. Furthermore, because it lacks an Fg-region, this monoclonal antibody cannot bind to the neonatal Fc receptor (FcRn) and consequently does not actively cross the placenta. (25, 26) In a recently published paper on pregnancy outcomes in 625 patients treated with CZP (every patient receiving CZP during the first trmester and one third of the patients receiving CZP during the whole pregnancy), no increase in the incidence of adverse events has been reported, compared to the healthy population. (27) There are studies comparing the concentration of each TNFi (IFX, ADA, ETA, and CZP) in the umbilical cord and neonatal peripheral blood of neonates whose mothers had been exposed to biologic therapy during pregnancy. (28, 29, 30) Concentrations of IFX and ADA were significantly higher in the umbilical cord than in the mother's serum (IFX by 160% and ADA by 153%). At the same time, concentration of CZP in the umbilical cord was slightly higher than in the mother's serum (by 3.9%). Moreover, IFX and ADA were traceable in the neonatal blood up to 6 months after cessation of the mother's treatment, while the concentrations of CZP were undetectable. (29) According to the EULAR 2016 recommendations, CZP application is possible during the whole pregnancy due to its molecule size and low bioavailability, as well as to a decreased utero-placental transfer. Treatment is also compatible with breastfeeding. (19)

ETA is a genetically engineered fusion protein which consists of two identical TNF-α soluble receptor molecules (TNFR2) bound to an IgG1 Fc fragment. (8, 31) In most of the reports published to date there was no association of ETA treatment with adverse prgnancy outcomes. Nevertheless, some reports question the effect of ETA on the occurrence of fetal malformations (such as the aforementioned VACTERL). (32, 33) There is no strict instruction for a safe interval between the last application and conception. In the official product information it is advised to stop treatment with ETA at least 3 weeks before conceiving, since it crosses the placenta and is secreted into breast milk. It is also advised not to vaccinate babies within 16 weeks after their mother had the last drug application. (8) Still, according to the last EULAR recommendations for the therapy of pregnant patients, ETA can be safely administered until the 30th to 32nd gestational week and even during the whole pregnancy if the disease activity is high. It is safe during breastfeeding due to its low

sljednji odobreni lijek iz skupine TNFi-ja koji se primjenjuje za liječenje RA od 2009., a za liječenje AS-a i PsA od 2013. Ovo humanizirano monoklonsko protutijelo razlikuje se od ostalih TNFi-ja prema pegiliranom Fab-odsječku, dok mu Fc-regija nedostaje. Pegilacija poboljšava topljivost lijeka i produljuje mu poluživot te smanjuje njegovu imunogeničnost. Nadalje, zbog nedostatka Fc-regije ovo monoklonsko protutijelo ne može se vezati za neonatalni Fc-receptor (FcRn) te ne prolazi aktivno kroz posteljicu tijekom trudnoće (24, 25). Nedavno objavljeni rad o ishodima 625 trudnoća žena koje su bile liječene primjenom CZP-a (u svih majka u prvom tromjesečju, a u trećine njih tijekom cijele trudnoće) ne opisuje povećanu učestalost neželjenih događaja u usporedbi sa zdravom populacijom (26). Objavljena su ispitivanja koja su uspoređivala koncentraciju pojedinih TNFi-ja (IFX, ADA, ETA i CZP) u pupkovini i perifernoj krvi novorođenčadi majka koje su bile izložene biološkoj terapiji tijekom trudnoće (27 – 29). Dok su koncentracije IFX-a i ADA bile znatno više u pupkovini nego u majčinoj krvi (IFX 160% i ADA 153%), koncentracija CZP-a u pupkovini bila je tek za 3,9% viša od one u majčinoj krvi. Nadalje, IFX i ADA bili su mjerljivi u krvi novorođenčadi do 6 mjeseci nakon prestanka terapije u majke, dok su koncentracije CZP-a bile nemjerljive (28). Prema preporukama EULAR-a iz 2016., primjena CZP-a moguća je tijekom cijele trudnoće zbog veličine molekule i niske bioraspoloživosti te smanjenog prijenosa kroz uteroplacentalnu barijeru, a primjena lijeka kompatibilna je i s dojenjem (18).

ETA je fuzijski protein stvoren genetičkim inženjeringom koji se sastoji od dvije identične molekule topljivog receptora za TNF-α (TNFR2), vezane za Fc regiju humanog IgG1. Odobren je za liječenje RA, PsA, poliartikularnoga juvenilnog idiopatskog artritisa, AS-a i plak-psorijaze (8, 30). U većini objavljenih radova nije nađena poveznica primjene ETA-e s neželjenim ishodima trudnoće, iako postoje neki izvještaji o malformacijama (već spomenuti sindrom VACTERL) gdje se utjecaj navedenog lijeka dovodi u pitanje (31, 32). Ne postoji točna odrednica za sigurnosni interval od posljednje primjene do začeća. U službenom opisu lijeka savjetuje se prestanak terapije najmanje tri tjedna prije začeća te se upozorava na izlučivanje lijeka kroz posteljicu i u majčino mlijeko. Savjetuje se ne cijepiti dojenčad u 16 tjedana od posljednje primjene lijeka u majke (8). Ipak, prema posljednjim smjernicama EULAR-a za primjenu lijekova u trudnih bolesnica, ETA se može sa sigurnošću primjenjivati do 30. ili 32. tjedna trudnoće, pa čak i tijekom cijele trudnoće ako je riječ o aktivnoj bolesti. Siguran je pri dojenju zbog niske bioraspoloživosti i veličine molekule (18). Ni u jedne od prikazanih bolesnica koje su bile liječene ETA-om neposredno prije začeća i za vrijeme trudno-

bioavailability and size. (19) None of the patients described here and treated with ETA before or during pregnancy, presented with adverse pregnancy outcomes or impairment in the neonatal development.

IFX is a chimeric human-mouse monoclonal antibody of the IgG1 subclass, engineered by recombinant DNA technology. It has the same affinity for both the soluble and transmembrane forms of TNF. According to the official drug instruction, treatment with IFX during pregnancy and breastfeeding is not advised, and a minimum period of 6 months without therapy is recommended. (9) Some reports mention a minimum period of 2 months, due to its half-life. Regarding adverse pregnancy outcomes, there is no statistically significant distinction between patients on IFX and the healthy population, apart from a few exceptions probably associated with concomitant DMARD therapy. (19, 33) In fact, according to the newest EULAR guidelines, treatment with IFX is safe up to the 20th gestational week or longer, and there are no contraindications for IFX during breastfeeding. However, since there is a potential harmful effect on the neonatal immune response, vaccination with live vaccines is contraindicated during the first 6 months after birth. Three of the patients described here were on IFX just before or during pregnancy. The patient who was on regular therapy with IFX (along with MTX weekly, although it is questionable whether the patient had been taking MTX and in what dose, since she later stated she had been taking 5 mg weekly instead of the prescribed 15 mg weekly) carried out the pregnancy without complications and gave birth to a healthy baby in the 36th gestational week.

ADA is a recombinant completely human monoclonal antibody of the IgG1 subclass. It binds to the soluble TNF-α molecule, thus blocking its interaction with the receptors. Like other TNFis, it is a risk category B medication according to the FDA. ADA crosses the placenta and consequently it can induce a risk of infections in newborns. The EMA recommended cessation of ADA treatment at least 5 months prior to conception, as well as withholding newborns from live vaccines for 5 months after the mother had the last treatment application. (10) According to the EULAR guidelines as well as the guidelines of the British Society for Rheumatology (BSR), pregnant patients can be treated with ADA up to the 20th gestational week or longer, and it is safe during breastfeeding. (19, 34) One of our patients had been taking ADA until she was 4 weeks pregnant, and the pregnancy as well as fetal development continued without complications.

GOL is an IgG1-κ human monoclonal antibody. It binds to soluble and transmembrane TNF-α. According to the offical medication instructions, the EMA recommends discontinuation of GOL 6 months before će nije bilo neželjenih učinaka na tijek trudnoće, kao ni na zdravlje novorođenčeta.

IFX je kimeričko humano-mišje monoklonsko protutijelo IgG1 proizvedeno tehnologijom rekombinantnog DNK, a veže se jednakim afinitetom za topljivi i transmembranski oblik TNF-α. Prema službenim uputama, ne savjetuje se uzimanje infliksimaba za vrijeme trudnoće i dojenja te se preporučuje prekid terapije minimalno 6 mjeseci prije začeća (9), no u literaturi se spominje i razdoblje od 2 mjeseca prije začeća, s obzirom na poluvijek lijeka u organizmu. U pogledu štetnih učinaka na ishode trudnoće nema statistički značajne razlike između bolesnica liječenih IFX-om i zdrave populacije, osim nekoliko iznimaka koje se mogu povezati i s istodobnom primjenom DMARD-a (19, 32). Dapače, prema najnovijim EULAR-ovim smjernicama, IFX se smije davati bolesnicama do 20. tjedna trudnoće, pa i dulje, a siguran je i tijekom dojenja. Ipak, upozorava se na potencijalni štetni učinak na imunosni odgovor novorođenčeta te je cijepljenje živim cjepivima kontraindicirano u prvih 6 mjeseci djetetova života. Tri su prikazane bolesnice primale IFX neposredno prije ili za vrijeme trudnoće. Bolesnica koja je do trećeg tromjesečja primala redovito IFX uz MTX (uz napomenu da se postavlja pitanje je li bolesnica doista uzimala MTX i u kojoj dozi; prema njezinim navodima, doza MTX-a bila je 5 mg na tjedan umjesto propisanih 15 mg) uredno je iznijela trudnoću te rodila zdravo dijete u 36. tjednu.

Adalimumab je rekombinantno, potpuno humano monoklonsko protutijelo klase IgG1. Veže se s topljivim TNF-α i tako blokira njegovu interakciju s receptorima. Kao i ostali TNFi-ji, svrstan je u kategoriju rizika „B" prema FDA. Adalimumab prolazi kroz posteljicu i tako može dovesti do povišenog rizika od infekcije u djeteta. Preporuka EMA-e jest da se prekine s primjenom ADA-e najmanje 5 mjeseci prije začeća te da se dojenčad ne cijepi živim cjepivima 5 mjeseci od posljednje primjene lijeka u majke (10). Prema najnovijim EULAR-ovim smjernicama i smjernicama Britanskoga reumatološkog društva (BSR), ADA se može davati bolesnicama do 20. tjedna trudnoće, pa i dulje, a siguran je i tijekom dojenja (18, 33). Jedna prikazana bolesnica liječena je primjenom ADA-e, a terapija je prekinuta u 4. tjednu trudnoće te su kasniji tijek trudnoće i razvoj ploda protekli bez komplikacija.

Golimumab je humano monoklonsko protutijelo IgG1 κ. Veže se s topljivim TNF-α, kao i s TNF-α vezanim na membranu. U službenom opisu lijeka EMA preporučuje prekinuti primjenu GOL-a najmanje 6 mjeseci prije začeća, a zbog izlučivanja lijeka kroz posteljicu i u majčino mlijeko dojenčad se ne smije cijepiti živim cjepivima najmanje 6 mjeseci od posljednje primjene lijeka u majke (7). Do danas se nije pokazao štetan učinak GOL-a na razvoj ploda i tijek trudnoće,

pregnancy. Because GOL crosses the placenta and is secreted into the mother's milk, newborns cannot be vaccinated with live vaccines at least 6 months after the last treatment application in the mother. (7) Adverse events in pregnancy and fetal development due to treatment with GOL have not been described so far. Nevertheless, because of the lack of information and experience, the EULAR advises avoiding GOL treatment in pregnancy. Despite some authors' suggestion that patients sholud not breastfeed within 6 months after the last treatment application, according to the EULAR guidelines GOL treatment is compatible with breastfeeding. (19, 34) Three of our patients had been taking GOL. Two of them stopped therapy according to the guidelines, 6 months prior to conceiving, and the third stopped therapy 2 months before pregnancy. None of these patients experienced complications during the pregnancy or further neonatal development.

TCZ is an IgG1 humanized monoclonal antibody targeted against the IL-6 receptor. Unlike TNFi, it is classified as a risk category C medication; there is not enough information to assess its safety in pregnancy and breastfeeding. The recommended minimum period from therapy cessation to conception is 3 months. Although research on the effect of TCZ in pregnancy is scarce, most of the papers do not report adverse events. (35, 36) Still, there is not enough data to reach definite conclusions, as there is the matter of an increased number of spontaneous abortions in animal models. (37) Given all of the reasons mentioned above, the EULAR advises withholding from TCZ just before or during pregnancy. Since there is also a lack of information on the concentration of secreted medication in breast milk, breastfeeding is not advised while on therapy. All three patients described here stopped taking TCZ at the time of conception. One patient delivered a healthy baby, another patient's course of pregnancy has been without complications so far. The third patient had a spontaneous abortion in the 7th gestational week.

Along with biologic therapy, csDMARDs are almost always concomitant therapy. The effect of different csDMARDs on pregnancy and fetal development is well known and has been thorughly described. As stated in the EULAR and BSR guidelines issued in 2016, csDMARDs which are safe during pregnancy and lactation are SSZ, hydroxychloroqine and chloroqine, azathioprine, cyclosporine, and tacrolimus. Mycophenolate mofetil and tofacitinib should be discontinued 2 months before conception because they increase the risk of fetal malformations. The latter two DMARDs are also not compatible with breastfeeding. Cyclophosphamide (CYC) is teratogenic and, although it can be used exceptionally in the 2nd and 3rd trimesters, it is contraindicated in the first trimester of pregnancy. Breastfeeding is not advised while on therapy with

no zbog manjka podataka i iskustva EULAR savjetuje izbjegavanje ove terapije tijekom trudnoće. Iako neki autori preporučuju da žene koje primaju GOL ne doje najmanje 6 mjeseci od posljednje primljene doze, prema najnovijim smjericama EULAR-a, terapija GOL-om kompatibilna je s dojenjem (18, 33). Tri prikazane bolesnice liječene su primjenom GOL-a. Dvije su bolesnice prekinule terapiju prema preporukama, 6 mjeseci prije začeća, dok ju je treća prekinula 2 mjeseca prije začeća. U sve tri bolesnice nije bilo nikakvih komplikacija tijekom trudnoće i porođaja, kao ni u njihove novorođenčadi.

TCZ je humanizirano monoklonsko protutijelo potklase IgG1. Za razliku od TNFi-ja, svrstan je u kategoriju rizika „C" prema FDA. Nema dovoljno podataka za procjenu sigurnosti primjene lijeka u trudnoći i dojenju. Preporučeno minimalno razdoblje od prestanka uzimanja lijeka do začeća jest 3 mjeseca. Iako su istraživanja malobrojna, u većini radova nije nađena učestala pojava nepoželjnih ishoda trudnoće (34, 35). Podataka ipak nema dovoljno za donošenje zaključaka pa ostaje otvoreno pitanje češćih spontanih pobačaja primijećenih na životinjskim modelima (36). Prema smjernicama EULAR-a, savjetuje se izbjegavati primjenu TCZ-a neposredno prije i tijekom trudnoće. Nedostaju podatci o koncentraciji izlučenog lijeka u majčinu mlijeku, zbog čega se savjetuje izbjegavati ovu terapiju za vrijeme dojenja (19). Sve tri bolesnice prikazane u ovom radu, koje su liječene TCZ-om, prekinule su terapiju nakon začeća. Jedna bolesnica rodila je zdravo dijete, u druge se bilježi uredno napredovanje trudnoće. Treća je bolesnica imala spontani pobačaj u 7. tjednu trudnoće.

Uz biološku terapiju bolesnice gotovo redovito uzimaju i terapiju nekim od konvencionalnih DMARD-a, s različitim učinkom na tijek i ishod trudnoće. Prema posljednjim preporukama EULAR-a i BSR-a iz 2016., konvencionalni DMARD-i koji se mogu davati u liječenju tijekom trudnoće i dojenja jesu SSZ, hidroksiklorokin i klorokin, azatioprin, ciklosporin i takrolimus. Prema smjernicama, mikofenolat-mofetil i tofacitinib moraju se prekinuti 2 mjeseca prije začeća, zbog povišenog rizika od malformacija, a nisu kompatibilni ni s dojenjem. Ciklofosfamid je teratogen i kontraindiciran u 1. tromjesečju zbog povišenog rizika od razvoja malformacija ploda, no u iznimnim slučajevima može se davati u 2. i 3. tromjesečju. Svakako se ne savjetuje dojiti uz ovu terapiju (18, 33). Dvije su od prikazanih bolesnica tijekom trudnoće uzimale MTX i LEF, koji su kontraindicirani u trudnoći. MTX je antagonist folne kiseline koji interferira s produkcijom purina. Ima izrazita abortivna svojstva, a strukturne anomalije izazvane MTX-om povezane su s vremenom kada se daje i dozom (> 10 mg na tjedan) (37). Zadržava se u organizmu od nekoliko tjedana do nekoliko mjeseci pa se

CYC. (19, 34) Two of our patients were taking MTX and LEF during pregnancy, although both csDMARDs are contraindicated in pregnant patients. MTX is a folic-acid antagonist and it interferes with purine production. It is a potent abortifacient and MTX-induced structural anomalies are related to the time of administration and the dose given (>10mg/week). (38) Given that its washout period is long and lasts from a few weeks to several moths, women (and men) taking MTX should use contraception during the therapy and up to 6 months after discontinuation. (39) As reported by Spanish authors in 2009, the incidence of elective abortions was higher in women on MTX at the time of conception (18%), and the number of miscarriages before the 20th gestational week was also somewhat higher (23% vs 15%) than in healthy controls. (40) So far, there are no official instructions on whether pregnancies started in patients on MTX should be artificially terminated or just closely monitored and MTX promptly discontinued. We described a case of a pregnant patient on MTX (and IFX) during the first two trimesters (at MTX 5 mg/week), without any adverse effects in either the mother or the child.

LEF is contraindicated during pregnancy and lactation. The FDA has labeled it as a risk category X medication and therefore it should be either avoided as a treatment option in women of childbearing age, or taken along with contraception. The washout time for LEF is extremely long and can last up to 2 years. This period can be reduced with cholestiramine; a teratogenic effect is not expected when the plasma concentration of the active metabolite is below 0.02 mg/L. A comparison of patients on cholestiramine who had been taking LEF just before or at the time of conception with the healthy population yielded no significant differences concerning fetal malformations. (43, 44) We reported the case of a patient with an unplanned pregnancy who was taking LEF and therefore had to undergo a medically induced abortion.

CONCLUSION

Our results are concordant with the reports published in the medical literature to date. During pregnancy or at the time of conception, 15 of our patients had been taking one of the TNFis and 1 patient was on the IL-6 blocker; the minimum advised period without therapy before conception was not achieved. Only two patients, both receiving GOL, complied with the offical recommendation and discontinued biologic therapy 6 months prior to pregnancy. Both of them had normal pregnancies and delivered healthy babies. Of the mentioned 16 patients, three had medically advised artifical abortions; in two cases because the patients were on X-labeled csDMARDs (MTX and LEF) and the probability of a teratogenic effect was high. The third pa-

ženama (i muškarcima) na terapiji MTX-om preporučuje kontracepcija tijekom uzimanja MTX-a do 6 mjeseci nakon prestanka terapije (38). U radu španjolskih autora, objavljenom 2009. g., incidencija elektivnih pobačaja u žena koje su uzimale MTX tijekom začeća bila je veća (18%) nego u općoj populaciji, kao i broj spontanih pobačaja prije 20. tjedna (u 23% naspram 15%) (39). Zasad nema točnih smjernica o tome treba li se trudnoća započeta uz MTX arteficijalno završiti ili valja samo promptno ukinuti terapiju, a trudnoću pozorno pratiti. Opisali smo bolesnicu koja je uzimala MTX (uz IFX) u dozi od navodno 5 mg na tjedan tijekom prva dva tromjesečja trudnoće, bez neželjenih učinaka na trudnoću i dijete.

