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REVIEW PAPER PREGLEDNI RAD

ASSOCIATION OF BIOLOGICAL THERAPY AND MALIGNANCY IN INFLAMMATORY RHEUMATIC DISEASES

POVEZANOST BIOLOŠKE TERAPIJE I MALIGNIH BOLESTI U UPALNIM REUMATSKIM BOLESTIMA

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Abstract

Inflammatory rheumatic diseases are chronic, progressive autoimmune diseases which affect the musculoskeletal system and other organ systems. Nowadays, a large number of patients is treated with biological therapy. Although biological drugs selectively affect specific molecules of the immune system, they weaken the overall immune system of the body. Therefore, the patients are more susceptible to infections and other diseases such as lymphomas, breast and skin cancers and melanomas. Chronic inflammation which occurs due to autoimmune disease is also a risk factor for malignant development. So far, studies have not proven direct correlation between biological therapy and solid or haematologic tumours. On the other hand, the increased risk for developing skin cancer in patients on tumour necrosis factor alpha inhibitors has been described. In this review paper we analysed the available medical literature on the risks for malignant disease development in patients with rheumatic diseases who are on biological disease – modifying anti-rheumatic drugs.

Key-words: inflammatory rheumatic disease, biological therapy, malignant disease

Sažetak

Sistemske upalne reumatske bolesti jesu kronične, progresivne autoimunosne bolesti koje zahvaćaju lokomotorni sustav i druge organske sustave. Danas je sve više bolesnika liječeno biološkom terapijom. Iako biološki lijekovi selektivno djeluju na specifične molekule imunosnog sustava, oni smanjuju opću obrambenu funkciju organizma, zbog čega su bolesnici podložniji infekcijama, ali i nekim malignim bolestima poput limfoma, karcinoma kože, dojke ili melanoma. Također, sama kronična upala u sklopu autoimunosne bolesti jest rizični čimbenik za razvoj tumorske bolesti. Prema do sada objavljenim studijama, nije dokazana jednoznačna povezanost primjene bioloških lijekova s razvojem solidnih i hematoloških tumora. Suprotno tomu, istraživanja su pokazala povezanost primjene inhibitora tumorske nekroze alfa i razvoja tumora kože. U ovom preglednom radu analizirana je dostupna medicinska literatura o rizicima za razvoj malignih bolesti u bolesnika s reumatološkim bolestima koji su liječeni biološkim antireumatskim lijekovima koji mijenjaju tijek bolesti.

Ključne riječi: upalna reumatska bolest, biološki lijekovi, maligna bolest

INTRODUCTION

Systemic inflammatory rheumatic diseases are a group of chronic inflammatory diseases of unknown aetiology that affect the musculoskeletal system, but also other organ systems. They are characterised by an inadequate immune reaction of the human body (1,2). In medical treatment, the basis of therapy are non-steroidal anti-inflammatory drugs NSAIDs), glucocorticoids and drugs that modify the course of the disease (disease-modifying antirheumatic drugs, DMARDs) (3,4). The so-called conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) have been used in treatment for several decades, and due to the progress of science and a better knowledge of the pathophysiology of these diseases, the new generations of drugs, biological and targeted synthetic disease-modifying antirheumatic drugs (bDMARDs and tsDMARDs) were developed. Their effects are primarily achieved by blocking certain proinflammatory cytokines. In addition, some of them also inhibit the signal required for the activation of T lymphocytes or act on the depletion of B lymphocytes. Care should be taken when prescribing therapy because, although these drugs act specifically and selectively on the immune system, they reduce the general defence function of the body, so patients are more susceptible to infections, but also to some malignant diseases such as lymphoma, skin cancer, breast cancer or melanoma. Due to the immune background in pathogenesis and the predominantly immunosuppressive approach in the treatment of systemic autoimmune diseases, the risk of malignancy is increased (5). Chronic inflammation can contribute to the process of tumorigenesis (6). It has been proven in animal models that tumour necrosis factor alpha (TNF-α) can inhibit, but also promote tumour development depending on the dose and biological conditions (7). The connection between biological therapy and the development of malignant diseases is the topic of continuous interest of many researchers, considering the pronounced immunomodulatory effect of biological drugs during their long-term use. Tumour necrosis factor inhibitors (TNFi) are associated with a variety of potentially dangerous adverse effects, but the risks must be interpreted in the context of the beneficial effects that are experienced with TNFi use. It is important to keep in mind that conventional drugs used for the treatment of inflammatory rheumatic diseases come with their own harmful effects, just like the disease itself (8). A list of biological DMARDs used in the treatment of inflammatory rheumatic diseases is shown in Table 1. In this paper, which is part of the master's thesis written at the School of Medicine of the University of Zagreb, the available medical literature (with a special emphasis on more recent works) from the most important databases was analysed, covering the topic of the risks for the development of malignant diseases in

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Sistemske upalne reumatske bolesti skupina su kroničnih upalnih bolesti nepoznate etiologije koje zahvaćaju lokomotorni sustav, ali i druge organske sustave. Karakterizirane su neadekvatnom imunološkom reakcijom u vlastitom organizmu (1,2). U medikamentnom liječenju osnova terapije su nesteroidni protuupalni lijekovi (skr. NSAR; engl. *non-steroid anti-inflammatory drugs*, skr. NSAIDs), glukokortikoidi i lijekovi koji mijenjaju tijek bolesti (DMARD; prema engl. *disease modifying antirheumatic drugs*) (3,4). Već nekoliko desetljeća primjenjuju se tzv. konvencionalni sintetski DMARD-ovi (csDMARD, prema engl. *conventional synthetic DMARD*), a zahvaljujući napretku znanosti i boljem poznavanju patofiziologije ovih bolesti razvijene su nove generacije lijekova, biološki (bDMARD) i ciljani sintetski DMARD-ovi (tsDMARD, prema engl. *targeted synthetic DMARD*). Njihovi učinci prvenstveno se ostvaruju blokadom pojedinih proinflamatornih citokina. Osim toga, neki od njih inhibiraju i signal potreban za aktivaciju limfocita T ili pak djeluju na depleciju limfocita B. Pri propisivanju terapije treba biti oprezan jer, iako ovi lijekovi djeluju specifično selektivno na imunološki sustav, oni smanjuju opću obrambenu funkciju organizma pa su bolesnici podložniji infekcijama, ali i nekim malignim bolestima poput limfoma, karcinoma kože, dojke ili melanoma. Zbog imunosne podloge u patogenezi i pretežno imunosupresivnog pristupa u liječenju sistemskih autoimunosnih bolesti, povećan je rizik za pojavu malignoteta (5). Kronična upala može pridonijeti procesu tumorogeneze (6). Na životinjskim modelima je dokazano da čimbenik tumorske nekroze alfa (TNF-α; prema engl. *tumor necrosis factor alpha*) može inhibirati, ali i promovirati razvoj tumora ovisno o dozi i biološkim uvjetima (7). Povezanost biološke terapije i razvoja malignih bolesti predmet je kontinuiranog interesa brojnih istraživača, s obzirom na izražen imunomodulatorni učinak bioloških lijekova tijekom njihove dugoročne primjene. Inhibitori čimbenika tumorske nekroze (TNFi) povezuju se s različitim potencijalno opasnim štetnim učincima, no rizici se moraju interpretirati u kontekstu korisnih učinaka uz primjenu TNFi. Važno je imati na umu da i konvencionalni lijekovi koji se koriste u liječenju upalnih reumatskih bolesti imaju svoje štetne učinke, kao i sama bolest (8). Popis bioloških DMARD-ova koji se koriste u liječenju upalnih reumatskih bolesti prikazan je u tablici 1. U ovom radu, koji je dio diplomskog rada na Medicinskom fakultetu Sveučilišta u Zagrebu, analizirana je dostupna medicinska literatura iz najvažnijih baza, s posebnim naglaskom na recentnije radove, o rizicima za razvoj malignih bolesti u bolesnika s reumatološkim bolestima koji su liječeni biološkim DMARD-ovima.