Primjena LEF-a kontraindicirana je u trudnoći i dojenju. Prema FDA, riječ je o kategoriji „X“, stoga žene u reproduktivnoj dobi ne smiju uzimati LEF bez istodobne uporabe pouzdane kontracepcije. LEF se iznimno dugo zadržava u organizmu; vrijeme „ispiranja“ lijeka može trajati i do 2 godine. Ovo se razdoblje može skratiti primjenom kolestiramina. Teratogeni se učinak ne očekuje pri koncentraciji aktivnog metabolita u plazmi nižoj od 0,02 mg/L (40, 41). U trudnica izloženih LEF-u neposredno prije trudnoće i za vrijeme začeća nisu nađene znatnije razlike u razvoju fetalnih malformacija u usporedbi sa zdravom populacijom ako je učinjeno ispiranje lijeka kolestiraminom (42, 43). U radu prikazana bolesnica neplanirano je zanijela za vrijeme uzimanja LEF-a pa je zbog toga trudnoća arteficijalno prekinuta.

ZAKLJUČAK

Prikazani se rezultati ne razlikuju od rezultata objavljenih u dostupnoj medicinskoj literaturi. Od prikazanih bolesnica njih 15 primalo je jedan od lijekova koji pripadaju skupini TNFi-ja i jedna je bolesnica uzimala blokator IL-6 tijekom trudnoće ili neposredno prije začeća, tj. minimalno razdoblje od prestanka primjene lijeka do samog začeća nije ostvareno. Dvije su bolesnice, obje liječene GOL-om, poštovale navedeno minimalno razdoblje te je od posljednje primjene lijeka do začeća prošlo 6 mjeseci. Obje su rodile zdravo dijete. Od opisanih 16 bolesnica tri su imale medicinski indiciran prekid trudnoće. Dvije od njih uzimale su csDMARD-e (MTX i LEF), koji su zbog svojih teratogenih karakteristika svrstani u kategoriju rizika „X“. Treća je bolesnica uzimala IFX i prekinula je terapiju u vrijeme začeća, no medicinski je indiciran prekid trudnoće zbog teških malformacija ploda, koje se ipak ne mogu sa sigurnošću povezati s IFX-om za koji se navodi da je siguran u primjeni tijekom trudnoće.

S obzirom na veliku prevalenciju upalnih reumatskih bolesti u bolesnica generativne dobi, potrebno je pažljivo planirati diferentnu terapiju da bi se izbjegli štetni učinci na reproduktivno zdravlje. Nadalje, važno

tient was on IFX and discontinued it at the time of conception. Unfortunately, the pregnancy had to be terminated because of severe fetal malformations. Still, it is not possible to associate the occurrence of fetal malformations with IFX with certainty, since it has been reported as relatively safe during pregnancy.

Given that the prevalence of inflammatory rheumatic disease is high in patients of childbearing age, careful therapy planning is of utmost importance in order to avoid adverse effects and impairment of reproductive health. Furthermore, it is also necessary to consider the treatment of male patients, as it affects family planning as well. The emphasis is on proper timing; rheumatic disase should be well under control and in a stable remission for a period of at least 3–6 months before pregnancy is attempted. Neither the FDA nor the EMA have declared biologic therapy safe during pregnancy and lactation. Nevertheless, expert rheumatologists, gynecologists, and neonatologists agree on the acceptable safety of some biologc agents in pregnant patients. For the time being, there is no evidence that biologic therapy should be discontinued after conception. Depending on the biologic agent they are taking, patients are advised to stop therapy in the 32nd gestational week at the latest, mostly for the sake of the infant's safety and prevention of early neonatal infections. A multidisciplinary approach including rheumatologists, obstetric gynecologists, and neonatologists along with mother counseling is essential in a careful pregnancy monitoring.

Acknowledgement

We thank all the expert rheumatologists form the Division of Clinical Immunology and Rheumatology, Department of Internal Medicine, UHC Zagreb, who took part in the treatment of the patients described in this article.

Abbreviations

ADA – Adalimumab
AS – Ankylosing spondylitis
BASDAI – Bath Ankylosing Spondylitis Disease Activity Index
BSR – British Society for Rheumatology
CZP – Certolizumab-pegol
DAS 28-SE – Disease Activity Score 28 (calculated using erythrocyte sedimentation rate)
DMARD – Disease-modifying antirheumatic drug
EMA – European Medicines Agency
ETA – Etanercept
EULAR – European League Against Rheumatism
Fab – Antigen-binding fragment
Fc(-regija) – Fragment crystallizable region
FcRn – Neonatal Fc receptor

je voditi računa i o muškarcima koji boluju od upalnih reumatskih bolesti te o utjecaju njihova liječenja na planiranje obitelji. Svakako se naglašava planiranje trudnoće u mirnoj fazi reumatske bolesti, tj. nakon najmanje 3 – 6 mjeseci stabilne remisije. FDA i EMA nisu proglasile nijedan biološki lijek sigurnim u vrijeme trudnoće i laktacije. Ipak, stručnjaci reumatolozi, ginekolozi i neonatolozi došli su do konsenzusa da se neki od lijekova mogu s relativno velikom sigurnošću uzimati i tijekom trudnoće. Zasad nema dokaza o opravdanom prekidu trudnoće u bolesnica koje su zanijele za vrijeme biološke terapije. Trudnicama se savjetuje prekid biološke terapije, ovisno o lijeku koji uzimaju, najkasnije do 32. tjedna trudnoće, ponajviše zbog sigurnosti novorođenčeta i sprječavanja infekcija u ranoj dojenačkoj dobi. Naglašena je potreba multidisciplinarnog pristupa u pomnom nadzoru trudnoće u koji moraju biti uključeni reumatolog, ginekolog-opstetričar i pedijatar-neonatolog, uz savjetovanje s majkom.

Zahvala

Zahvaljujemo svim liječnicima specijalistima Zavoda za kliničku imunologiju i reumatologiju Klinike za unutarnje bolesti KBC-a Zagreb koji su sudjelovali u liječenju bolesnica prikazanih u ovom članku.

Popis kratica

ADA – Adalimumab
AS – Ankilozantni spondilitis
BASDAI – Indeks aktivnosti bolesti za ankilozantni spondilitis
BSR – Britansko reumatološko društvo
CZP – Certolizumab-pegol
DAS 28-SE – Indeks aktivnosti bolesti 28 (izračunat prema vrijednosti sedimentacije eritrocita
DMARD – Antireumatici koji mijenjaju tijek bolesti
EMA – Europska medicinska agencija
ETA – Etanercept
EULAR – Europska liga protiv reumatizma
Fab – Dio koji veže antigen
Fc(-regija) – Područje kristalizirajućeg dijela
FcRn – Neonatalni Fc receptor
FDA – Agencija za hranu i lijekove
GK – Glukokortikoid
GOL – Golimumab (Simponi)
HLA-B27 – humani leukocitni antigen B27
IFX – Infliksimab
IgG1 – Imunoglobulin G1
IgM – Imunoglobulin M
LEF – Leflunomid
MTX – Metotreksat
NSAID – Nesteroidni antireumatik
PsA – Psorijatični artritis

FDA – Food and Drug Administration /
GK – Glucocorticoid
GOL – Golimumab (Simponi)
HLA-B27 – Human leukocyte antigen B27
IFX – Infliximab
IgG1 – Immunoglobulin G1
IgM – Immunoglobulin M
LEF – Leflunomide
MTX – Methotrexate
NSAID – Non-steroidal anti-inflammatory drug
PsA – Psoriatic arthritis
RA – Rheumatoid arthritis
SE – Erythrocyte sedimentation rate
SnSA – Seronegative spondyloarthropathy
SSZ – Sulphasalazine
TCZ – Tocilizumab
TNF-α – Tumor necrosis factor-α
TNFi – Tumor necrosis factor-α inhibitor
TNFR2 – Tumor necrosis factor receptor 2
VACTERL – **V**ertebral defects, **A**nal atresia, **C**ardiac defects, **T**racheo-esophageal fistula, **R**enal anomalies, **L**imb abnormalities

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

RA – Reumatoidni artritis
SE – Sedimentacija eritrocita
SnSA – Seronegativna spondiloartropatija
SSZ – Sulfasalazin
TCZ – Tocilizumab
TNF-α – Čimbenik nekroze tumora-α
TNFi – Inhibitor čimbenika nekroze tumora-α
TNFR2 – Receptor 2 čimbenika nekroze tumora
VACTERL – Defekti kralježnice, atrezija anusa, srčana oštećenja, traheoezofagealna fistula, anomalije bubrega, defomiteti udova

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

REFERENCES / LITERATURA

1. Verstappen SM, King Y, Watson KD, Symmons DPM, Hyrich KL. Anti-TNF therapies and pregnancy: outcome of 130 pregnancies in the British Society for Rheumatology Biologics Register. Ann Rheum Dis. 2011;70(5):823–6.
2. Bogas M, Leandro MJ. Biologic Therapy and Pregnancy. A Systematic Literature Review. Acta Reumatol Port. 2011;36(3): 219–32.
3. Diav-Citrin O, Otcheretianski-Volodarsky A, Shechtman S, Ornoy A. Pregnancy outcome following gestational exposure to TNF-alpha-inhibitors: a prospective, comparative, observational study. Reprod Toxicol. 2014;43:78–84.
4. Calligaro A, Hoxha A, Ruffatti A, Punzi L. Are biological drugs safe in pregnancy? Reumatismo. 2015;66(4):304–17.
5. Østensen M. The use of biologics in pregnant patients with rheumatic disease. Expert Rev Clin Pharmacol. 2017;10(6): 661–9.
6. US Food and Drug Administration. United States FDA pharmaceutical pregnancy categories. Dostupno na: http://depts.washington.edu/druginfo/Formulary/Pregnancy.pdf. Pristupljeno: 21. 8. 2014.
7. EMA. Simponi, INN-golimumab. Product information. Dostupno na: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000992/WC500052368.pdf. Pristupljeno: 3. 4. 2018.
8. EMA. Enbrel, INN-etanercept. Product information. Dostupno na: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000262/WC500027361.pdf. Pristupljeno: 3. 4. 2018.
9. EMA. Remicade, INN-infliximab. Product information. Dostupno na: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000240/WC500050888.pdf. Pristupljeno: 3. 4. 2018.
10. EMA. Humira, INN-adalimumab. Product information. Dostupno na: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000481/WC500050870.pdf. Pristupljeno: 3. 4. 2018.
11. EMA. RoActemra, INN-tocilizumab. Product information. Dostupno na: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000955/WC500054890.pdf. Pristupljeno: 3. 4. 2018.
12. Hyrich KL, Verstappen SM. Biologic therapies and pregnancy: the story so far. Rheumatology. 2014;53(8):1377–85.
13. Anić B, Čikeš N. Primjena lijekova u trudnica s upalnim reumatskim bolestima. Reumatizam. 2006;53:55–8.
14. Sentić M, Barešić M, Anić B i sur. Trudnoća u bolesnica koje primaju biološki lijek zbog upalne reumatske bolesti. Liječ Vjesn. 2010;132:317–8.
15. Bakula M, Cerovec M, Anić B, Čikeš N. Trudnoća u bolesnice s reumatoidnim artritisom koja je liječena metotreksatom i infliksimabom. Reumatizam. 2016;63(1):6–9.
16. Levy RA, de Jesús GR, de Jesús NR, Klumb EM. Critical review of the current recommendations for the treatment of systemic

inflammatory rheumatic diseases during pregnancy and lactation. Autoimmun Rev. 2016;15(10):955–63.

17. Pottinger E, Woolfy RT, Exton LS, Burden AD, Nelson-Piercy C, Smith CH. Exposure to biological therapies during conception and pregnancy: a systematic review. Br J Dermatol. 2018; 178(1):95–102.
18. Götestam Skorpen C, Hoeltzenbein M, Tincani A i sur. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. Ann Rheum Dis. 2016;75(5):795–810.
19. Carter JD, Valeriano J, Vasey FB. Tumor necrosis factor inhibition and VATER association: a causal relationship? J Rheumatol. 2006;33:1014–7.
20. Koren G, Inoue M. Do tumor necrosis factor inhibitors cause malformations in humans? J Rheumatol. 2009;36(3):465–6.
21. Carter JD, Ladhani A, Ricca LR, Valeriano J, Vasey FB. A safety assessment of tumor necrosis factor antagonists during pregnancy: a review of the Food and Drug Administration database. J Rheumatol. 2009;36(3):635–41.
22. Chambers CD, Johnson DL. Emerging data on the use of antitumor necrosis factor-alpha medications in pregnancy. Birth Defects Res A Clin Mol Teratol. 2012;94:607–11.
23. Porter ML, Lockwood SJ, Kimball AB. Update on biologic safety for patients with psoriasis during pregnancy. Int J Wom Dermatol. 2017;3(1):21–5.
24. Pasut G. Pegylation of biological molecules and potential benefits: Pharmacological properties of certolizumab pegol. BioDrugs. 2014;28(1):15–23.
25. Porter C, Armstrong-Fisher S, Kopotsha T i sur. Certolizumab pegol does not bind the neonatal Fc receptor (FcRn): consequences for FcRn-mediated in vitro transcytosis and ex vivo human placental transfer. J Reprod Immunol. 2016;116:7–12.
26. Clowse ME, Wolf DC, Förger F i sur. Pregnancy outcomes in subjects exposed to certolizumab pegol. J Rheumatol. 2015; 42(12):2270–8.
27. Marin J, Acosta Felquer ML, Soriano ER. Spotlight on certolizumab pegol in the treatment of axial spondyloarthritis: efficacy, safety and place in therapy. Open Access Rheumatol. 2018;10:33–41.
28. Mahadevan U, Wolf DC, Dubinsky M i sur. Placental transfer of antitumor necrosis factor agents in pregnant patients with inflammatory bowel disease. Clin Gastroenterol Hepatol. 2013; 11(3):286–92.
29. Mariette X, Förger F, Abraham B i sur. Lack of placental transfer of certolizumab pegol during pregnancy: results from CRIB, a prospective, postmarketing, pharmacokinetic study. Ann Rheum Dis. 2018;77(2):228–33.
30. Lim H, Lee SH, Lee HT i sur. Structural Biology of the TNFα Antagonists Used in the Treatment of Rheumatoid Arthritis. Int J Mol Sci. 2018;19(3). pii: E768.
31. Johnson DL, Jones KL, Chambers CD. Pregnancy outcome in women exposed to etanercept: the OTIS autoimmune diseases in pregnancy project. Dostupno na: www.otispregnancy.org/readResource.php?r=108642.
32. Krause ML, Amin S, Makol A. Use of DMARDs and biologics during pregnancy and lactation in rheumatoid arthritis: what the rheumatologist needs to know. Ther Adv Musculoskel Dis. 2014;6(5):169–84.
33. Flint J, Panchal S, Hurrell A. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding-Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. Rheumatology (Oxford). 2016;55(9):1693–7.
34. Weber-Schoendorfer C, Schaefer C. Pregnancy outcome after tocilizumab therapy in early pregnancy-a case series from the German Embryotox Pharmacovigilance Center. Reprod Toxicol. 2016;60:29–32.
35. Nakajima K, Watanabe O, Mochizuki M i sur. Pregnancy outcomes after exposure to tocilizumab: A retrospective analysis of 61 patients in Japan. Mod Rheumatol. 2016;26(5):667–71.
36. Hoeltzenbein M, Beck E, Rajwanshi R i sur. Tocilizumab use in pregnancy: Analysis of a global safety database including data from clinical trials and post-marketing data. Semin Arthritis Rheum. 2016;46(2):238–45.
37. Methotrexate 2.5 mg tablets. Dostupno na: https://www.medicines.org.uk/emc/product/511/smpc. Pristupljeno: 3. 4. 2018.
38. Martínez Lopez JA, Loza E, Carmona L. Systematic review on the safety of methotrexate in rheumatoid arthritis regarding the reproductive system (fertility, pregnancy, and breastfeeding). Clin Exp Rheumatol. 2009;27:678–84.
39. Agencija za lijekove i medicinske proizvode. Leflunomid; Arava. Uputa o lijeku. Dostupno na: http://www.almp.hr/upl/lijekovi/PIL/UP-I-530-09-06-02-174.pdf. Pristupljeno: 3. 4. 2018.
40. Arava 20 mg tablets. Dostupno na: http://www.medicines.org.uk/emc/medicine/26344. Pristupljeno: 3. 4. 2018.
41. Cassina M, Johnsson DL, Robinson LK i sur. Pregnancy Outcome in Women Exposed to Leflunomide Before or During Pregnancy. Arthritis Rheum. 2012;64(7):2085–94.
42. Hajdyla-Banaś I, Banas T, Rydz-Stryszowska I i sur. Pregnancy course and neonatal outcome after exposure to leflunomide - 2 case reports and review of literature. Przegl Lek. 2009;66 (12):1069–71.
43. Bermas BL. Non-steroidal anti inflammatory drugs, glucocorticoids and disease modifying anti-rheumatic drugs for the management of rheumatoid arthritis before and during pregnancy. Curr Opin Rheumatol. 2014;26(3):334–40.

Reumatizam 2019;66(1):26–32
https://doi.org/10.33004/reumatizam-66-1-3

CASE REPORT PRIKAZ BOLESNIKA

CASE REPORT OF A PATIENT WITH cANCA VASCULITIS WITHOUT AIRWAY INVOLVEMENT

PRIKAZ BOLESNICE S c-ANCA VASKULITISOM BEZ ZAHVAĆENOSTI DIŠNIH PUTOVA

Željka Kardum[1], Jasminka Milas Ahić[1,2], Ivana Kovačević[1], Ana Marija Lukinac[1], Ana Kovač[1], Kristina Kovačević Stranski[1], Višnja Prus[1,2]

[1]Division of Rheumatology, Clinical Immunology, and Allergology, Department of Internal Medicine, UHC Osijek, Osijek, Croatia / Zavod za reumatologiju, kliničku imunologiju i alergologiju, Odjel za internu medicinu, Klinički bolnički centar Osijek, Hrvatska
[2]Faculty of Medicine, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia / Medicinski fakultet Sveučilišta Josipa Jurja Strossmayera u Osijeku, Osijek, Hrvatska

Corresponding author / Adresa autora za dopisivanje:
Željka Kardum
Division of Rheumatology, Clinical Immunology and Allergology / Zavod za reumatologiju, kliničku imunologiju i alergologiju
Department of Internal Medicine / Klinika za unutarnje bolesti
University Hospital Center Osijek / Klinički bolnički centar Osijek
J. Huttlera 4
31000 Osijek
Croatia / Hrvatska
Phone / Tel.: 00385-91-3911 945
E-mail: zeljkakardum@gmail.com

Received/Primljeno: October 18, 2018 / 18. 10. 2018.
Accepted/Prihvaćeno: April 6, 2019 / 6. 4. 2019.