Table 1 Biologic disease modifying drugs used in rheumatology
Tablica 1. Biološki lijekovi koji se koriste u reumatološkim indikacijama

Name of the drug (abbreviated) / Ime lijeka (skraćenica)	Action mechanism / Mehanizam djelovanja	Molecule / Molekula	Route of administration / Put primjene	Indication in rheumatology / Indikacija u reumatologiji	Remark / Napomena
Adalimumab (ADA)	TNF-alpha inhibitor / Blokator TNFα	Monoclonal antibody, human Ig / Monoklonsko protutijelo, humani Ig	SC / s.c.	RA, AS, nr-axSpA, PsA	
Infliximab (IFX) / Infliksimab (IFX)			IV/SC / i.v./s.c.	RA, AS, PsA	
Certolizumab pegol (CZP)			SC / s.c.	RA, AS, nr-axSpA, PsA	
Golimumab (GOL)			SC / s.c.	RA, AS, nr-axSpA, PsA	
Etanercept (ETA)		Soluble receptor / Solubilni receptor	SC / s.c.	RA, AS, nr-axSpA, PsA	
Tocilizumab (TCZ)	IL-6 receptor inhibitor / Blokator receptora IL-6	Monoclonal antibody, human Ig / Monoklonsko protutijelo, humani Ig	i.v./s.c.	RA, GCA, JIA, CRS	
Sarilumab (SAR)			SC / s.c.	RA	
Abatacept (ABT)	It binds to the CD80/CD86 complex / Veže se na kompleks CD80/CD86	Soluble fusion protein / Solubilni fuzijski protein	IV / SC / i.v. / s.c.	RA	
Secukinumab (SEC) / Sekukinumab (SEC)	IL-17A inhibitor / Inhibitor IL-17A	Monoclonal antibody, human immunoglobulin / Monoklonsko protutijelo, humani imunoglobulin	SC / s.c.	AS, nr-axSpA, PsA	It binds to and neutralizes IL-17A with high affinity / S visokim afinitetom se veže i neutralizira IL-17A
Ixekizumab (IXE) / Iksekizumab (IXE)			SC / s.c.	AS, nr-axSpA, PsA	
Anakinra (ANA)	IL-1 receptor antagonist (IL-1Ra) / Blokator receptora za IL-1 (IL-1Ra)	Receptor antagonist / Antagonist receptora	SC / s.c.	RA, sJIA, Still's disease, adult Still's disease, CAPS, FMF / RA, sJIA, Stillova bolest, Stillova bolest odraslih, CAPS, FMF	
Ustekinumab (UST)	IL-12/IL-23 inhibitor / Inhibitor IL-12/IL-23	Monoclonal antibody / Monoklonsko protutijelo	SC / s. c.	PsA	It binds to the p40 subunit of both cytokines and blocks their binding to receptors / Veže se na podjedinicu p40 obaju citokina i blokira njihovo vezanje za receptore.
Rituximab (RTX) / Rituksimab (RTX)	CD20 positive B-lymphocite inhibitor / Inhibitor CD20+ B-limfocita	Monoclonal antibody, chimera (human-mouse) / Monoklonsko protutijelo, kimera (humano-mišje)	IV (SC*) / i.v. (s.c.*)	RA, GPA, MPA	*SC administration only in haematological indications / *s.c. primjena samo u hematološkoj indikaciji