Abstract

Antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV) is a small-vessel vasculitis, characterized by necrotizing inflammation of small vessels and positive ANCAs. cANCAs are directed against proteinase-3 (PR-3) and are specific for granulomatosis with polyangiitis (GPA, formerly known as Wegener's disease), although their role in the immunopathology of the disease is still unclear. This is why the European Medicines Agency suggested that cANCA positivity, in addition to the clinical picture, can be enough for the diagnosis of GPA. Granulomatosis with polyangiitis is characterized by granulomatous inflammation that usually involves the upper and lower respiratory tract, necrotizing vasculitis that affects small and medium-sized vessels, and often rapidly progressive glomerulonephritis. We present a patient with an unusual presentation of cANCA-associated vasculitis, who presented with arthritis, palpable purpura on legs, and pauci-immune necrotizing glomerulonephritis with highly positive cANCA antibodies, without any signs or symptoms of airway involvement. Although renal-limited ANCA vasculitis is recognized as a separate entity, our patient also had signs of skin and joint involvement and prominent constitutional symptoms that contributed to the diagnosis of systemic disease.

In this paper, we present a patient with an atypical course of GPA, which can also be called a limited form of the disease. An atypical course or limited form belongs to the group of sine syndromes in inflammatory rheumatic diseases, which are not very common, but should be considered in the differential diagnosis. To our knowledge, there are only a few described case reports with a similar presentation.

Keywords: Anti-neutrophil cytoplasmic antibody-associated vasculitis – diagnosis, pathology; Antibodies, anti-neutrophil cytoplasmic – analysis; Granulomatosis with polyangiitis – diagnosis, drug therapy, pathology; Purpura – etiology; Glomerulonephritis – etiology; Arthritis – etiology

Sažetak

Vaskulitis povezan s antineutrofilnim citoplazmatskim protutijelima (engl. *Anti-neutrophil Cytoplasmatic Antibody* – ANCA) ili skraćeno ANCA vaskulitis (engl. *ANCA-associated vasculitis* – AAV) jest vaskulitis malih krvnih žila karakteriziran nekrotizirajućom upalom malih krvnih žila i pozitivnim antineutrofilnim citoplazmatskim protutijeli-

ma. Protutijela c-ANCA usmjerena su na proteinazu 3 (PR-3) i karakteristična za granulomatozu s poliangiitisom (GPA), prije poznatu kao Wegenerova bolest, premda njihova uloga u imunopatologiji bolesti još nije razjašnjena. Upravo zbog visoke specifičnosti protutijela Europska agencija za lijekove predložila je da pozitivna protutijela c-ANCA uz popratnu kliničku sliku budu dovoljna za dijagnozu GPA. Granulomatozu s poliangiitisom karakteriziraju granulomatozna upala koja uobičajeno zahvaća gornje i donje dišne putove, nekrotizirajući vaskulitis što zahvaća male i srednje velike krvne žile i često prisutan brzoprogresivni glomerulonefritis. U ovom radu prikazana je bolesnica s neuobičajenom prezentacijom c-ANCA vaskulitisa uz prisutne artritis, palpabilnu purpuru na nogama, *pauciimuni* nekrotizirajući glomerulonefritis i visokopozitivna protutijela c-ANCA, međutim, bez znakova i simptoma zahvaćanja dišnih putova. Premda je ANCA vaskulitis ograničen na bubreg otprije poznat kao poseban entitet, naša je bolesnica također imala prisutno zahvaćanje kože i zglobova te izražene konstitucijske simptome, što upućuje na sustavni oblik bolesti.

Prikazana je bolesnica s atipičnim oblikom GPA, koji se može nazvati i ograničenim oblikom bolesti. Atipični ili ograničeni oblik bolesti pripada skupini sindroma *sine* u upalnim reumatskim bolestima, koji nisu česti, ali ih je potrebno razmotriti pri diferencijalnoj dijagnozi. Prema našim saznanjima, samo je nekoliko opisanih prikaza bolesnika sa sličnom prezentacijom bolesti.

Ključne riječi: Vaskulitis povezan s antineutrofilnim citoplazmatskim protutijelima – dijagnoza, patologija; Antineutrofilna citoplazmatska protutijela – analiza; Granulomatoza s poliangiitisom – dijagnoza, farmakoterapija, patologija; Purpura – etiologija; Glomerulonefritis – etiologija, patologija; Artritis – etiologija

INTRODUCTION

Antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis is a small-vessel vasculitis characterized by necrotizing inflammation of small vessels and positive ANCAs. ANCA-associated vasculitis is subdivided into granulomatosis with polyangiitis (GPA, formerly known as Wegener's granulomatosis), microscopic vasculitis (MPA), eosinophilic granulomatosis with polyangiitis (EGPA or Churg-Strauss vasculitis), and ANCA-positive renal-limited vasculitis (RLV) as a special entity (1). ANCA-associated vasculitis is characterized by positive ANCA antibodies. These antibodies are directed against proteinase 3 (PR-3) or cANCA, and against myeloperoxidase (MPO) or pANCA antibodies. cANCA antibodies are characteristic for GPA, with high sensitivity (especially in active, systemic disease) (2) and specificity (3). Although the presence of cANCAs in GPA is well established, the immunopathology of the disease is still unclear, and individuals with no signs of active disease can have a high antibody titer (2). GPA is characterized by granulomatous inflammation that affects the upper and lower respiratory tract and blood vessel inflammation (vasculitis), which can damage organ systems. The areas most commonly affected by GPA include the sinuses, lungs, and kidneys, but any site can be affected (4).

The estimated annual incidence of GPA in Europe is about 2–12 per million and the prevalence of GPA is 24–157 per million (5).

Several diagnostic criteria are used to establish the diagnosis of GPA. The American College of Rheumatology (ACR) 1990 classification criteria for GPA include the following: 1) nasal or oral inflammation

UVOD

Vaskulitis povezan s antineutrofilnim citoplazmatskim protutijelima (engl. *Anti-neutrophil Cytoplasmatic Antibody* – ANCA) ili skraćeno ANCA vaskulitis (engl. ANCA-associated vasculitis – AAV) karakteriziraju nekrotizirajuća upala malih krvnih žila i pozitivan nalaz ANCA-e. Vaskulitisi povezani s ANCA-om dijele se na granulomatozu s poliangiitisom (GPA) koja je prije bila poznata pod nazivom Wegenerova granulomatoza, mikroskopski vaskulitis (MPA), eozinofilnu granulomatozu s poliangiitisom (EGPA ili Churg-Straussin vaskulitis) i ANCA-pozitivni vaskulitis ograničen na bubrege (RLV) kao poseban entitet (1). Značajka ANCA vaskulitisa jest pozitivan nalaz protutijela ANCA, koja mogu biti usmjerena na proteinazu 3 (PR-3) pa se nazivaju c-ANCA i na mijeloperoksidazu (MPO) te se zovu p-ANCA. Protutijela c-ANCA karakteristična su za GPA, s visokim razinama osjetljivosti (osobito kod aktivne, sistemske bolesti) (2) i specifičnosti (3). Iako je prisutnost protijela cANCA kod GPA dobro utvrđena, imunopatologija bolesti još nije razjašnjena i osobe bez ikakvih znakova aktivne bolesti mogu imati visok titar tih protutijela (2). GPA je karakteriziran granulomatoznom upalom što zahvaća gornje i donje dišne putove te upalom krvnih žila (vaskulitisom) koji može uništiti organske sustave. Organi koje GPA najčešće zahvaća jesu sinusi, pluća i bubrezi, ali može zahvatiti bilo koji organ ili dio tijela (4).

Procjenjuje se da godišnja incidencija GPA u Europi iznosi 2 – 12 na milijun osoba, a prevalencija 24 – 157 na milijun osoba (5).

Pri postavljanju dijagnoze GPA rabi se nekoliko dijagnostičkih kriterija. Klasifikacijski kriteriji Američkog društva za reumatologiju (ACR) iz 1990. godine za

(painful or painless oral ulcers, or purulent or bloody nasal discharge); 2) abnormal chest radiograph showing nodules, fixed infiltrates, or cavities; 3) abnormal urinary sediment (microscopic hematuria with or without red cell casts); 4) granulomatous inflammation on biopsy of an artery or perivascular area (6). The presence of two or more of these four criteria yielded a sensitivity of 88% and a specificity of 92%.

The European Medicines Agency (EMA) algorithm suggested that the surrogate markers might permit the diagnosis of GPA to be made in the absence of a biopsy (7). These surrogate markers include: 1) lower airways: radiograph evidence of fixed pulmonary infiltrates, nodules, or cavitations for more than one month, or bronchial stenosis; upper airways: bloody nasal discharge and crusting for more than one month or nasal ulceration; 2) chronic sinusitis, otitis media, or mastoiditis for more than three months; retro-orbital mass or inflammation; subglottic stenosis; saddle nose deformity/destructive sinonasal disease; 3) glomerulonephritis: hematuria associated with red cell casts or >10 dysmorphic red cells; or 2+ hematuria or 2+ proteinuria on the dipstick; and 4) positive ANCAs in patients with surrogate markers for GPA allow a diagnosis of GPA without a biopsy.

The clinical presentation of the disease in approximately 90% of the cases includes ear-nose-throat (ENT) symptoms like nasal crusting, sinus pain, chronic rhinosinusitis, nasal obstruction, or bloody nasal discharge. Symptoms related to pulmonary involvement are present in approximately two–thirds of the patients. Respiratory symptoms mostly include cough, hemoptysis, dyspnea, and pleuritic pain (8). Among patients with GPA, it is unusual for pulmonary symptoms to occur in the absence of upper respiratory tract symptoms or signs. Renal involvement is the third main manifestation of GPA and usually includes glomerulonephritis associated with few or no immune deposits in the glomeruli (pauci-immune glomerulonephritis) visible on immunofluorescence and electron microscopy (9). Neurological involvement is present in one–third of the patients. In 10–50% of the patients, skin lesions are present, with palpable purpura on the legs and feet as the most common manifestation. Constitutional symptoms, such as fever and weight loss, are present in 30–80% of the patients. Non-erosive polyarthritis affecting medium- and large-size joints is described in two–thirds of the patients. Other manifestations include eye involvement (mainly episcleritis) and, rarely, gastrointestinal and cardiac manifestations (10).

The treatment of GPA is comprised of the induction regimen (with high-dose glucocorticoids and immunosuppressant agents) followed by maintenance treatment (with less toxic agents if possible). For the induc-

GPA uključuju ovo: 1) upalu nosne ili usne šupljine (bolne ili bezbolne ulceracije u ustima ili gnojni ili krvavi iscjedak iz nosa); 2) abnormalni radiografski nalaz pluća koji pokazuje čvoriće, fiksne plućne infiltrate ili kavitacije; 3) abnormalni sediment urina (mikroskopska hematurija s eritrocitnim cilindrima ili bez njih); 4) patohistološki nalaz granulomatozne upale arterije ili perivaskularnog područja (6). Prisutnost dvaju ili više ovih kriterija ima osjetljivost od 88% i specifičnost od 92%.

Europska agencija za lijekove (EMA) ponudila je algoritam prema kojem se dijagnoza GPA može postaviti na temelju zamjenskih biljega i bez biopsije (7). Ti zamjenski biljezi uključuju ovo: 1) donji dišni putovi: radiografski dokazani fiksni plućni infiltrati, čvorići ili kavitacije tijekom više od mjesec dana ili bronhalna stenoza; 2) gornji dišni putovi: krvavi iscjedak iz nosa i krustacije tijekom više od mjesec dana ili nosne ulceracije; kronični sinusitis, otitis media ili mastoiditis tijekom više od tri mjeseca; upala retroorbitalnog tkiva, subglotalna stenoza; deformitet nosa u obliku sedlastog nosa / destruktivna bolest nosa i sinusa; 3) glomerulonefritis: hematurija s eritrocitnim cilindrima ili > 10 dismorfnih eritrocita; ili hematurija 2+ ili proteinurija 2+ na urinskoj testnoj vrpci; 4) pozitivna protutijela ANCA u bolesnika sa zamjenskim biljezima za GPA dopuštaju dijagnozu GPA bez biopsije.

Klinička prezentacija bolesti u približno 90% bolesnika uključuje otorinolaringološke simptome poput stvaranja krasta u nosu, bol u sinusima, kronični rinosinusitis, opstrukciju nosa ili krvavi iscjedak iz nosa. Simptomi koji upućuju na zahvaćenost pluća prisutni su u približno dvije trećine bolesnika. Respiratorni simptomi uglavnom uključuju kašalj, hemoptizu, dispneju i pleuralnu bol (8). Kod bolesnika s GPA nije uobičajeno da se plućni simptomi pojavljuju bez simptoma i znakova zahvaćenosti gornjih dišnih putova. Bubrežni poremećaj treća je glavna manifestacija GPA, obično u obliku glomerulonefritisa povezanog s vrlo malo ili nimalo imunodepozita u glomerulima (*pauciimuni* glomerulonefritis) vidljivih imunofluorescencijom ili elektronskom mikroskopijom (9). Neurološki znakovi prisutni su u trećine bolesnika. U 10 – 50% bolesnika prisutne su kožne lezije s palpabilnom purpurom na nogama i stopalima kao najčešćom manifestacijom. Konstitucijski simptomi poput vrućice i gubitka tjelesne težine prisutni su u 30 – 80% bolesnika. Neerozivni poliartritis srednje velikih i velikih zglobova nalazi se u dvije trećine bolesnika. Druge manifestacije uključuju zahvaćenost oka (uglavnom episkleritis) i, rijetko, gastrointestinalne i srčane manifestacije (10).

Liječenje GPA sastoji se od indukcijskog liječenja (visokim dozama glukokortikoida i imunosupresiva), a zatim terapije održavanja (prema mogućnosti manje toksičnim lijekovima). Pri indukcijskom liječenju bo-

tion treatment in life-threatening or organ-threatening disease, cyclophosphamide and rituximab are recommended in rapidly progressive kidney failure, and diffuse alveolar hemorrhage, plasma exchange therapy is an option. In the case of limited disease, the first choice of treatment can be mycophenolate mofetil (MMF) or methotrexate (11).

CASE REPORT

A 46-year-old Caucasian female patient had initial symptoms of weight loss, and swelling and pain in both ankles 4 months prior to workup in our clinic. She had no relevant history of chronic illness and was not taking any therapy.

One month after the patient's symptoms had started, she was examined by a physiatrist due to the swelling and pain in her ankles and purpuric rash on her legs that resolved spontaneously. Reactive arthritis was suspected and she was recommended to take 4 mg of methylprednisolone, which she took for a couple of weeks and then stopped since her symptoms persisted despite the therapy. Three months later, the patient was admitted to the Infectious Diseases Department in a General County Hospital due to persistent intermittent high fever (with maximum axillary temperature of 38.6°C). Antibiotics were started empirically, but there was no resolution of the symptoms. Blood and urine cultures were negative, chest X-ray scan and abdominal ultrasound were unremarkable. Tumor markers were negative, and since no infectious cause was found, the patient was discharged from the hospital and referred to a rheumatologist. But due to the reappearance of the purpuric rash on her legs, she was examined at the University Hospital Center Emergency Department and was then admitted to the Department of Rheumatology, Clinical Immunology, and Allergology.

On admission, the patient's major complaint was high fever that had been present in the previous 3 months, weight loss (8 kg in that period), and arthralgia of the ankle joints. Physical examination revealed palpable purpura on the legs and swollen, painful ankles. Her family history was negative for autoimmune diseases. The patient had been taking ibuprofen 600 mg three times daily. Laboratory findings during her stay at the Infectious Diseases Department showed anemia with elevated ESR and CRP and hypergammaglobulinemia. The patient denied bloody discharge from her nose, wheezing, dyspnea, or cough. Physical examination revealed no saddle nose. Her chest and heart sounds were normal, there was no liver and spleen enlargement, and no peripheral lymphadenopathy was present. The laboratory findings showed elevated CRP 84.7 mg/L (ref. range <5), ESR 70 mm/3.6 KS (range: 4–24), anemia with hemoglobin 108 g/L (range: 119–157), and ferritin 283.9 ug/L (range: 10–

lesti koja ugrožava život ili organe ciklofosfamid i rituksimab preporučuju se kod brzoprogredirajućeg zatajenja bubrega, a kod difuznog alveolarnog krvarenja mogući je izbor terapijska izmjena plazme. Ako je bolest ograničena, prvi izbor liječenja mogu biti mikofenolatmofetil (MMF) ili metotreksat (11).

PRIKAZ BOLESNICE

Početni simptomi žene u dobi od 46 godina bili su gubitak tjelesne težine te oticanje i bol u oba gležnja 4 mjeseca prije obrade u našoj klinici. Dotad nije bolovala ni od kakve kronične bolesti i nije uzimala nikakvu terapiju.

Mjesec dana nakon početka simptoma bolesnicu je pregledao fizijatar zbog oticanja i bolnosti gležnjeva te purpurnog osipa na nogama koji se spontano povukao. Zbog sumnje na reaktivni artritis bolesnici je preporučeno da uzima 4 mg metilprednizolona, što je i činila nekoliko tjedana, a zatim prestala jer su simptomi trajali unatoč terapiji. Tri mjeseca poslije bolesnica je primljena na Odjel za zarazne bolesti Opće županijske bolnice zbog perzistentne intermitentne vrućice (najviša aksilarna temperatura od 38,6° C). Započeta je empirijska terapija antibioticima, ali nije dovela do povlačenja simptoma. Kulture krvi i urina bile su negativne, rendgenogram srca i pluća te ultrazvuk abdomena bili su bez obilježja. Tumorski biljezi bili su negativni, a budući da nije nađen infektivni uzročnik, bolesnica je otpuštena iz bolnice te upućena reumatologu. Međutim, zbog ponovne pojave purpurnog osipa po nogama pregledana je na Odjelu za hitnu pomoć Sveučilišne bolnice te primljena na Odjel za reumatologiju, kliničku imunologiju i alergologiju.

Nakon prijma bolesnica se najviše žalila na visoku tjelesnu temperaturu prisutnu tijekom prethodna 3 mjeseca, gubitak tjelesne težine (8 kg u tom razdoblju) i artralgiju u području gležnjeva. Na fizikalnom pregledu uočeni su palpabilna purpura na nogama te otečeni, bolni gležnjevi. U obiteljskoj anamnezi nije bilo autoimunosnih bolesti. Bolesnica je uzimala ibuprofen u dozi od 600 mg tri puta na dan. Laboratorijski nalazi tijekom njezina boravka na Odjelu za zarazne bolesti pokazali su anemiju s povišenom sedimentacijom eritrocita i vrijednošću CRP-a te hipergamaglobulinemiju. Negirala je krvavi iscjedak iz nosa, piskanje pri disanju, dispneju ili kašalj. Na fizikalnom pregledu nije nađen sedlasti nos, šum disanja i srčani tonovi bili su normalni, nije bilo povećanja jetre i slezene ni periferne limfadenopatije. Laboratorijski nalazi pokazali su povišenu vrijednost CRP-a od 84,7 mg/L (referentni raspon: < 5), sedimentaciju eritrocita od 70 mm/3,6 ks (raspon: 4 – 24), anemiju uz vrijednosti hemoglobina od 108 g/L (raspon: 119 – 157) i feritina od 283,9 µg/L (raspon: 10 – 120). Klirens kreatinina bio je 1,41 mL/s 1,73 m^2 (raspon: 1,60 – 2,94), uz 24-satnu proteinuriju

120). Creatinine clearance was 1.41 mL/s1.73m^2 (range: 1.60–2.94), with 24-hour proteinuria of 767 mg/dU (<150); BUN and creatinine levels were normal. Autoantibodies were tested and showed positive ANA 1:320 on cytoplasmic fluorescence, with positive actin antibodies, ENA screen, and cardiolipin antibodies. RF and anti-CCP were negative with normal C3 and C4. pANCA and anti-GBM were negative. cANCAs were highly positive: 771 (positive >25, tested on xMAP Luminex assay 200).

The patient was examined by an ear-nose-throat specialist. Rhinoscopy, laryngoscopy, and otoscopy were performed and no signs of upper airway involvement were found. Chest X-ray was unremarkable, as well as US of the abdomen, ECG, heart ultrasound, and ophthalmological exam. Repeated urine erythrocyte morphology revealed 13%, 21% and 18% of dysmorphic erythrocytes in samples taken on 3 consecutive days. Cytological urine sediment was negative for malignant cells and bacteria. Blood and urine cultures were negative, so prednisolone 1 mg/kg was initiated. Kidney biopsy was performed and a diagnosis of rapidly progressive pauci-immune glomerulonephritis was confirmed.

Additionally, testing showed negative HBV, HCV antibodies, and QuantiFeron TB Gold test. EBV and CMV antibodies revealed past contact. MSCT of the paranasal cavities was unremarkable. Lung function tests (spirometry and DLCo) were normal. Immunofixation electrophoresis revealed two oligoclonal bands (IgG type kappa). Bone marrow aspiration was performed and was unremarkable.

The diagnosis of cANCA-associated vasculitis was made and treatment was started with an induction regimen that included glucocorticoids in tapering dosage and cyclophosphamide (15 mg/kg every two weeks for the first three cycles, followed by application every three weeks for 6 months). After the initial treatment, the symptoms rapidly improved, and the arthritis, fever, and purpura completely resolved. The patient's appetite improved and she gained weight. Her laboratory results were: CRP 10 mg/L (ref. range< 5), ESR 25 mm/3.6 KS (range: 4–24), hemoglobin 130 g/l (range: 119–157), with no erythrocyturia or proteinuria. cANCAs remained positive (440, positive >25). After the remission was achieved, maintenance treatment with azathioprine was continued. The patient had no signs and symptoms of pulmonary involvement during the treatment or at follow-up. Because of the unusual presentation of the disease, the ENT examination was repeated and no signs of upper airway involvement were found. Initially, no MSCT of chest organs had been done due to technical reasons, but during the follow-up, a HRCT of lungs was ultimately performed and showed no signs of interstitial lung involvement, no hilar or

od 767 mg/dU (< 150); BUN i kreatinin imali su normalne vrijednosti. Testovima na autoantitijela nađeni su pozitivan ANA 1 : 320 citoplazmatskom fluorescencijom te pozitivna protutijela na aktin, ENA probir i kardiolipinska protutijela. RF i anti-CCP bili su negativni, uz normalne C3 i C4. p-ANCA i anti-GBM bili su negativni. Protutijela c-ANCA bila su visokopozitivna: 771 (pozitivan nalaz: > 25, ispitano testom xMAP Luminex 200).

Na otorinolaringološkom pregledu bolesnici su učinjene rinoskopija, laringoskopija i otoskopija, no nisu nađeni znakovi zahvaćenosti gornjih dišnih putova. Rendgenogram srca i pluća bio je bez osobitosti, kao i ultrazvuk abdomena, EKG, ultrazvuk srca te oftalmološki pregled. Ponovljena analiza morfologije eritrocita u urinu pokazala je 13, 21 i 18% dismorfnih eritrocita u uzorcima uzetima 3 dana zaredom. Citološka analiza sedimenta urina bila je negativna na zloćudne stanice i bakterije. Kulture krvi i urina bile su negativne pa se započelo s primjenom prednizolona u dozi od 1 mg/kg. Provedena je biopsija bubrega kojom je potvrđena dijagnoza brzoprogresivnoga *pauciimunoga* glomerulonefritisa.

Usto, rezultati testova protutijela na HBV i HCV, kao i testa QuantiFeron-TB Gold bili su negativni. Protutijela na EBV i CMV upozorila su na prethodni kontakt s tim virusima. MSCT paranazalnih sinusa bio je uredan. Testovi plućne funkcije (spirometrija i DLCo) bili su normalni. Imunofiksacijska elektroforeza pokazala je dvije oligoklonske vrpce (IgG tipa kapa). Provedena je aspiracija koštane srži i nalaz je bio uredan.

Postavljena je dijagnoza c-ANCA vaskulitisa i započeto liječenje indukcijskom terapijom koja se sastojala od glukokortikoida u postupno sve nižoj dozi i ciklofosfamida (15 mg/kg svaka dva tjedna za vrijeme prva tri ciklusa, a zatim primjena svaka tri tjedna tijekom 6 mjeseci). Nakon toga početnog liječenja simptomi su se brzo poboljšali, a artritis, vrućica i purpura potpuno su se povukli. Bolesnici se poboljšao apetit i dobila je na tjelesnoj težini. Laboratorijski rezultati bili su ovi: CRP 10 mg/L (referentni raspon: < 5), sedimentacija eritrocita 25 mm/3,6 ks (raspon: 4 – 24), hemoglobin 130 g/L (raspon: 119 – 157), bez eritrociturije ili proteinurije. Protutijela c-ANCA ostala su pozitivna (440; pozitivan nalaz: > 25). Budući da je postignuta remisija, nastavljeno je s njezinim održavanjem primjenom azatioprina. Tijekom liječenja i kasnijih kontrolnih pregleda bolesnica nije imala znakova i simptoma zahvaćenosti pluća. Zbog neobične prezentacije bolesti ponovljen je otorinolaringološki pregled, no nisu nađeni znakovi bolesti u gornjim dišnim putovima. Početno nije obavljen MSCT torakalnih organa zbog tehničkih razloga, ali tijekom kontrolnih pregleda naposljetku je učinjen HRCT pluća koji nije pokazao nikakvih znakova intersticijskih plućnih promjena

mediastinal lymphadenopathy, no effusions or consolidates, and no infiltrates on the lung parenchyma.

DISCUSSION

Our patient had an unusual presentation of cANCA vasculitis, which was successfully treated. cANCA antibodies are characteristic for GPA, although their role in the immunopathology of the disease is still unclear because a high titer is possible although remission has been achieved (12–14). cANCA antibodies are highly specific for GPA, with high sensitivity, especially in the systemic form of the disease (2, 3). This is why EMA suggests that the diagnosis of GPA can be based on cANCA positivity and established clinical features of the disease (7). The most common presentation of GPA includes airway involvement (10), and there are few case reports of patients with cANCA vasculitis without known airway involvement (15–18).

Such cases are described as a partial or atypical form of Wegener's disease. In 1985, Hensen *et al.* reported a case of a 30-year-old patient with an angiocentric granulomatous change on her lip and rapidly progressive crescentic glomerulonephritis (15). The patient also had skin changes on her legs that were proven to be discoid lupus by a biopsy. The diagnosis of atypical Wegener's disease was made. Kawikaza *et al.* reported a 68-year-old woman with arthralgia, ophthalmologic manifestations, chronic renal failure due to RPGN, and highly positive cANCA-positive antibodies, who had no airway involvement (16).

Our patient had biopsy-proven crescentic, pauci-immune glomerulonephritis, with highly positive cANCA antibodies. Although the term renal limited vasculitis is known, in most cases these are forms of pANCA-positive renal-limited vasculitis (17). In a retrospective, epidemiologic survey, Fujimoto tried to establish the incidence of ANCA-positive RLV (18). Findings showed that among the RLV patients there were no cANCA- positive ones, and 91% of them were pANCA-positive.

Our patient, apart from the renal involvement, had arthritis and typical skin changes with prominent constitutional symptoms (fever, weight loss). As she had no airway involvement, she did not meet the ACR criteria (7) necessary for a diagnosis of GPA. However, due to cANCA positivity, which is a hallmark of GPA, especially at high titers as found in our case, accompanied by pauci-immune glomerulonephritis as well as joint and skin involvement, the diagnosis of atypical GPA was clear.

These atypical forms of the disease are very rare in clinical practice and there are only a few literature reports. That is why Rovensky introduced the term *sine syndromes*, which represents atypical forms of inflammatory rheumatic diseases, the courses of which are often severe (19). Sine syndromes do not meet the

ni hilarnu ili medijastinalnu limfadenopatiju ni izljev ili konsolidaciju ili infiltrate plućnog parenhima.

RASPRAVA

Naša je bolesnica imala neobičnu prezentaciju c-ANCA vaskulitisa koji je uspješno liječen. Protutijela c-ANCA karakteristična su za GPA, iako njihova uloga u imunopatologiji ove bolesti još nije razjašnjena, jer mogu biti prisutna i u visokom titru unatoč postignutoj remisiji (12 – 14). Ta su protutijela visokospecifična za GPA te imaju visoku osjetljivost, osobito pri sistemskim oblicima bolesti (2, 3). Zbog toga je EMA predložila da se dijagnoza GPA temelji na pozitivnom nalazu protutijela c-ANCA i prisutnim kliničkim znakovima bolesti (7). Najčešći klinički oblik GPA zahvaća dišne putove (10), no opisano je i nekoliko bolesnika s c-ANCA vaskulitisom bez poznate zahvaćenosti dišnih putova (15 – 18).

Takvi su slučajevi opisani kao djelomični ili atipični oblik Wegenerove granulomatoze. Hansen i suradnici opisali su 1985. godine 30-godišnju bolesnicu s angiocentričnom granulomatoznom promjenom na usni i brzoprogresivnim glomerulonefritisom s polumjesecima (15). Bolesnica je imala kožne promjene i na nogama za koje se na biopsiji pokazalo da su diskoidni lupus. Postavljena je dijagnoza Wegenerove bolesti. Kakizawa i suradnici opisali su 68-godišnju ženu s artralgijom, oftalmološkim manifestacijama, kroničnim zatajenjem bubrega zbog brzoprogresivnoga glomerulonefritisa te s visokopozitivnim protutijelima c-ANCA u koje su dišni putovi bili pošteđeni (16) .

Naša je bolesnica imala biopsijom potvrđen *pauciimuni* glomerulonefritis s polumjesecima i visokopozitivna protutijela c-ANCA. Iako je poznat izraz vaskulitis ograničen na bubrege, najčešće je riječ o oblicima pANCA-pozitivnog vaskulitisa ograničenoga na bubrege (17). U retrospektivnom epidemiološkom ispitivanju Fujimoto pokušao je ustanoviti incidenciju ANCA-pozitivnog vaskulitisa ograničenoga na bubrege (18). Rezultati su pokazali da među tim bolesnicima nije bilo onih s pozitivnim protutijelima c-ANCA i da je njih 91% bilo p-ANCA-pozitivno.

U naše su bolesnice, osim zahvaćenosti bubrega, bili prisutni artritis i tipične kožne promjene s izrazitim konstitucijskim simptomima (vrućica, gubitak tjelesne težine). Budući da dišni putovi nisu bili zahvaćeni, prema ACR-u (7), nije zadovoljavala kriterije potrebne za dijagnozu GPA. Međutim, zbog pozitivnih protutijela c-ANCA koja su tipična za GPA, osobito ako su prisutna u visokom titru kao kod naše bolesnice, u kombinaciji s *pauciimunim* glomerulonefritisom te zahvaćenošću kože i zglobova, bilo je jasno da je riječ o atipičnom GPA.

Ti atipični oblici bolesti vrlo su rijetki u kliničkoj praksi i u literaturi je opisano svega nekoliko slučajeva. Zato je Rovenský uveo izraz sindromi *sine* što obuhva-

standard criteria used to assist in the classification of patients with rheumatological disorders.

CONCLUSION

In this paper we presented a patient with an atypical presentation of GPA, with renal, joint, and skin involvement. At the time of the initial symptoms and throughout the clinical course of the disease, the patient had no signs and symptoms of airway involvement. This was also confirmed by diagnostic procedures. These atypical forms of the disease are important for consideration, due to the timely establishment of a proper diagnosis and initiation of optimal treatment. This is why in rheumatology, *sine syndromes* are a reminder to clinicians that unusual presentations of inflammatory rheumatic diseases are always possible and should be considered.

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

ća atipične oblike upalnih reumatskih bolesti koje često imaju težak tijek (19). Sindromi *sine* ne ispunjavaju standardna mjerila koja pomažu u klasifikaciji bolesnika s reumatološkim bolestima.

ZAKLJUČAK

U ovom smo radu prikazali bolesnicu s atipičnom prezentacijom GPA, kojoj su bili zahvaćeni bubrezi, koža i zglobovi. U vrijeme prvih simptoma te tijekom cijelog tijeka bolesti bolesnica uopće nije imala znakove zahvaćenosti dišnih putova, što je potvrđeno i dijagnostičkim postupcima. Važno je imati na umu ove atipične oblike bolesti radi pravodobnog postavljanja točne dijagnoze i započinjanja optimalnog liječenja. Stoga su sindromi *sine* u reumatologiji podsjetnik kliničarima da su neobične prezentacije upalnih reumatskih bolesti uvijek moguće i potrebno ih je uzeti u obzir.

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

REFERENCES / LITERATURA

1. Jennette JC, Falk RJ, Andrassy K i sur. Nomenclature of systemic vasculitides. Proposal of an international consensus conference. Arthritis Rheum. 1994;37(2):187–92.
2. Finkielman JD, Lee AS, Hummel AM i sur.; WGET Research Group. ANCA are detectable in nearly all patients with active severe Wegener's granulomatosis. Am J Med. 2007;120(7):643.e9–14.
3. Stone JH, Talor M, Stebbing J i sur. Test characteristics of immunofluorescence and ELISA tests in 856 consecutive patients with possible ANCA-associated conditions. Arthritis Care Res. 2000;13(6):424–34.
4. Bacon PA. The spectrum of Wegener's granulomatosis and disease relapse. N Engl J Med. 2005;352(4):330–2.
5. Mohammad AJ, Jacobsson LT, Westman KW i sur. Incidence and survival rates in Wegener's granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome and polyarteritis nodosa. Rheumatology (Oxford). 2009;48(12):1560–5.
6. Leavitt RY, Fauci AS, Bloch DA, Michel BA, Hunder GG, Arend WP i sur. The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis. Arthritis Rheum. 1990;33(8):1101–7.
7. Abdulkader R, Lane SE, Scott DG, Watts RA. Classification of vasculitis: EMA classification using CHCC 2012 definitions. Ann Rheum Dis. 2013;72(11):1888.
8. Jennette JC, Falk RJ. Small-vessel vasculitis. N Engl J Med 1997;337(21:1512–23.
9. Falk RJ, Hogan S, Carey TS, Jennette JC. Clinical course of antineutrophil cytoplasmic autoantibody-associated glomerulonephritis and systemic vasculitis. The Glomerular Disease Collaborative Network. Ann Intern Med. 1990;113(9):656–63.
10. Lynch JP, White E, Tazelaar H, Langford CA. Wegener's granulomatosis: evolving concepts in treatment. Semin Respir Crit Care Med. 2004;25(5):491–521.
11. Yates M, Watts RA, Bajema IM, Cid MC, Crestani B, Hauser T i sur. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. Ann Rheum Dis. 2016;75(9):1583–94.
12. Kallenberg CG. Pathogenesis of ANCA-associated vasculitides. Ann Rheum Dis. 2011;70(Suppl. 1):i59–63.
13. Tervaert JW, van der Woude FJ, Fauci AS, Ambrus JL, Velosa J, Keane WF i sur. Association between active Wegener's granulomatosis and anticytoplasmic antibodies. Arch Intern Med. 1989;149(11):2461–5.
14. Boomsma MM, Stegeman CA, van der Leij MJ, Oost W, Hermans J, Kallenberg CG i sur. Prediction of relapses in Wegener's granulomatosis by measurement of antineutrophil cytoplasmic antibody levels: a prospective study. Arthritis Rheum. 2000;43(9):2025–33.
15. Hansen LS, Silverman S Jr, Pons VG, Hales M, Greenspan JS, Sagebiel RW i sur. Limited Wegener's granulomatosis: report of a case with oral, renal, and skin involvement. Oral Surg Oral Med Oral Pathol. 1985;60(5):524–31.
16. Kakizawa T, Ichikawa K, Yamauchi K i sur. Atypical Wegener's granulomatosis with positive cytoplasmic antineutrophil cytoplasmic antibodies, ophthalmologic manifestations, and slowly progressive renal failure without respiratory tract involvement. Intern Med. 1999;38(8):679–82.
17. Oliet A, Praga M, Vidaur F, Elósegui A, Usera G, Bello I. Periglomerular granulomatosis. A limited form of Wegener's granulomatosis with exclusive renal involvement? Arch Intern Med. 1988;148(6):1377–9.
18. Fujimoto S, Uezono S, Hisanaga S i sur. Incidence of ANCA-associated primary renal vasculitis in the Miyazaki Prefecture: the first population-based, retrospective, epidemiologic survey in Japan. Clin J Am Soc Nephrol. 2006;1(5):1016–22.
19. Rovenský J. Atypical Forms of Granulomatosis with Polyangiitis (Wegener's). U: Rovenský J, Herold M, Vašáková M (ur.). Sine Syndromes in Rheumatology. Beč: Springer-Verlag; 2013., str. 45–9.

Reumatizam 2019;66(1):33–36
https://doi.org/10.33004/reumatizam-66-1-4

CASE REPORT PRIKAZ BOLESNIKA

OSTEITIS PUBIS AND OSTEOMYELITIS PUBIS IN PREGNANCY – TWO CASE REPORTS

OSTEITIS PUBIS I OSTEOMIJELITIS PUBIS U TRUDNOĆI – PRIKAZ DVIJU BOLESNICA

Neven Tučkar[1], Ivka Djaković[1], Ida Marija Šola[1], Matej Mustapić[2], Ozren Grgić[1], Vesna Košec[1]

[1]Department of Gynecology and Obstetrics, Sestre Milosrdnice University Hospital Center, Zagreb, Croatia / Klinika za ženske bolesti i porodništvo, Klinički bolnički centar Sestre milosrdnice, Zagreb, Hrvatska
[2]Department of Diagnostic and Interventional Radiology, Sestre Milosrdnice University Hospital Center, Zagreb, Croatia / Klinički zavod za dijagnostičku i intervencijsku radiologiju, Klinički bolnički centar Sestre milosrdnice, Zagreb, Hrvatska

Corresponding author / Adresa autora za dopisivanje:
Ida Marija Šola
Department of Gynecology and Obstetrics / Klinika za ženske bolesti i porodništvo
Sestre Milosrdnice University Hospital Center / Klinički bolnički centar Sestre milosrdnice
Vinogradska c. 29
10000 Zagreb
Croatia / Hrvatska
Tel. / Phone: +385981623560
E-mail: zlatomaterino@gmail.com

Received / Primljeno: March 11, 2019 / 11. 3. 2019.
Accepted / Prihvaćeno: May 27, 2019 / 27. 5. 2019.