Abbreviations / Skraćenice: AS – ankylosing spondylitis / ankilozantni spondilitis, CAPS – cryopyrin-associated autoinflammatory syndrome / autoinflamatorni sindrom povezan s kriopirinom (engl. cryopyrin associated autoinflammatory syndrome), CRS – cytokine release syndrome / sindrom otpuštanja citokina (engl. cytokine release syndrome), FMF – familial Mediterranean fever / obiteljska mediteranska vrućica (engl. familial mediterranean fever), GCA – giant cell arteritis / gigantocelularni arteritis, GPA – granulomatosis with polyangiitis / granulomatozni poliangiitis, Ig – immunoglobulin / imunoglobulin, IL – interleukin, IV/i.v. – intravenous / intravenski, JIA – juvenile idiopathic arthritis / juvenilni idiopatski artritis, jPsA – juvenile psoriatic arthritis / juvenilni psorijatički artritis, MPA – microscopic polyangiitis / mikroskopski polinagiitis, nr-axSpA – non-radiographic axial spondyloarthritis / neradiografski aksijalni spondiloartritis, PO/p.o. – peroral / peroralno, PsA – psoriatic arthritis / psorijatični artritis, RA – rheumatoid arthritis / reumatoidni artritis, SC/s.c. – subcutaneous / supkutano.

patients with rheumatic diseases who were treated with biological DMARDs.

RISK OF DEVELOPING MALIGNANT DISEASES

According to data from the literature, patients suffering from rheumatoid arthritis (RA) have a 10–15%

RIZIK ZA OBOLIJEVANJE OD MALIGNIH BOLESTI

Prema podatcima iz literature, bolesnici koji boluju od reumatoidnog artritisa (RA) imaju 10–15% veći ukupni rizik za razvoj nekih malignoma u usporedbi s općom populacijom, primjerice karcinoma pluća i limfoma (standardizirani omjer incidencije; skr. SIR,

higher total risk of developing some malignancies compared to the general population, for example lung cancer and lymphoma (standardized incidence ratio 1, 2–4), non-melanoma skin cancers (SIR 1–3) and possible melanoma and leukaemia (9). The increased risk may be related to the simultaneous use of other drugs, but also the result of chronic, poorly controlled inflammation (10). On the other hand, due to the chronic use of NSAIDs, including cyclooxygenase-2 (COX-2) inhibitors, a lower incidence of colon adenocarcinoma and breast cancer is noted (11). According to some studies, methotrexate, which is often used in combination with TNF-alpha inhibitors may also be associated with an increased risk of developing lymphoma (5). Many of the conducted studies do not include a sufficient number of subjects in order to obtain a reliable result about a higher risk for the development of a malignant disease. Unlike RA, which was the topic of numerous studies in relation to the impact of TNF-alpha inhibitors, when it comes to other autoimmune diseases, as well as some biological drugs, the data on the increased risk are still insufficient. We must highlight the paper written by Kwan et al. in 2020, in which the risk for the development of a malignant disease in patients with seronegative spondyloarthropathies (SnSpA) was analysed (12). It is a systematic review article and meta-analysis that included 14,245 patients. Demographic and pathogenetic differences between patients with seronegative spondyloarthropathy (SnSpA) and RA are highlighted. Patients with SnSpA, especially those with the axial form of the disease, are mainly affected much earlier than patients with RA. In addition to that, considering the treatment guidelines, they were previously exposed to biological therapy. The pathophysiological aspect is also significant, considering the role of Th17 cells in the development of the disease, but also in tumorigenesis. The authors analysed the risk for the development of malignant disease depending on the type of SnSpA, which can be axial (e.g. ankylosing spondylitis, AS and non-radiographic axial spondyloarthritis, nr-axSpA) or peripheral (e.g. psoriatic arthritis, PsA or enteropathic arthritis, EA) and on therapy (biological drug vs. csDMARD and other types of biological drugs, TNF-alpha inhibitors, IL-17 inhibitors and others). Despite a comprehensive and detailed analysis, ultimately no increased risk was proven in patients with SnSpA, both with the disease itself and with biological therapy, regardless of the biological drug. The paper notes the need for trials that would include patients in a longer follow-up period. With psoriasis, independent of the development of PsA, an increased risk for the development of non-melanoma skin cancers, lymphomas and lung cancers has been described. There is speculation about the effect of IL-17, which promotes angiogenesis, but is also a mediator in immune defence processes against tumours. An