Abstract

Pubic pain frequently accompanies uneventful pregnancies and is a common symptom in pregnancy. Still, in some cases, especially when it is associated with walking difficulties, persistent and/or severe pubic pain, and inflammation that can be confirmed by laboratory parameters, it should be taken with additional caution. Differential diagnosis should include osteitis pubis, a non-bacterial, self-limited inflammation that leaves no permanent consequences, but also, more importantly, osteomyelitis of the pubic symphysis. This is a rare bacterial infection in pregnancy, important to be diagnosed in time and treated early and properly since it can leave serious long-term complications such as fistulas that require prolonged treatment and sometimes even surgery. A multidisciplinary approach is mandatory to exclude all the other potential causes of pubic pain and make a timely diagnosis of osteomyelitis. We present two patients with pubic pain during pregnancy, with two different diagnoses and treatment options, and a favorable outcome that was the result of a multidisciplinary approach.

Keywords: Pelvic pain – etiology; Osteitis – diagnosis, therapy; Osteomyelitis – diagnosis, therapy; Pregnancy complications, infectious – diagnosis, therapy; Pubic symphysis – pathology

Sažetak

Pubična bol najčešće je prisutna u urednim trudnoćama i čest je simptom u trudnoći. Ipak, katkad, a osobito ako uzrokuje tegobe pri kretanju, jaka je i/ili perzistentna te ako je povezana s upalom dokazanom laboratorijskim parametrima, trebala bi uputiti na pojačan oprez. Diferencijalna dijagnoza trebala bi uključiti osteitis pubis – nebakterijsku, samoograničavajuću upalu pubične simfize koja ne ostavlja trajne posljedice, ali i puno važnije, osteomijelitis pubis – bakterijsku infekciju pubične simfize koja se rijetko vidi u trudnoći, a zakasnjelo dijagnosticiranje te kasno i neodgovarajuće liječenje mogu ostaviti dugoročne komplikacije kao što su fistule koje nalažu dugotrajno, katkad i kirurško liječenje. Multidisciplinarni pristup obvezatan je radi isključivanja svih potencijalnih uzroka pubične boli i ranog postavljanja dijagnoze osteomijelitisa pubične simfize. Prikazujemo dvije trudnice s pubičnom boli u trudnoći, no s različitom dijagnozom i liječenjem te povoljnim ishodom koji je rezultat multidisciplinarnog pristupa.

Ključne riječi: Zdjelična bol – etiologija; Osteitis – dijagnoza, liječenje; Osteomijelitis – dijagnoza, liječenje; Infekcijske komplikacije u trudnoći – dijagnoza, liječenje; Preponska simfiza – patologija

INTRODUCTION

Pubic pain is frequently present in uneventful pregnancies. When the pain is constant and/or associated with inflammation and increased laboratory parameters like leukocytes, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR), it should be taken seriously.

Osteitis pubis is a self-limited, non-bacterial inflammation of the pubic symphysis that heals spontaneously without permanent consequences (1–3). Osteomyelitis pubis is a rare bacterial inflammation of the pubic symphysis not often seen in pregnancy (2, 4). The latter is difficult to diagnose and, if unrecognized or treated inadequately, can leave serious short- or long-term complications (2, 3, 5).

We present two patients with severe pubic pain during pregnancy, with two different diagnoses and treatment options.

PATIENT DESCRIPTIONS

Patient 1

A 38-year-old primigravida in the 32nd week of pregnancy was admitted to the obstetric department with severe pubic pain. She could not walk. The pain had lasted for a week and was progressive. Obstetric examination was normal. Ultrasonographic examination of the fetus was also normal. On cardiotocography no contractions were detected. Inflammatory laboratory parameters were not increased at admission and during hospital stay. Urinary infection was excluded.

The pain was managed by analgesics and the patient was released in good condition after three days. After two weeks, the pain had disappeared. The patient was admitted again in the 40th week of pregnancy and gave birth to a female newborn weighing 3,420 g, 50 cm in length, and Apgar score 10/10. At the follow-up visit after 30 days, there was no presence of pain in the pubic symphysis.

Patient 2

A 29-year-old woman, gravida 3, in the 19th week of pregnancy, was admitted to the obstetric department with strong pelvic pain lasting for three days. She had a history of urinary tract infection earlier in the pregnancy. Urinary tract infection was excluded but inflammatory parameters were elevated (leukocytes 11.8x 10^9/L and CRP 32.6 mg/L). Physical examination revealed pain on palpation of the pubic symphysis. Obstetric findings, transvaginal ultrasonographic cervical assessment, and ultrasonographic examination of the fetus were normal. Other causes of pelvic pain were excluded by an abdominal surgeon and a gastroenterologist. Magnetic resonance imaging (MRI) of the pelvis revealed an inflammation of the pubic symphysis with

UVOD

Pubična bol često je prisutna u urednim trudnoćama. Ako je bol stalno prisutna ili povezana s upalom i povišenim vrijednostima laboratorijskih parametara kao što su broj leukocita, C-reaktivni protein (CRP) i brzina sedimentacije eritrocita (SE), potreban je ozbiljan pristup.

Osteitis pubis samoograničavajuća je, nebakterijska upala pubične simfize koja spontano cijeli bez trajnih posljedica (1 – 3). Osteomijelitis pubis, pak, rijetka je bakterijska upala pubične simfize koja se ne susreće često u trudnoći (2, 4). Teško ju je dijagnosticirati i, ako ostane neprepoznata ili bude neodgovarajuće liječena, može ostaviti teške kratkoročne ili dugoročne posljedice (2, 3, 5).

Donosimo prikaz dviju trudnica s jakom pubičnom boli različitih uzroka, koje su bile i različito liječene.

PRIKAZ BOLESNICA

BOLESNICA br. 1

Prvorotkinja u dobi od 38 godina primljena je u 32. tjednu trudnoće u Kliniku za ženske bolesti i porodništvo zbog jake pubične boli. Bolesnica nije mogla hodati. Bol je trajala tjedan dana i pojačavala se. Nalaz opstetričkog pregleda bio je uredan. Ultrazvučni pregled fetusa također je bio normalan. Kardiotokografijom nisu otkrivene kontrakcije. Upalni laboratorijski parametri u vrijeme prijma i tijekom boravka u bolnici nisu bili povišeni. Urinarna infekcija bila je isključena.

Bol je liječena primjenom analgetika i bolesnica je nakon tri dana otpuštena u dobru stanju. Dva tjedna poslije bol je nestala. Bolesnica je ponovo primljena u 40. tjednu trudnoće kada je rodila djevojčicu težine 3420 g, duljine 50 cm i Apgarina indeksa 10/10. Na kontrolnom pregledu nakon 30 dana nije bilo boli u pubičnoj simfizi.

BOLESNICA br. 2

Trećerotkinja u dobi od 29 godina primljena je u 19. tjednu trudnoće u Kliniku za porodništvo zbog jake boli u zdjelici koja je trajala već tri dana. U anamnezi je imala infekciju mokraćnih putova prije u trudnoći. Infekcija mokraćnih putova bila je isključena, ali su upalni parametri bili povišeni (leukociti 11,8 × 10^9/L i CRP 32,6 mg/L). Na fizikalnom pregledu bila je prisutna bol na palpaciju pubične simfize. Opstetrički nalaz i nalazi pregleda grla maternice transvaginalnim ultrazvukom i ultrazvučnog pregleda fetusa bili su uredni. Ostali uzroci boli u zdjelici isključeni su na temelju nalaza abdominalnog kirurga i gastroenterologa. Na snimkama zdjelice magnetskom rezonancijom (MR) pokazali su se upala pubične simfize s edemom koštane srži i okolnih mekih tkiva te tekućina u simfizi (slika 1.). Drugog

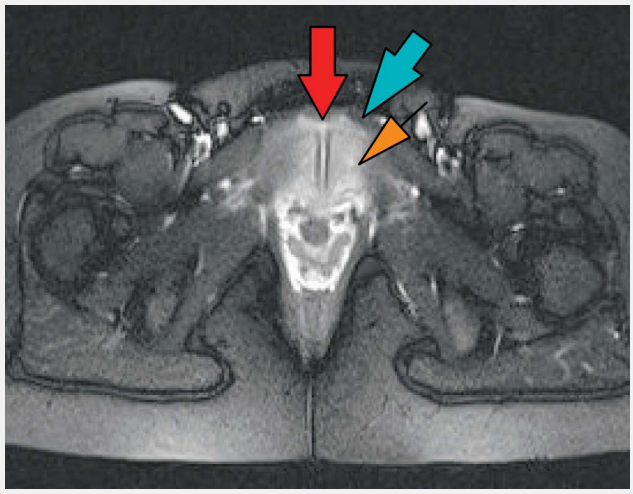


Figure 1. Axial fat-suppressed proton density-weighted MR image shows inflammatory changes of the pubic symphysis – parasymphyseal bone marrow edema (yellow arrow) with symphyseal fluid (red arrow) and peripubic soft tissue edema (blue arrow).

Slika 1. Aksijalna snimka magnetskom rezonancijom (MR) na temelju gustoće protona s potiskivanjem signala iz masnog tkiva pokazuje upalne promjene pubične simfize – edem koštane srži parasimfizealno (žuta strjelica) sa simfizealnom tekućinom (crvena strjelica) i edemom peripubičnoga mekog tkiva (plava strjelica)

bone marrow edema, surrounding soft tissue edema, and fluid within the symphysis (Figure 1). On the second day after admission antibiotic treatment with Cefazolin 3x1g intravenously was started, but despite that the CRP level rose to 157.8 mg/L. Subsequently, Cefazolin therapy was stopped after two days, and Clindamycin 3x600 mg and Garamycin 1x240mg were administered intravenously for seven days. Non-steroidal anti-inflammatory drugs (NSAIDs) were also administered. Regression of symptoms occurred with a decrease of the inflammatory parameters. Physical therapy started and the patient was released on the 14th hospital day. Serology for Chlamydia was positive. After one week the patient was free of pain. The rest of the pregnancy proceeded without any complications. The patient gave birth to a female newborn weighing 2880 g, 48cm in length, Apgar score 10/10, in the 40th week of pregnancy.

DISCUSSION

Osteomyelitis in pregnancy is a very rare condition (2). The presenting symptoms of osteitis pubis and osteomyelitis of the pubic symphysis are very similar and definitive diagnosis is not simple. As mild pubic pain is a common condition in pregnancy, osteomyelitis of the pubic symphysis may be diagnosed late and treatment delayed (3). The pathogenesis of osteitis pubis is uncertain. Possible etiologies include infection, mechanical trauma to the symphysis, local vascular damage of reflex sympathetic history (6). Given the low cost, wide availability, and ease of administration, the application of ice, NSAIDs, and physical rehabilitation are suggested as the first line of therapy for both acute and chronic cases of osteitis pubis (7–9). Osteitis pubis leaves no permanent damage. On the other hand, the consequences of untreated or late-treated osteomyelitis can be serious with short- and long-term complications, which can be local or systemic. The most serious

dana nakon prijma započelo je antibiotsko liječenje intravenskom primjenom cefazolina u dozi od 3 × 1 g na dan, no unatoč tomu vrijednost CRP-a povisila se na 157,8 mg/L. Dva dana poslije ukinuta je terapija cefazolinom i započela je intravenska primjena klindamicina od 3 × 600 mg na dan te gentamicina (Garamycin*) u dozi od 1 × 240 mg na dan tijekom sedam dana. Primijenjeni su i nesteroidni protuupalni lijekovi (NSAIL-i). Nastupilo je ublaženje simptoma uz pad vrijednosti upalnih parametara. Uvedena je i fizikalna terapija te je bolesnica otpuštena nakon 14 dana hospitalizacije. Serološki nalaz na klamidiju bio je pozitivan. Tjedan dana poslije bolesnica više nije imala boli. Ostatak trudnoće protekao je bez ikakvih komplikacija. Bolesnica je rodila djevojčicu težine 2880 g, duljine 48 cm i Apgarina indeksa 10/10 u 40. tjednu trudnoće.

RASPRAVA

Osteomijelitis u trudnoći vrlo je rijetko stanje (2). Simptomi osteitisa pubis vrlo su slični simptomima osteomijelitisa pubične simfize, stoga konačnu dijagnozu nije jednostavno postaviti. U trudnoći je često prisutna blaga pubična bol pa osteomijelitis pubične simfize može biti zakasnjelo dijagnosticiran i kasno liječen (3). Patogeneza osteitisa pubis nije točno utvrđena. Mogući uzroci uključuju infekciju, mehaničku traumu simfize, lokalne vaskularne anomalije i refleksnu simpatičku distrofiju (6). Kao prva linija liječenja i kod akutnih i kod kroničnih slučajeva osteitisa pubis preporučuju se led, NSAIL-i i fizikalna rehabilitacija s obzirom na njihovu nisku cijenu, široku dostupnost i jednostavnost primjene (7 – 9). Osteitis pubis ne ostavlja trajne posljedice. S druge strane, neliječeni ili kasno liječeni osteomijelitis može imati teške posljedice, s kratkoročnim i dugoročnim lokalnim ili sistemskim komplikacijama. Najteže komplikacije poput fistula nalažu dugotrajno liječenje, a katkad i kirurški zahvat

complications, such as fistulas, require prolonged treatment and sometimes even surgery (5). Pregnancy is an especially sensitive period in a woman's life and affects the psychosocial aspects of wellbeing. Any life- or health-threatening condition can affect future decisions regarding pregnancy.

The favorable outcome in our case was the result of a multidisciplinary approach. Early diagnosis is possible only if all the other conditions that may mimic osteomyelitis are excluded before obvious signs of infection occur.

CONCLUSION

In cases of pelvic and groin pain in pregnancy, especially when associated with walking difficulties and severe pubic pain, differential diagnosis should include osteomyelitis of the pubic symphysis. A multidisciplinary approach is mandatory to exclude all the other causes of pubic pain. In the diagnostic process and consequent treatment, different clinicians should be involved, such as obstetricians, urologists, gastroenterologists, abdominal surgeons, physiatrists, and sometimes even anesthesiologists for pain relief.

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

(5). Trudnoća je osobito osjetljivo razdoblje u životu žene i utječe na psihosocijalne aspekte kvalitete njezina života. Svako zdravstveno stanje koje ugrožava zdravlje ili život žene može utjecati na njezinu odluku o budućim trudnoćama.

Povoljan ishod u prikazu bolesnice koji smo opisali bio je rezultat multidisciplinarnog pristupa. Rano postavljanje dijagnoze moguće je samo ako se isključe sva druga stanja koja oponašaju osteomijelitis prije nego što se pojave vidljivi znakovi infekcije.

ZAKLJUČAK

Kod boli u zdjelici i preponama tijekom trudnoće, osobito kad je povezana s tegobama pri hodanju i jakom pubičnom boli, diferencijalna dijagnoza mora uključiti osteomijelitis pubične simfize. Obvezatan je multidisciplinarni pristup da bi se isključili svi drugi uzroci pubične boli. U dijagnostičkom postupku i liječenju koje zatim slijedi moraju sudjelovati razni klinički specijalisti: od opstetričara, urologa i gastroenterologa do abdominalnog kirurga, fizijatra, a katkad i anesteziologa radi uklanjanja boli.

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

REFERENCES / LITERATURA

1. Yax J, Cheng D. Osteomyelitis pubis: a rare and elusive diagnosis. West J Emerg Med. 2014;15(7):880–2.
2. Gamble K, Dardarian TS, Finstein J, Fox E, Sehdev H, Randall TC. Osteomyelitis of the pubic symphysis in pregnancy. Obstet Gynecol. 2006;107(2 Pt 2):477–81.
3. Knoeller SM, Uhl M, Herget GW. Osteitis or osteomyelitis of the pubis? A diagnostic and therapeutic challenge: report of 9 cases and review of the literature. Acta Orthop Belg. 2006;72 (5):541–8.
4. Eskridge C, Longo S, Kwark J, Robichaux A, Begneaud W. Osteomyelitis pubis occurring after spontaneous vaginal delivery: a case presentation. J Perinatol. 1997;17(4):321–4.
5. Dunk RA, Langhoff-Roos J. Osteomyelitis of the pubic symphysis after spontaneous vaginal delivery. BMJ Case Rep. 2010; 2010. pii: bcr 0120102610.
6. Sexton DJ, Heskestad L, Lambeth WR, McCallum R, Levin LS, Corey GR. Postoperative pubic osteomyelitis misdiagnosed as osteitis pubis: report of four cases and review. Clin Infect Dis. 1993;17(4):695–700.
7. Rodriguez C, Miguel A, Lima H, Heinrichs K. Osteitis pubis syndrome in the professional soccer athlete: a case report. J Athl Train. 2001;36(4):437–40.
8. Choi H, McCartney M, Best TM. Treatment of osteitis pubis and osteomyelitis of the pubic symphysis in athletes: a systematic review. Br J Sports Med. 2011;45(1):57–64.
9. McMurtry CT, Avioli LV. Osteitis pubis in an athlete. Calcif Tissue Int. 1986;38(2):76–7.

Reumatizam 2019;66(1):37–42
https://doi.org/10.33004/reumatizam-66-1-5

CASE REPORT PRIKAZ BOLESNIKA

THE IMPORTANCE OF ANTENATAL ULTRASOUND SCREENING FOR CONGENITAL OSTEOCHONDRODYSPLASIA – TWO CASE REPORTS

VAŽNOST ULTRAZVUČNOG ANTENATALNOG PROBIRA NA KONGENITALNE OSTEOHONDRODISPLAZIJE – PRIKAZ DVAJU BOLESNIKA

Ivka Djaković[1], Vesna Gall[1], Vanja Saftić[2], Petra Radulović[3], Nada Bilić[4], Vesna Košec[1]

[1]Department of Gynecology and Obstetrics, Sestre Milosrdnice University Hospital Center, Zagreb, Croatia / Klinika za ženske bolesti i porodništvo, Klinički bolnički centar Sestre milosrdnice, Zagreb, Hrvatska
[2]Child Protection Center of Zagreb, Zagreb, Croatia / Poliklinika za zaštitu djece, Zagreb, Hrvatska
[3]Ljudevit Jurak Department of Pathology, Sestre Milosrdnice University Hospital Center, Zagreb, Croatia / Klinički zavod za patologiju „Ljudevit Jurak", Klinički bolnički centar Sestre milosrdnice, Zagreb, Hrvatska
[4]Department of Anesthesiology and Intensive Care, Sestre Milosrdnice University Hospital Center, Zagreb, Croatia / Zavod za anesteziologiju, intenzivnu medicinu i liječenje boli, Klinički bolnički centar Sestre milosrdnice, Zagreb, Hrvatska

Corresponding author / Adresa autora za dopisivanje:
Vesna Gall
Department of Gynecology and Obstetrics / Klinika za ženske bolesti i porodništvo
Sestre Milosrdnice University Hospital Center / Klinički bolnički centar Sestre milosrdnice
Vinogradska 29
10000 Zagreb, Croatia / Hrvatska
Tel. / Phone: +38513787361
Fax number / Faks: +38513768272
E-mail: gall.vesna@gmail.com

Received / Primljeno: June 8, 2018 / 8. 6. 2018.
Accepted / Prihvaćeno: January 9, 2019 / 9. 1. 2019.

Abstract

Osteochondrodysplasias comprise a large, genetically heterogeneous group of disorders characterized by abnormalities of cartilage and bone growth. They are often associated with abnormalities in other organ systems. They are classified as lethal or non-lethal skeletal dysplasias. Thanatophoric dysplasia is the most common form of lethal skeletal dysplasia with an incidence of 0.69 per 10.000 births. Heterozygous achondroplasia is the most common non-lethal dysplasia with an incidence of 0.15 per 10.000 births. We will present two cases of skeletal dysplasia. The first case is the case of lethal osteochondrodysplasia in the fetus of a 41-year-old multiparous woman, who came to our hospital in active preterm labor, in the 33th week of uncontrolled pregnancy. The second case is the case of non-lethal osteochondrodysplasia in the fetus of a 31-year-old multiparous woman. The fetal short femur length was detected in the 30th week of pregnancy.

Keywords: Thanatophoric dysplasia – diagnostic imaging; Achondroplasia – diagnostic imaging; Ultrasonography, prenatal – methods; Imaging, three-dimensional; Fetal diseases – diagnostic imaging; Bone and bones – abnormalities

Sažetak

Osteohondrodisplazije velika su skupina rijetkih genskih bolesti karakterizirana poremećajem rasta i razvoja hrskavice i kosti. Često su povezane s malformacijama drugih organskih sustava. Mogu se podijeliti na letalne i neletalne skeletne displazije. Tanatoforična displazija jedna je od najčešćih letalnih skeletnih displazija s učestalošću pojavljivanja od 0,69 na 10.000 porođaja, dok je heterozigotna ahondrodisplazija među najčešćim neletalnim displazijama s učestalošću od 0,15 na 10.000 porođaja. Prikazat ćemo dva novorođenčeta s osteohondrodisplazijom. Prvi je prikaz letalne osteohondrodisplazije kod novorođenčeta 41-godišnje višerotkinje koja je u 33. tjednu nekontrolirane trudno-

će došla u našu Kliniku zbog započetog porođaja. Drugi je prikaz neletalne osteohondrodisplazije u novorođenčeta 31-godišnje višerotkinje kod kojeg se od 30. tjedna trudnoće prate kraće kosti udova.

Ključne riječi: Tanatoforična displazija – dijagnostički slikovni prikaz; Ahondroplazija – dijagnostički slikovni prikaz; Prenatalna ultrasonografija – metode; Trodimenzionalni slikovni prikaz; Fetusne bolesti – dijagnostički slikovni prikaz; Kosti – anomalije

INTRODUCTION

Skeletal dysplasias comprise a heterogeneous group of disorders characterized by abnormalities of cartilage and bone growth, resulting in an abnormal shape and size of the skeleton and disproportion of the long bones, spine, and head (1, 2). These disorders affect approximately 2.4–4.5 in 10,000 births (3). The classification of skeletal dysplasia is extremely difficult due to the large number of diseases and diverse ways of expressing and overlapping of their features (4–6). In 1997, the International Working Group on Bone Dysplasias proposed a newly revised "International Nomenclature and Classification of the Osteochondrodysplasias" (7, 8). The diseases were classified based on the gene and/or genetic disorders. The classification and nomenclature must be constantly updated due to the increasing number of molecular discoveries. This classification includes about 300 disorders, about 50 of which are recognizable at birth. Some skeletal dysplasias are hereditary, and family history is very important. Advancements in technology and the introduction of ultrasound in pregnancy monitoring have enabled very early detection and monitoring of skeletal dysplasia. These disorders begin to manifest in the early stages of fetal development (9). Most of the skeleton begins to ossify early in the development, which can be detected by ultrasound examination. With respect to their prognosis and clinical outcomes, there are two groups of skeletal dysplasias: lethal and non-lethal dysplasias.

The most common types of lethal skeletal dysplasias are thanatophoric dysplasia, homozygous achondroplasia, achondrogenesis, osteogenesis imperfecta types II and III, perinatal lethal hypophosphatasia, and short rib polydactyly syndrome. The main characteristic of these types of lethal skeletal dysplasias is that death occurs while *in utero,* during childbirth, or shortly after birth.

The most common types of non-lethal skeletal dysplasias are heterozygous achondroplasia and osteogenesis imperfecta types I and IV. They are characterized by subsequent disability and chronic diseases of the locomotor system (2).

We report two cases of skeletal dysplasia diagnosed prenatally, one with a lethal outcome and one with a non-lethal outcome.

UVOD

Skeletne displazije heterogena su skupina bolesti obilježena poremećenim rastom i razvojem hrskavice i kostiju, s posljedično abnormalnim oblikom i abnormalnom veličinom skeleta te disproporcijom dugih kostiju, kralježnice i lubanje (1, 2). Ovi se poremećaji pojavljuju u približno 2,4 – 4,5 novorođenčadi na 10.000 porođaja (3). Klasifikacija skeletnih displazija iznimno je teška zbog velikog broja takvih poremećaja te njihove raznolike ekspresije i preklapanja obilježja (4 – 6). Međunarodna radna skupina za koštane displazije (engl. *the International Working Group on Bone Dysplasias*) predložila je 1997. godine novu, revidiranu klasifikaciju osteohondrodiplazija prema genskim i/ili genetičkim poremećajima pod naslovom „Međunarodna nomenklatura i klasifikacija osteohondrodisplazija" (engl. *International Nomenclature and Classification of the Osteochondrodysplasias*) (7, 8). Budući da se sve više poremećaja otkriva na molekularnoj razini, tako se klasifikacija i nomenklatura neprekidno moraju obnavljati. Spomenuta klasifikacija uključuje tristotinjak poremećaja od kojih je pedesetak prepoznatljivo odmah nakon rođenja. Osifikacija skeleta započinje u ranoj fazi fetalnog razvoja. Napredak tehnologije i uvođenje ultrazvuka u praćenje trudnoće omogućili su izrazito rano otkrivanje skeletnih displazija i njihovo praćenje od ranih stadija fetalnog razvoja kada započinje osifikacija skeleta i kada se displazije počinju manifestirati (9). S obzirom na prognozu i klinički ishod, postoje dvije skupine skeletnih displazija: letalne i neletalne.

Najčešće vrste letalnih skeletnih displazija jesu tanatoforična displazija, homozigotna ahondroplazija, ahondrogeneza, osteogenesis imperfecta tipa II i III, perinatalna letalna hipofosfatazija i sindrom kratkog rebra s polidaktilijom. Glavno obilježje ovih vrsta letalnih skeletnih displazija jest da smrt nastupa intrauterino, tijekom porođaja ili neposredno nakon njega.

Najčešće vrste neletalnih skeletnih displazija jesu heterozigotna ahondroplazija i osteogenesis imperfecta tipa I i IV. Njihove su značajke kasnija onesposobljenost i kronične bolesti lokomotornog sustava (2).

Prikazujemo dva bolesnika s prenatalno dijagnosticiranom skeletnom displazijom, u jednoga s letalnim, a u drugoga s neletalnim ishodom.

Case 1

A 41-year-old multiparous woman was admitted to our hospital in active preterm labor in the 33rd week of gestation from uncontrolled pregnancy. She had three prior uncomplicated pregnancies and two artificial abortions. An ultrasound examination after admission revealed a short femur and polyhydramnios. Femur length (FL) was 27 mm for 18+2/7 weeks of gestation, while the biparietal diametar (BPD) and the abdominal circumference (AC) were normal for the gestational age. The amniotic fluid index (AFI) was 35 cm (>90th percentile). The male infant was delivered vaginally two hours after admission (weight 2050 g, length 36 cm, Apgar score 2, 1, 1). After unsuccessful resuscitation, the newborn died. The performed chest X-ray showed homogeneous opacities in both lungs without ventilated lung parenchyma. The clinical examination revealed disproportionately short arms and legs, a narrow chest, curved thigh bones, flattened bones of the spine (platyspondyly) and shortened thoracic ribs, as well as the typical "telephone-shaped" long bones. The description is consistent with thanatophoric dysplasia type I. The cause of death was respiratory failure (Figure 1).

Case 2

A 31-year-old multiparous woman was admitted to our hospital in the 37th week of gestation after an ultrasound examination that showed short femur length in the fetus. She had two prior uncomplicated pregnancies. The short femur length was first noticed in the 30th week of gestation. The ultrasound revealed FL of 54 mm at 28+5/7 weeks of gestation and humerus length (HL) of 49 mm at 28+6/7 weeks of gestation (<3rd percentile). BPD and AC were normal for the gestational age. Other morphology and AFI were normal. The woman vaginally delivered a male infant (weight 3310 g, length 49 cm, Apgar score 10, 10) in the 39th week of pregnancy. There were morphological signs of achondroplasia including short upper arms and legs (rhizomelic type), a typical trident hand (Figure 2), an enlarged neurocranium, frontal bossing, flattened nasal bridge, flattened anteroposterior diameter of the chest, protruding abdomen, and mid-face hypoplasia (Figure 3).

DISCUSSION

In early fetal development, the appearance and shape of long bones require special attention. Ultrasound examination in suspected skeletal dysplasia should include measurement of all long bones, classification of the shortening, and an evaluation of bone quality and presence of bone fractures (1). Attention should also be paid to the appearance of the chest and the size of the heart. A detailed evaluation of the skull and the

Bolesnik 1

Četrdesetjednogodišnja višerotkinja primljena je u našu Kliniku u 33. tjednu nekontrolirane trudnoće zbog preuranjenog početka porođaja. Prethodne tri trudnoće protekle su bez komplikacija, a imala je i dva namjerna pobačaja. Ultrazvučnim pregledom nakon prijma otkriveni su kratki femur i polihidramnion. Duljina femura (LF) ploda iznosila je 27 mm u tjednu gestacije 18 + 2/7, dok su biparijetalni promjer (BPD) i abdominalna cirkumferencija (AC) bili primjereni gestacijskoj dobi. Indeks plodne vode iznosio je 35 cm (> 90. percentila). Novorođenče muškog spola porođeno je vaginalnim putem dva sata nakon prijma (tjelesne mase od 2050 g i duljine 36 cm, Apgarina indeksa 2/1/1). Nakon neuspješne resuscitacije novorođenče je preminulo. Rendgenska snimka srca i pluća pokazala je homogena zasjenjenja u oba plućna krila bez vidljive prozračnosti plućnog parenhima. Tijekom kliničkog pregleda opazili smo neproporcionalno kratke ruke i noge, uzak prsni koš, zakrivljene natkoljenične kosti, platispondiliju (izravnanje kralježaka) i kratka torakalna rebra te atipičan izgled dugih kostiju u obliku „telefonske slušalice". Opis odgovara tanatoforičnoj displaziji tipa I. Uzrok smrti bilo je respiratorno zatajenje (slika 1.).

Bolesnik 2

U našu Kliniku primljena je 31-godišnja višerotkinja u 37. tjednu gestacije nakon što je na ultrazvučnom pregledu kod fetusa otkrivena skraćena duljina femura. Prvi je put to bilo opaženo u 30. tjednu gestacije. Prethodno je imala dvije nekomplicirane trudnoće. Duljina femura (FL) izmjerena ultrazvukom iznosila je 54 mm u tjednu gestacije 28 + 5/7, dok je duljina humerusa (HL) bila 49 mm u tjednu gestacije 28 + 6/7 (< 3. percentila). BPD i AC bili su normalni za gestacijsku dob. Druge morfološke značajke i AFI bili su primjereni. Vaginalnim porođajem rođen je dječačić (težak 3310 g i dugačak 49 cm, Apgarina indeksa 10/10) u 39. tjednu trudnoće. Odmah su bili vidljivi znakovi ahondroplazije: kratke nadlaktice i noge (rizomeličnog tipa), tipičan trozubi izgled šake (slika 2.), povećani neurokranij, izražene čeone izbočine, splošteni hrbat nosa, smanjen anteroposteriorni promjer prsnog koša, protrudirani abdomen i hipoplazija središnjeg dijela lica (slika 3.).

RASPRAVA

U ranom stadiju fetalnog razvoja potrebno je obratiti pozornost na izgled i oblik dugih kostiju. Ultrazvučni pregled pri sumnji na skeletnu displaziju uključuje mjerenje svih dugih kostiju, kategorizaciju skraćenja kosti i procjenu njihove kvalitete te eventualnih koštanih fraktura (1). Isto je tako potrebno procijeniti

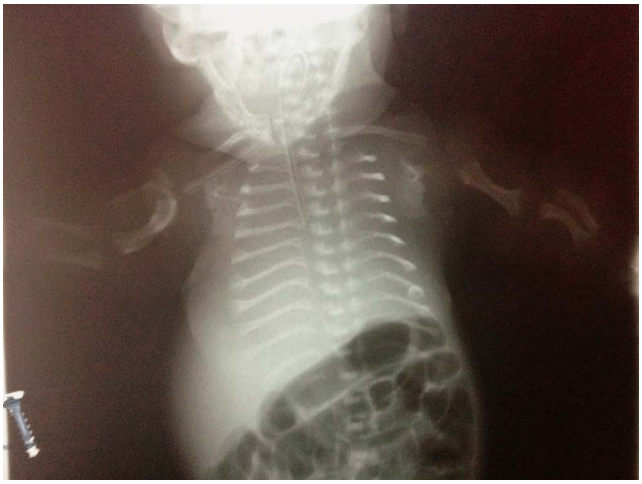


Figure 1. Chest X-ray of a newborn with thanatophoric dysplasia type I showed homogeneous opacities in both lungs without ventilated lung parenchyma.
Slika 1. Rendgenska slika novorođenčeta s tanatoforičnom displazijom tipa I pokazuje homogena zasjenjenja u oba plućna krila bez ventilacije plućnog parenhima

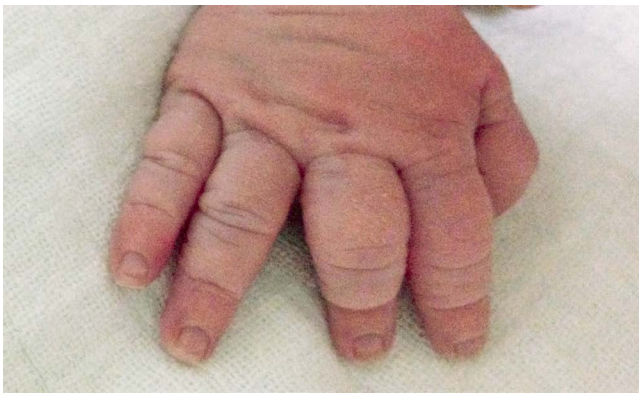


Figure 2. Typical trident hand in a newborn with achondroplasia.
Slika 2. Tipična ruka poput trozupca u novorođenčeta s ahondroplazijom

shape of the hands and feet is important, as well as an examination of the abdominal organs and amniotic fluid index. Polyhydramnion, intrauterine growth restriction, ventriculomegaly, flattened chest, and micromelia are often associated with skeletal dysplasia and can be diagnosed with 2D ultrasound. With the help of 3D ultrasound, morphological characteristics such as flattened facial features, hypoplastic ribs, and scapular anomalies can be detected. 3D-CT can provide more detailed images, but its use is controversial in the prenatal period.

The involvement of the affected bone segments can be divided into five classes: rhizomelic, mesomelic, acromelic, acromesomelic, or micromelic shortening (10).

Skeletal dysplasias are often associated with one or more of these conditions: head anomalies (craniosynostosis, disproportionally large head), cataract, myo-

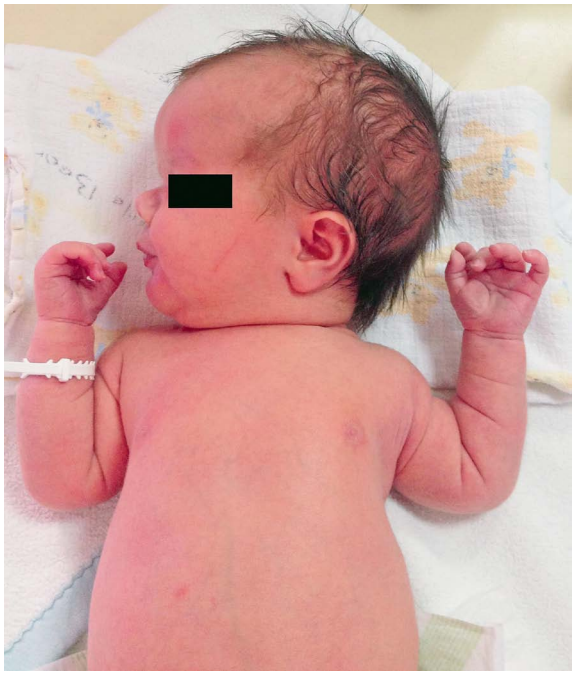


Figure 3. Newborn with achondroplasia. The neonate has an enlarged neurocranium, short upper arms, frontal bossing, flattened nasal bridge, flattened anteroposterior diameter of the chest, protruding abdomen, and midface hypoplasia.
Slika 3. Novorođenče s ahondroplazijom. Novorođenče ima povećani neurokranij, kratke gornje udove, izbočen frontalni dio, splošteni hrbat nosa, smanjen anteroposteriorni promjer prsnog koša, izbočeni trbuh i hipoplaziju sredine lica

izgled prsnog koša i veličinu srca. Važni su detaljan pregled lubanje, oblika šaka i stopala, kao i abdominalnih organa te indeks plodne vode. Polihidramnion, intrauterini zastoj u rastu, ventrikulomegalija, splošteni prsni koš i mikromelija često su povezani sa skeletnom displazijom i mogu se dijagnosticirati 2D ultrazvukom. S pomoću 3D ultrazvuka mogu se otkriti morfološke značajke poput sploštenog lica, hipoplastičnih rebara i anomalija lopatice. Detaljnije snimke mogu se dobiti 3D kompjutorskom tomografijom (CT), ali upotreba te metode u prenatalnom razdoblju još je sporna.

Stupanj zahvaćenosti kosti može se podijeliti u pet kategorija: rizomelično, mezomelično, akromelično, akromezomelično i mikromelično skraćenje (10).

Skeletne displazije često su povezane s jednim ili više ovih stanja: anomalije glave (kraniosinostoza, neproporcionalno velika glava), katarakta, miopija, rascjep usne i nepca, mentalna retardacija, atrijski septalni defekt, perzistentni ductus arteriosus, transpozicija velikih krvnih žila, Majewskijev sindrom, polidaktilija, sindaktilija, abducirani (tzv. autostoperski) palac na ruci ili nozi i ostalo.

Incidencija tanatoforične displazije iznosi 1 na 30.000 – 50.000 živorođenih. Značajke ove vrste displazije jesu kratki udovi (20 tjedana gestacije), velika glava, kratak vrat, uski prsni koš, izrazite čeone izboči-

pia, cleft lip and palate, mental retardation, atrial septal defect, ductus arteriosus persistens, transposition of the big vessels, Majewsky syndrome, polydactyly, syndactyly, hitchhiker or abducted thumb/first toe, and others.

Thanatophoric dysplasia has an incidence of 1 per 30,000 to 1 per 50,000 live births. It is characterized by short-limb dysplasia (20 weeks of gestation), a large head, short neck, narrow thorax, frontal bossing, mid-face hypoplasia, short and small fingers, thin flattened vertebrae, short ribs and bones, a short and curved femur ("telephone-shaped"), macrocranium, normal trunk length, normal mineralization, and no fractures. It is associated with brain abnormalities, and the presence of polyhydramnion in 50% of the cases (11). Newborns with thanatophoric dysplasia are either stillborn or die shortly after birth due to severe respiratory insufficiency from a reduced thoracic capacity and hypoplastic lungs (12, 13).