prema engl. *standardized incidence ratio*) (1,2–4), nemelanomskih karcinoma kože (SIR 1–3) te moguće melanoma i leukemije (9). Povišeni rizik može biti povezan s istodobnim uzimanjem drugih lijekova, ali i posljedica kronične, slabo kontrolirane upale (10). S druge strane, zbog kronične upotrebe NSAR-a (engl. NSAID), uključujući inhibitore ciklooksigenaze-2, bilježi se niža incidencija adenokarcinoma kolona i karcinoma dojke (11). Prema nekim studijama metotreksat (skr. MTX, prema engl. *methotrexate*), koji se često koristi u kombinaciji s TNF-alfa inhibitorima, također može biti povezan s povišenim rizikom za razvoj limfoma (5). Mnoge provedene studije ne obuhvaćaju dovoljan broj ispitanika da bi se sa sigurnošću dobio pouzdan rezultat o višem riziku za razvoj maligne bolesti. Za razliku od RA, vezano za koji su provedene brojne studije o utjecaju TNF-alfa inhibitora, za ostale autoimunosne bolesti, kao i za neke biološke lijekove, podatci o povišenom riziku još su uvijek nedostatni. Izdvajamo rad Kwana i sur. iz 2020. godine u kojemu je analiziran rizik za razvoj maligne bolesti u bolesnika sa seronegativnim spondiloartropatijama (skr. SnSpA) (12). Riječ je o sustavnom preglednom članku i meta-analizi kojom je bilo obuhvaćeno 14.245 bolesnika. Ističu se demografske i patogenetske razlike između bolesnika sa seronegativnom spondiloartropatijom (SnSpA) i RA. Naime, bolesnici oboljeli od SnSpA, posebice aksijalnim oblikom bolesti, obolijevaju znatno ranije nego bolesnici s RA. Također, obzirom na smjernice liječenja, ranije su izloženi biološkoj terapiji. Patofiziološki aspekt je također značajan, s obzirom na ulogu Th17-stanica u razvoju bolesti, ali i u tumorogenezi. Autori su analizirali rizik za razvoj maligne bolesti ovisno o tipu SnSpA, aksijalni (npr. ankilozantni spondilitis, skr. AS i neradiografski aksijalni spondiloartritis) ili periferni oblik (npr. psorijatički artritis, skr. PsA ili enteropatski artritis) i o terapiji (biološki lijek vs. csDMARD te vrste bioloških lijekova; TNF-alfa inhiitori, inhibitori IL-17 i ostali). Unatoč sveobuhvatnoj i detaljnoj analizi, u konačnici nije dokazan povišen rizik u bolesnika sa SnSpA, kako uz samu bolest, tako i uz biološku terapiju, bez obzira na biološki lijek. U radu se napominje potreba za ispitivanjima koja bi obuhvatila bolesnike u duljem razdoblju praćenja. Uz psorijazu, neovisno o razvoju PsA, opisuje se povišeni rizik za razvoj nemelanomskih kožnih karcinoma, limfoma i karcinoma pluća. Spekulira se o učinku IL-17 koji potiče angiogenezu, no ujedno je i medijator u imunosnim procesima obrane od tumora. Povišen rizik za razvoj gore navedenih tumorskih bolesti, uključivo i tumor mokraćnog mjehura, u bolesnika sa psorijazom, opisuje se i u drugom preglednom radu iz 2020. godine, no nije pronađena povezanost s biološkom terapijom, kao niti povišen rizik za razvoj tumora

increased risk for the development of the above-mentioned tumour diseases, including bladder tumours, in patients with psoriasis is also described in another review from 2020, but no connection with biological therapy was found, nor was there an increased risk for the development of tumours in patients with psoriatic arthritis (13). In studies that researched the risk of malignancy in inflammatory rheumatic diseases, SIR was predominantly used, which is obtained by comparing the recorded and expected incidence of malignancy, the relative risk (RR) and the odds ratio (OR). The advantage of using RR over SIR is higher specificity in the analysis of the risk associated with the therapy.