Heterozygous achondroplasia has an autosomal dominant mode of inheritance. It is a short-limb dysplasia (by 20 weeks of gestation) with typical features such as short rhizomelic arms and legs, enlarged neurocranium, frontal bossing, significant macrocranium, flattening of the nasal bridge, mid-face hypoplasia, flattening of the anteroposterior diametar of the chest, and protruding abdomen.

In the first case, the final diagnosis was confirmed by pathological examination and diagnosis. In the second case, the diagnosis was made after the delivery on the basis of typical morphological signs, but the final diagnosis has to be confirmed by molecular testing.

Prenatal diagnosis is important in order to prepare the parents for the possible outcomes (14, 15). It is difficult to accept the potential illness of an unborn child. With 3D or 4D ultrasound, the anomalies can be visualized, and parents can accept the potential illness (16, 17). The use of 4D, real-time ultrasound gives physicians the possibility to discuss the disease and counsel the patients with the help of images that are more understandable to the general population (6, 7, 17).

2D ultrasound is very important in screening for skeletal dysplasia. Their low incidence, large variability of characteristics, and, in most cases, lack of family history make the diagnosis of skeletal dysplasias difficult.

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

ne i hipoplazija srednjeg dijela lica, kratki i mali prsti, tanki splošteni kralješci, kratka rebra, kratke kosti, kratak i zakrivljen femur (u obliku „telefonske slušalice"), makrokranija, normalna duljina trupa te normalna mineralizacija kostiju i izostanak fraktura. Povezana je s abnormalnostima mozga, a u 50% bolesnika prisutan je i polihidramnion (11). Novorođenčad s tanatoforičnom displazijom rađa se kao mrtvorođena ili umire ubrzo nakon rođenja zbog teške respiratorne insuficijencije uzrokovane smanjenim kapacitetom prsnog koša i hipoplastičnim plućima (12, 13).

Heterozigotna ahondroplazija ima autosomno dominantni način nasljeđivanja. Riječ je o displaziji kratkih udova (do 20. tjedna gestacije) s tipičnim obilježjima poput rizomeličnog skraćenja ruku i nogu, povećanog neurokranija, izraženih čeonih izbočina, znatne makrokranije, zaravnanog hrpta nosa, hipoplazije srednjeg dijela lica, smanjenog anteroposteriornog promjera prsnog koša te protrudiranog abdomena.

U prvog bolesnika konačna je dijagnoza bila potvrđena patohistološkim pregledom i dijagnozom. U drugoga je dijagnoza postavljena nakon rođenja na temelju tipičnih morfoloških obilježja, ali konačna se dijagnoza mora tek potvrditi molekularnim testiranjem.

Prenatalna dijagnoza važna je da bi se roditelji pripremili na mogući ishod (14, 15). Roditeljima je teško prihvatiti bolest nerođena djeteta. Zahvaljujući 3D ultrazvuku ili 4D ultrazvuku, anomalije se u fetusa mogu vizualizirati, što roditeljima može pomoći da prihvate poremećaj kod svojeg djeteta (16, 17). Upotreba 4D ultrazvuka sa snimanjem u stvarnom vremenu liječnicima olakšava razgovor s roditeljima jer im mogu pokazati slike koje su razumljivije općoj populaciji (6, 7, 17).

2D ultrazvuk iznimno je važan u probiru na skeletnu displaziju. Malena incidencija, velika varijabilnost te, u većini slučajeva, izostanak skeletne displazije u obiteljskoj anamnezi otežavaju postavljanje ove dijagnoze.

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

REFERENCES / LITERATURA

1. Kurjak A, Bonilla F, Marton I. Skeletne displazije. U: Kurjak A (ur.). Ultrazvuk u ginekologiji i perinatologiji. Zagreb: Medicinska naklada; 2007., str. 724–40.
2. Kurjak A, Kos M. Ultrazvučna dijagnostika fetalnih malformacija. U: Kurjak A (ur.). Ginekologija i perinatologija II. Varaždinske Toplice: Tonimir; 2003., str. 217–9.
3. Barkova E, Mohan U, Chitayat D, Keating S, Toi A, Frank J i sur. Fetal skeletal dysplasia in a tertiary care center: radiology, pathology, and molecular analysis of 112 cases. Clin Genet. 2015;87(4):330–7.
4. Polák P, Baxová A, Křepelová A, Balák M. [Prenatal diagnosis of skeletal dysplasia in first trimester of pregnancy X-linked dominant chondrodysplasia punctata]. Ceska Gynecol. 2014;79 (3):193–7.
5. Schramm T, Gloning KP, Minderer S i sur. Prenatal sonographic diagnosis of skeletal dysplasias. Ultrasound Obstet Gynecol. 2009;34(2):160–70.
6. Nol AE, Brown RN. Advences in evaluating the fetal skeleton. Int J Womens Health. 2014;6:489–500.
7. International Working Group on Constitutional Disease of Bone. International nomenclature and classification of the osteochondrodysplasias (1997). Am J Med Genet. 1998;79(5): 376–82.
8. Warman ML, Cormier-Daire V, Hall C, Krakow D, Lachman R, LeMerrer M i sur. Nosology and classification of genetic skeletal disorders: 2010 revision. Am J Med Genet A. 2011;155A (5):943–68.
9. Kronenberg HM. Developmental regulation of the growth plate. Nature. 2003;423(6937):332–6.
10. Cohen MM Jr. The new bone biology: pathologic, molecular, and clinical correlates. Am J Med Genet A. 2006;140(23): 2646–706.
11. Thomas RL, Hess LW, Johnson TR. Prepartum diagnosis of limb-shortening defects with associated hydramnios. Am J Perinatol. 1987;4(4):293–9.
12. Vogt C, Blaas HG. Thanatophoric dysplasia: autopsy findings over a 25-year period. Pediatr Dev Pathol. 2013;16(3):160–7.
13. Davanageri RS, Shokeen PD, Bannur HB, Patil KP. Thanatophoric dysplasia type I: a rare case report at fetal autorsy. J Lab Physicians. 2014;6(2):121–3.
14. Hasegawa K, Tanaka H. Children with short-limbed short stature in pediatric endocrinological services in Japan. Pediatr Int. 2014;56(6):809–12.
15. Parilla BV, Leeth EA, Kambich MP, Chilis P, MacGregor SN. Antenatal detection of skeletal dysplasias. J Ultrasound Med. 2003;22(3):255–8.
16. Krakow D, Williams J 3., Poehl M, Rimoin DL, Platt LD. Use of three-dimensional ultrasound imaging in the diagnosis of prenatal-onset skeletal dysplasias. Ultrasound Obstet Gynecol. 2003;21(5):467–72.
17. Vasilj O, Mišković B. Diagnosis and counseling of thanatophoric dysplasia with four-dimensional ultrasound. J Matern Fetal Neonatal Med. 2012;25(12):2786–8.

Reumatizam 2019;66(1):43–44
https://doi.org/10.33004/reumatizam-66-1-6

12th CENTRAL EUROPEAN CONGRESS OF RHEUMATOLOGY AND 20th ANNUAL CONGRESS OF THE CROATIAN SOCIETY FOR RHEUMATOLOGY

Zagreb, Croatia, December 6–8, 2018

The 12th Central European Congress of Rheumatology (CECR) was held in Zagreb, Croatia, on December 6-8, 2018. It was attended by rheumatologists from seven countries, including Austria, the Czech Republic, Croatia, Hungary, Poland, Slovakia, and Slovenia. The congress is traditionally held every other year, and in 2018 it took place in Croatia for the first time. The event was organized by the Croatian Medical Association's Society for Rheumatology, led by its President Prof. Branimir Anić and the President of the local Organizing Committee Prof. Simeon Grazio. It was held under the auspices of the President of the Republic of Croatia Kolinda Grabar Kitarović and the Croatian Medical Association headed by Prof. Željko Krznarić.

According to the customary scheme, each participating country selected a topic and presented it in the form of invited lectures. The lectures were followed by oral presentations from congress participants and a poster section. Wanting to present Croatia not only as a Middle European country, but also as a Mediterranean one, Prof. Maurizio Cutolo, former President of the European League Against Rheumatism (EULAR), gave the plenary lecture on the effect of the Mediterranean diet on the incidence and course of inflammatory rheumatoid diseases. Other topics selected by the participating countries were as follows: *Rheumatoid arthritis – beyond the disease* (Austria), *Biomarkers in rheumatology* (Czech Republic), *Epidemiology of SLE in Central Europe* (Croatia), *Advances in inflammatory myopathies and systemic sclerosis* (Hungary), *Specific aspects of spondyloarthritis* (Poland), *Imaging in rheumatology* (Slovakia), and *Giant cell arteritis* (Slovenia). The Young Rheumatologists section, moderated by Dr. Ivan Padjen, offered selected oral presentations from each country. The congress extended into the 20th Annual Congress of the Croatian Society for Rheumatology, with *Surgery and rheumatic diseases* as the main topic. A lecture titled *What happened with rheumatology in the last 25 years?* was given by Dr. Mirna Sentić and dedicated to the memory of Drago Čop.

There was also a course for nurses and medical technicians, traditionally organized as part of the congress, and a meeting of patient associations. A workshop on research writing, publishing, and communication was held for the second time in a row. Organized by Prof. Grazio and Dr. Armen Yuri Gasparyan, the editor-in-chief of Rheumatology International, it was as well attended this year as the year before.

The 2018 CECR was attended by a total of 502 participants from 21 countries.

Ivan Padjen

12. SREDNJOEUROPSKI REUMATOLOŠKI KONGRES I XX. GODIŠNJI KONGRES HRVATSKOGA REUMATOLOŠKOG DRUŠTVA

Zagreb, 6. – 8. prosinca 2018.

U Zagrebu je, u hotelu Westin, od 6. do 8. prosinca 2018. održan Srednjoeuropski reumatološki kongres (*Central European Congress of Rheumatology* – CECR). Riječ je o već tradicionalnom kongresu reumatologa iz sedam srednjoeuropskih država (Austrija, Češka, Hrvatska, Mađarska, Poljska, Slovačka i Slovenija), koji se održava svake druge godine, a ovo je bio prvi put da je održan u Hrvatskoj. Organizator kongresa bilo je Hrvatsko reumatološko društvo Hrvatskoga liječničkog zbora, na čelu s njegovim predsjednikom prof. dr. sc. Branimirom Anićem, dok je predsjednik lokalnog Organizacijskog odbora bio prof. dr. sc. Simeon Grazio. Kongres je održan pod visokim pokroviteljstvom predsjednice Republike Hrvatske Kolinde Grabar-Kitarović i Hrvatskoga liječničkog zbora (predsjednik prof. dr. sc. Željko Krznarić).

Koncept kongresa takav je da svaka od zemalja odabire jednu temu i predstavlja ju u sklopu pozvanih predavanja, a slijede odabrane usmene prezentacije sudionika kongresa te posterska sekcija. Želeći pokazati da je Hrvatska ne samo srednjoeuropska već i mediteranska zemlja, odnosno nastojeći to povezati, uvodno pozvano predavanje održao je prof. Maurizio Cutolo, nekadašnji predsjednik Europske lige protiv reumatizma (EULAR) s temom o utjecaju mediteranske dijete na incidenciju i tijek upalnih reumatskih bolesti. Slijedile su teme pojedinih zemalja koje su bile ove: Austrija – Reumatoidni artritis – izvan osnova bolesti; Češka – Biomarkeri u reumatologiji; Hrvatska – Epidemiologija SLE-a u srednjoj Europi; Mađarska – Novosti u upalnim miopatijama i sistemskoj sklerozi; Poljska – Specifični aspekti spondiloartritisa; Slovačka – Slikovni prikazi u reumatologiji; Slovenija – Arteritis divovskih stanica. Kongres je imao i sekciju mladih reumatologa s odabranim usmenim prezentacijama iz svih navedenih srednjoeuropskih zemalja (voditelj sekcije dr. sc. Ivan Padjen). U nastavku kongresa održan je XX. godišnji kongres Hrvatskoga reumatološkog društva o temi „Kirurgija i reumatske bolesti". Predavanje u spomen Dragi Čopu naslova „Što se dogodilo s reumatologijom u posljednjih 25 godina?" održala je prim. Mirna Sentić (KBC Zagreb), dok su uz kongres, što je već tradicionalno, održani tečaj medicinskih sestara i tehničara te sastanak udruga bolesnika.

Drugu godinu zaredom održana je radionica o pisanju znanstvenog rada, publiciranju i komunikaciji koju su organizirali prof. Simeon Grazio i doc. Armen Yuri Gasparyan (glavni i odgovorni urednik časopisa *Rheumatology International*), koja je i ove godine bila jako dobro posjećena.

Na srednjoeuropskom i nacionalnom reumatološkom kongresu ukupno je sudjelovalo 502-je sudionika iz 21 zemlje.

Ivan Padjen

INSTRUCTIONS FOR AUTHORS

ABOUT THE JOURNAL

Reumatizam (Rheumatism) is the official peer-reviewed journal of the Croatian Medical Association's Society for Rheumatology. It appears twice a year and publishes editorials, scientific and professional papers, short communications, review papers, preliminary reports, and case reports. It informs professionals in the field of rheumatology on developments in clinical and non-clinical aspects of their work. Additionally, supplements with abstracts or full texts presented at congresses or symposia are periodically published. The journal presents relevant information on diagnostic and therapeutic procedures, as well as on providing comprehensive care for individuals affected by rheumatic diseases and conditions. The papers are written in English or Croatian, and are published under the condition that they were not previously published in the same form. Reumatizam is indexed by MEDLINE/PubMed (Index Medicus) and Scopus.

The content of the journal Reumatizam may be used free of charge for educational and research purposes, with full reference to the source. Any other use is prohibited, except with explicit prior permission from the publisher.

PAPER SUBMISSION / MANUSCRIPT PUBLICATION

Articles are published in the Croatian (with title, abstract, keywords, table and figure titles and legends in English) or English languages (with title, abstract, keywords, table and figure titles and legends in Croatian). Instructions to Authors are in accordance with the instructions in the article: *International Committee of Medical Journal Editors (ICMJE) – Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals*, available at: http://www.icmje.org/index.html. For texts in English, authors who are not native speakers are advised to seek professional assistance to ensure the accuracy and quality of the translation. The publisher can provide such service upon payment.

Manuscripts are submitted on paper (three identical computer printouts) accompanied by an electronic version written in Microsoft Word format on a CD, DVD, or USB stick, or by e-mail (upon previous agreement with the Editor-in-Chief) to: Reumatizam, Editorial Board, Klinika za reumatologiju, fizikalnu medicinu i rehabilitaciju, Klinički bolnički centar Sestre milosrdnice, Vinogradska 29, 10000 Zagreb, Croatia (e-mail: glavni-urednik-reumatizam@reumatologija.org).

The order in which papers are published does not correspond to the order by which manuscripts have reached the editorial board. Manuscripts and other submitted materials will not be returned.

AUTHORSHIP

Persons designated as authors must qualify for authorship. Each author should have sufficiently participated in creating the paper in order to be able to take public responsibility for the appropriate portion of its content, and all authors should take responsibility for the paper as a whole, from its inception to the published form. All others who have participated in the work but are not authors should be mentioned in the acknowledgments.

Manuscripts should be accompanied by a written declaration that the paper has not been previously published or sub-

UPUTE AUTORIMA

O ČASOPISU

„Reumatizam" je službeni recenzirani časopis Hrvatskoga reumatološkog društva Hrvatskoga liječničkog zbora. Izlazi dva puta na godinu. Objavljuje uvodnike, znanstvene radove, stručne radove, kratka priopćenja, pregledne radove, preliminarna izvješća i prikaze bolesnika. Informira reumatologe o novostima u kliničkom i nekliničkom djelokrugu rada. Također, u časopisu se periodično kao suplement objavljuju sažetci ili cjeloviti radovi s kongresa i simpozija. Časopis čitatelju daje bitne informacije o dijagnostičkim i terapijskim procedurama, odnosno pružanju sveobuhvatne skrbi osobama oboljelima od reumatskih bolesti i stanja. Radovi su napisani hrvatskim ili engleskim jezikom, a objavljeni su pod uvjetom da nisu prethodno publicirani u istom obliku. „Reumatizam" je indeksiran u bazama *MEDLINE/PubMed (Index Medicus)* i *Scopusu*.

Sadržaj iz časopisa „Reumatizam" smije se bez naknade rabiti u nastavne i istraživačke svrhe, uz potpuno navođenje izvora. Svaka druga uporaba zabranjena je bez izričitog dopuštenja izdavača.

PREDAJA RADA / OBJAVA RUKOPISA

Objavljuju se članci na hrvatskom jeziku (s naslovom, sažetkom, ključnim riječima te s naslovom i legendom tablica i slika na engleskom jeziku) ili na engleskom jeziku (s naslovom, sažetkom, ključnim riječima te s naslovom i legendom tablica i slika na hrvatskom jeziku). Upute autorima sukladne su uputama u članku: *International Committee of Medical Journal Editors (ICMJE) – Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly work in Medical Journals* (Preporuke za provođenje, prikazivanje, uređivanje i objavljivanje radova u medicinskim časopisima) koje su dostupne na: http://www.icmje.org/index.html. Za tekstove na engleskom jeziku preporučuje se da autori koji nisu izvorni govornici engleskog jezika potraže savjet stručnjaka radi točnog i kvalitetnog prijevoda. Izdavač može osigurati takvu uslugu uz plaćanje.

Rukopisi se dostavljaju u papirnatom obliku (tri identična računalna ispisa), zajedno s elektroničkom verzijom napisanom u formatu Microsoft Word na CD-u, DVD-u, USB-*sticku* ili elektroničkom poštom (uz prethodni dogovor s glavnim urednikom) na adresu: „Reumatizam", Uredništvo, Klinika za reumatologiju, fizikalnu medicinu i rehabilitaciju, Klinički bolnički centar Sestre milosrdnice, Vinogradska 29, 10000 Zagreb, Hrvatska (e-adresa: glavni-urednik-reumatizam@reumatologija.org).

Radovi se ne objavljuju prema redoslijedu prispijeća rukopisa u uredništvo časopisa. Rukopisi i ostali dostavljeni materijali ne vraćaju se pošiljateljima.

AUTORSTVO

Osobe određene kao autori moraju biti kvalificirane za autorstvo. Svaki autor treba dostatno sudjelovati u izradi rada kako bi preuzeo javnu odgovornost za odgovarajući dio sadržaja rada, a svi autori trebaju preuzeti odgovornost za cjelokupan rad od početka rada do njegove objave. Svi koji su sudjelovali u radu, a nisu autori, trebaju biti spomenuti u zahvali.

mitted/accepted for publication elsewhere, and that it has been read and approved by all the authors, as well as by a declaration on absence of any financial or other confl ict of interest. Additionally, the manuscript should be accompanied by a declaration of copyright transfer to the journal.

PREPARATION OF PAPER / MANUSCRIPT

The text should be printed in 12-point sized letters on white bond ISO A4 paper (210 × 297 mm), double spaced on one side only, including the title page, abstract, text, acknowledgments, declaration on conflict of interest, references, tables, and legends. The left margin should be 35 mm wide, while the right, top, and bottom margins should all be 25 mm. All pages, including the title page, should be consecutively numbered in the lower right-hand corner.

The text of a scientific or professional paper should contain: title page, abstract and keywords, introduction, materials and methods, results, discussion, conclusions, acknowledgments (optional), declaration on conflict of interest, references, tables, legends, and figures.

Review papers should not exceed 15 pages (including tables and figures), scientific and professional papers should not exceed 12 pages (including tables and figures), and case reports should not exceed 8 pages (including tables and figures). Short communications and preliminary reports should not exceed 4 pages (including tables and figures) and 15 references.

TITLE PAGE

The title page should contain the title of the paper (which must be concise, clear, and informative) in the Croatian and English languages, and the full name of each author. In the next line the institutional affiliation of the author(s) should be listed, with the full name of the institution, street, house number, city, and country. If the authors of the paper have different institutional affiliations, after every name and surname, as well as before each affiliation, a corresponding number should be written in superscript.

This should be followed by the name, surname, and full address of the author responsible for correspondence, along with his/her phone number, fax number, and e-mail address.

ABSTRACT AND KEYWORDS

The second page should contain the abstract in the Croatian and English languages (up to 300 words), stating the purpose of the study or investigation, the basic procedures, main findings, and principal conclusions.

The abstract should emphasize new and important aspects of the study or observation. Below the abstract authors should list four to ten keywords or short phrases in Croatian and English, which will help indexers to cross-index the article and may be published with the abstract. Terms from the Index Medicus *Medical Subject Headings (MeSH)* list should be used. General and plural terms, and multiple concepts (for example using "and", "or") should be avoided. The abstract must not contain references.

INTRODUCTION

The introduction section should state the purpose of the paper and the aim of the study or observation. It is recommended to include relevant references only, without the data or conclusions from the paper.

Uz rukopis treba priložiti pisanu izjavu da rad prethodno nije bio objavljen ili ponuđen/prihvaćen za objavu u nekom drugom časopisu, da su ga pročitali i odobrili svi autori te izjavu da ne postoji financijski ili bilo kakav drugi sukob interesa. Također, uz rukopis treba priložiti i izjavu o prijenosu autorskih prava na časopis.

PRIPREMA RADA / RUKOPISA

Tekst treba biti otisnut slovima veličine 12 točaka na bijelom papiru formata A4 (210 × 297 mm) samo s jedne strane s dvostrukim proredom, 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.

Tekst znanstvenog ili stručnog rada treba sadržavati: naslovnu stranicu, sažetak i ključne riječi, uvod, materijal i metode, rezultate, raspravu, zaključke, zahvale (opcionalno), izjavu o sukobu interesa, referencije, tablice, legende i slike.

Pregledni radovi mogu biti opsega do 15 stranica (uključujući tablice i slike), znanstveni i stručni radovi do 12 stranica (uključujući tablice i slike), prikazi bolesnika do 8 stranica (uključujući tablice i slike). Kratka priopćenja i preliminarna izvješća opsega su do 4 stranice (uključujući tablice i slike) i do 15 referencija.

NASLOVNA STRANICA

Na naslovnoj stranici treba biti naslov rada (mora biti 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 autora. 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.

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

SAŽETAK I KLJUČNE RIJEČI

Druga stranica treba sadržavati sažetak na hrvatskom i engleskom jeziku (do 300 riječi) u kojem su navedeni cilj studije ili istraživanja, osnovni postupci, najvažnija otkrića te osnovni zaključci.

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

UVOD

U uvodu se navode svrha rada i razlog provođenja studije ili opservacije. Preporučuje se navesti samo relevantne referencije, bez podataka ili zaključaka iz rada.

MATERIAL AND METHODS

The selection criteria and all important characteristics of the studied or observed human subjects or laboratory animals should be stated in this section. The author(s) should specify the meaning of the descriptors in detail, explain how the data was collected, and identify methods, devices (with the manufacturer's name in parentheses), and procedures in sufficient detail to allow others to reproduce the results. For established methods references should be provided, while new or substantially modified methods should be described in detail, alongside with the reasons for their use and estimates of their limitations.

For drugs and chemicals generic names must be used. All measurements should be expressed in SI units. In texts in Croatian decimal commas are to be used, and in texts in English decimal points.

ETHICS / ETHICAL STANDARDS

In papers dealing with experiments on human subjects it should be clearly stated that all procedures were performed in accordance with the ethical standards of an institutional or regional committee responsible for human experimentation, as well as the Helsinki Declaration of 1975, as revised in 1983. The subjects' names and/or surnames must not be mentioned, especially in illustrative materials. Papers dealing with experiments on animals should state that institutional or national regulations for the care and use of laboratory animals were complied with.

STATISTICS

Statistical methods should be described with enough detail to enable a knowledgeable reader with access to the original data to verify the reported results. Whenever possible, the findings should be quantified and presented with appropriate measurement error or uncertainty indicators. The computer program that was used should be specified.

RESULTS

The results are to be presented in logical sequence in the text, tables, and illustrations. Not all the data from the tables or illustrations is to be reiterated in the text, only the important observations should be emphasized or summarized.

DISCUSSION

New and important aspects of the study and the conclusions that follow should be emphasized. Reiterating data or other material which was presented in the Introduction or the Results sections is discouraged. The discussion should elaborate the significance of the findings and their limitations, including the implications on future research, while avoiding statements and conclusions that are not completely supported by the data. Observations from the study should be compared with other relevant studies. When necessary, new hypotheses may be stated, clearly labelled as such.

CONCLUSIONS

The conclusions are to be derived from the authors' own results, separately from the discussion.

ABBREVIATIONS

Only standard abbreviations should be used. The full term for which an abbreviation stands must precede its first use in the text, unless it is a standard abbreviation for a unit of measurement. Abbreviations in the title of the paper should be avoided.

MATERIJAL I METODE

Navode se odabir i sve važne karakteristike ispitanika ili laboratorijskih životinja koje su studirane ili opservirane. Treba detaljno specificirati značenje deskriptora te objasniti kako su prikupljeni podatci, identificirati metode, aparate (s nazivom proizvođača u zagradi) te postupke s dovoljnim brojem detalja da bi se rezultati mogli reproducirati. Za metode treba navesti referencije ili detaljno opisati nove metode ili one metode koje su znatnije modificirane, 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

U radovima koji se bave eksperimentima na ljudima jasno treba navesti da su postupci provedeni sukladno etičkim standardima institucijskog ili regionalnog odbora odgovornog za izvođenje eksperimenata na ljudima te u skladu s Helsinškom deklaracijom iz 1975. godine, revidiranom 1983. godine. Ne smije se navoditi ispitanikovo ime i/ili prezime, osobito u ilustrativnim materijalima. U radovima koji se bave eksperimentima na životinjama treba navesti da je poštovan institucionalni ili nacionalni pravilnik o brizi za laboratorijske životinje i njihovu upotrebu.

STATISTIČKA OBRADA

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

REZULTATI

Rezultati se izlažu logičnim slijedom u tekstu, tablicama i ilustracijama. U tekstu se ne ponavljaju svi podatci iz tablica ili ilustracija već se naglašavaju ili sažimaju samo bitna opažanja.

RASPRAVA

Treba naglasiti nove i bitne aspekte studije te zaključke koji 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 objasniti važnost dobivenih rezultata i njihova ograničenja, uključujući i implikacije vezane uz buduća istraživanja, ali uz izbjegavanje izjava i zaključaka koji nisu potpuno potvrđeni dobivenim podatcima. Opažanja iz ove studije treba usporediti s ostalim relevantnim studijama. Kad je potrebno, mogu se navesti nove hipoteze uz jasno naglašavanje da su nove.

ZAKLJUČCI

Zaključci se izvode na osnovi vlastitih rezultata, odvojeno od rasprave.

KRATICE

Treba rabiti samo standardne kratice. Puni pojam za koji se rabi kratica mora biti naveden pri prvoj uporabi kratice u

SYMBOLS

Symbols must be explained in the text. An extensive list of symbols may be provided in the appendix.

TABLES

Each table is to be double spaced and printed on a separate page. Tables must not be submitted as photographs. Each table must have a title and be consecutively numbered in order of appearance in the text. Tables must be clear and simple. Any remarks should be written below the table, and referred to in the table by superscript lowercase letters. Tables should not reiterate results presented elsewhere in the paper (e.g., in a diagram).

FIGURES/ILLUSTRATIONS

All illustrations should be professionally drawn or photographed. Letters, numbers, and symbols must be legible even when reduced in size for publication. Each photograph must be consecutively numbered in order of appearance in the text, list the author's name, and have its top side marked. Each drawing must be consecutively numbered in order of appearance in the text, and have its top side marked. Drawings should be produced or printed in black ink on white bond paper. Color printouts or photocopies are not suitable for reproduction. Photocopies of photographs are not acceptable. Photographs depicting people may be published only when accompanied by a written permission of the person in the photograph, or if the person is unrecognizable. Pictures and tables taken from other sources should be accompanied by their publisher's and author's permission. When submitted in electronic form, figures/illustrations must be in TIFF or high quality JPEG format, with a minimum width of 1500 pixels. Illustrations in other formats might be accepted only with prior consent of the editorial board. The editorial board reserves the right not to publish illustrations that fail to meet these requirements.

ACKNOWLEDGMENTS

In the acknowledgments one should mention all associates who did not meet the criteria for authorship, such as individuals who provided technical writing assistance, or a department chair who provided general support. Financial and material support should also be mentioned.

DECLARATION ON CONFLICT OF INTEREST

Authors must declare whether or not there is a financial relationship between them and the organization/company that sponsored the research. This note must be added in a separate section preceding the references. When no conflict of interest exists, authors should write: "The authors declare that there is no conflict of interest."

REFERENCES

References are to be listed using the *Vancouver reference style* which specifies the numerical referencing system, according to the recommendations of the American *National Library of Medicine*. The most frequently used examples can be found in the article *ICMJE Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals: Sample References* (http://www.nlm.nih.gov/bsd/uniform_requirements.html). Detailed instructions can be found in the book Citing Medicine (http://www.ncbi.nlm.nih.gov/books/NBK7256).

References in the text, tables, and legends should be consecutively numbered using Arabic numerals in parentheses,

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 s dvostrukim proredom na posebnoj stranici. Tablice se ne smiju slati kao fotografije. Svaka tablica mora imati naslov i redni broj prema redoslijedu pojavljivanja u tekstu. Tablica mora biti pregledna i jednostavna. Primjedbe trebaju biti napisane ispod tablice, uz oznaku u tablici malim slovima u superskriptu. Tablice ne bi trebale ponavljati rezultate koji su prezentirani bilo gdje drugdje u radu (npr., u grafikonu).

SLIKE/ILUSTRACIJE

Sve ilustracije trebaju biti profesionalno nacrtane ili snimljene. Slova, brojevi i simboli moraju biti čitki i u smanjenom obliku u kojem će se objaviti. Svaka fotografija 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 izrađeni ili otisnuti crnom tintom na bijelom papiru. Otisci u boji ili fotokopije nisu pogodni za reprodukciju. Fotokopije fotografija nisu prihvatljive. Fotografije osoba mogu se objavljivati samo uz pismeno dopuštenje osobe na fotografiji ili osoba mora biti neprepoznatljiva. Preuzete slike i tablice iz drugih izvora treba popratiti dopuštenjem njihova izdavača i autora.

Ako se dostavljaju u elektroničkom obliku, slike/ilustracije moraju biti u formatu TIFF ili JPEG visoke kvalitete, najmanje širine 1500 piksela. Ilustracije u ostalim formatima mogu biti prihvaćene samo uz prethodno odobrenje uredništva. Uredništvo pridržava pravo ne objaviti ilustracije koje ne zadovoljavaju ove uvjete.

ZAHVALA

U zahvali treba navesti sve suradnike koji nisu zadovoljili kriterije za autorstvo, poput osoba koje su pružile tehničku pomoć pri pisanju ili predstojnika koji je pružio opću potporu. Financijska i materijalna potpora također treba biti navedena.

IZJAVA O SUKOBU INTERESA

Autori moraju izjaviti postoji li financijski odnos između njih i organizacije/tvrtke koja je sponzorirala istraživanje. Ova bilješka mora se dodati u odvojenom odjeljku prije popisa literature. Ako nema sukoba interesa, autori trebaju napisati: "Autori izjavljuju da nisu u sukobu interesa."

LITERATURA

Literatura se navodi primjenom *Vancouverskih pravila* koja propisuju numerički način citiranja, prema preporukama američke *National Library of Medicine*. Najčešći primjeri mogu se naći u članku *ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals: Sample References* (http://www.nlm.nih.gov/bsd/uniform_requirements.html). Detaljne upute mogu

in order of appearance. If there is more than one number, they should be separated by commas.

In the list of references **authors** and/or **editors** are to be listed by their surname(s) and initials of their name(s). After the initial(s) no period is added, except when the initial immediately precedes the title of the reference. Multiple authors/editors' names are separated by commas. If there are more than six authors/editors, after the first three names "et al." should be written, and the others should be omitted. In the **title** capital letters are used only for the first letter of the first word in the title, and in the words that are commonly written with capital letters. When **page numbers** are included, identical initial digits should be omitted (e.g., 123-5 instead of 123-125). Each reference should end with a period, except when the reference ends with a URL.

In texts in the **English** language, when listing references published in other languages it is recommended to list the title in English (if it exists) or to translate it into English (in which case it should be put in square brackets), while at the end of the reference the original language is to be mentioned.

When listing papers which have been accepted but not yet published, "In press" should be added at the end. Authors should obtain written permission when citing such a paper, as well as confirmation that the paper has been accepted for publication.

Journal articles

Journal titles should be listed by their usual abbreviations *(NLM Title Abbreviation)*, which can be found in the *National Library of Medicine* catalogue (http://www.ncbi.nlm.nih.gov/nlmcatalog/journals). Publishers of journals are not to be listed. It is obligatory to include the year of publication, volume, and page numbers. If the journal carries continuous pagination, the month and issue along with the parentheses may be omitted.

[Example] Article from a journal, 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] Article from a journal, continuous pagination:

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

[Example] Article from a supplement:

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

It is obligatory to include the place of publication, publisher, and year of publication. Page numbers are to be included only when a part of the book is cited.

[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 texbook 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. p. 151–85.

se naći u knjizi *Citing Medicine* (http://www.ncbi.nlm.nih.gov/books/NBK7256).

Literaturu u tekstu, tablicama i legendama treba navoditi arapskim brojevima u zagradi, prema redoslijedu pojavljivanja. Ako brojeva ima više, odvajaju se zarezima.

U popisu literature **autori** i/ili **urednici** navode se prezimenom/prezimenima i inicijalima imena. Iza inicijala ne stavlja se točka, osim ako je riječ o inicijalu neposredno prije naslova. Ako autora/urednika ima više, odvajaju se zarezima. Ako ih ima više od šest, nakon prva tri treba napisati „i sur.", a ostale ispustiti. U **naslovu** se velika slova rabe samo za početno slovo prve riječi u naslovu i u riječima koje se uobičajeno pišu velikim slovima. Kad se navode **brojevi stranica**, treba ispustiti iste početne znamenke stranica (npr. 123-125 postaje 123-5). Na kraju svake referencije stavlja se točka.

U tekstovima na **engleskom** jeziku pri navođenju radova objavljenih na drugim jezicima preporučuje se navesti naslov na engleskom (ako postoji) ili ga prevesti na engleski (u tom slučaju treba ga staviti u uglate zagrade), a na kraju se navodi izvorni jezik rada.

Pri navođenju prihvaćenih, ali još neobjavljenih radova, na kraju treba dodati: „U tisku." Autori trebaju dobiti pismeno odobrenje za citiranje takvog rada zajedno s potvrdom da je rad prihvaćen za objavu.

Članak u časopisu

Naslovi časopisa trebaju se navoditi uobičajenim kraticama *(NLM Title Abbreviation)* koje se mogu naći u katalogu *National Library of Medicine* (http://www.ncbi.nlm.nih.gov/nlmcatalog/journals). Za časopise se ne navodi izdavač. Obvezatno se navode godište, volumen i stranice časopisa. Ako časopis ima kontinuiranu paginaciju, može se izostaviti mjesec/broj u godištu časopisa i pripadajuća zagrada.

[Primjer] Članak iz časopisa, više od šest autora:

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(Suppl 2):ii14–7.

Knjige

Obvezatno se navode mjesto izdanja, izdavač i godina izdanja. Brojevi stranica navode se samo kada se citira dio knjige.

[Primjer] Knjiga (autori):

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, urednici. Oxford texbook of rheumatology. 3. izd. New York: Oxford University Press; 2004.

[Primjer] Poglavlje u knjizi:

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

Conference proceedings

If the conference paper was published in a journal or a supplement, the instructions for journals and supplements should be followed. If the conference paper was published in a book, after the book's title the words "Proceedings of" followed by the conference name, date(s), place, and country are to be added.

[Example] Conference paper, published in a supplement:

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

[Example] Conference paper, published in a book:

8. Babić-Naglić Đ. Physical activity and exercises. In: Ivanišević G, editor. [Thalassotherapy, kinesitherapy 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. p. 49-55. Croatian.

[Example] Conference proceedings (book):

9. Gordon DA, editor. Immune reactions and experimental models in rheumatic diseases. Proceedings of the Fourth Canadian Conference on Research in the Rheumatic Diseases; 1970 Oct 15-17; Toronto, Canada. Toronto: University of Toronto Press; 1972.

Web publications

References of web publications should contain the date of access and URL, except when the publication has a DOI.

[Example] Article from a journal on the Internet:

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

[Example] Article from a journal on the Internet, contains 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 [cited 2013 Oct 8]. Available from: http://www.intechopen.com/books/osteoarthritis-diagnosis-treatment-and-surgery

[Example] Web page:

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

REVIEW PROCESS

The review process is conducted anonymously. Each paper is reviewed by two reviewers, and a copy of their evaluation is sent anonymously to the author. When producing the final version of the paper, the author should take into consideration the reviewers' assessment or explain his/her standpoint based on fact.

The editorial board reserves the right to adapt the style of each paper to certain standards of uniformity.

Izlaganje na znanstvenom skupu

Ako je izlaganje objavljeno u časopisu ili suplementu, treba slijediti upute za časopis ili suplement. Ako su izlaganja objavljena u knjizi, nakon naslova knjige dodaje se napomena „Zbornik izlaganja na", naziv skupa te vrijeme, mjesto i država održavanja.

[Primjer] Izlaganje na znanstvenom skupu, objavljeno u suplementu:

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

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

8. Babić-Naglić Đ. Fizička aktivnost i vježbe. U: Ivanišević G, urednik. Talasoterapija, kineziterapija i aromaterapija u Hrvatskoj. Zbornik izlaganja na 14. lošinjskoj 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, urednik. 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.

Mrežne publikacije

Citati mrežnih publikacija trebaju uključivati URL i datum pristupa, osim ako je riječ o publikaciji koja ima DOI.

[Primjer] Članak iz časopisa na internetu:

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, sadrži 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.

[Primjer] Knjiga/monografija na internetu:

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

[Primjer] Mrežna stranica:

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

PROCES OCJENE RADA

Proces ocjene rada provodi se anonimno. Svaki rad šalje se dvojici recenzenata, a preslik njihova mišljenja dostavlja se anonimno autoru. Autor treba uzeti u obzir mišljenja recenzenata pri izradi konačne verzije rada ili argumentirano obrazložiti svoje mišljenje.

Uredništvo zadržava pravo prilagoditi stil rada određenim standardima ujednačenosti.

http://www.reumatologija.org

http://www.reumatizam.hlz.hr