STUDIES OF OVERALL RISK FOR MALIGNANT DISEASE

The results of the studies published so far are conflicting. Some speak in favour, and others against the increased overall risk for the development of a malignant disease, regardless of its site. Initial concern about a possible association between TNF-alpha inhibitors and malignancy was based on a report by the Food and Drug Administration (FDA) from the United States of America (USA) which was published in 2002 and which included 26 cases of lymphoma, predominantly non-Hodgkin's lymphoma (NHL) in patients with RA and Crohn's disease who were treated with etanercept (ETN) or infliximab (IFX). Lymphoma remission was verified in 2 of the mentioned 26 patients after discontinuing the use of TNF-alpha inhibitors. However, in the aforementioned report, data were presented without comparison with a control group (14). A subsequent FDA report further raised concerns over the alleged association between malignancies and the listed drugs in children and adolescents treated for juvenile idiopathic arthritis (JIA) and inflammatory bowel disease (IBD) (8). The FDA analysis indicated a total of 48 cases of malignant diseases in a 10 year period (1998–2008) in patients treated with TNF-alpha inhibitors. Almost half of the 48 patients suffered from lymphoma (Hodgkin and non-Hodgkin type), and the rest had leukaemia, melanoma and solid tumours. Based on these reports, a meta-analysis was performed that included 9 clinical studies with a total of 3,493 RA patients who were treated with TNF-alpha inhibitors, drugs such as adalimumab (ADA) or infliximab (IFX). The results showed that the risk of developing malignancy in patients treated with these drugs was 3.3 times higher than in patients on placebo (OR 3.3; 95% confidence interval (CI, 1.2–9.1) (15). The frequency of cancer was higher in patients treated with higher doses of drugs. Out of the 26 malignant diseases registered in patients treated with TNF-alpha inhibitors, 15 had solid tumours. Only one solid tumour was recorded in the control group (patients on placebo).

u bolesnika sa psorijatičkim artritisom (13). U studijama koje su proučavale rizik pojave malignih bolesti u upalnim reumatskim bolestima pretežno se koristio SIR, koji se dobiva usporedbom zabilježene i očekivane incidencije maligniteta, relativni rizik (RR) i omjer šansi (OR, prema engl. *odds ratio*). Prednost korištenja RR pred SIR jest viša specifičnost u analizi rizika povezanog s terapijom.

STUDIJE UKUPNOG RIZIKA ZA MALIGNU BOLEST

Rezultati do sada objavljenih studija su oprečni. Neki govore u prilog, a drugi protiv povišenoga ukupnog rizika za razvoj maligne bolesti, neovisno o njenom sijelu. Početna zabrinutost o mogućoj povezanosti TNF-alfa inhibitora i maligniteta temeljila se na izvješću Agencije za hranu i lijekove (skr. FDA, prema engl. *Food and Drug Administration*) iz Sjedinjenih Američkih Država (skr. SAD; engl. USA) iz 2002. godine o 26 slučajeva limfoma, pretežno non-Hodgkin limfoma (NHL) u bolesnika s RA i Crohnovom bolesti koji su bili liječeni etanerceptom (ETN) ili infliksimabom (IFX, prema engl. *infliximab*). U dva od navedenih 26 bolesnika verificirana je remisija limfoma nakon prekida primjene TNF-alfa inhibitora. Međutim, u spomenutom izvješću, prikazani su podatci bez usporedbe s kontrolnom skupinom (14). Sljedeći izvještaj FDA još je više povećao zabrinutost zbog navoda o povezanosti malignih bolesti i navedenih lijekova u djece i adolescenata koji su bili liječeni od juvenilnoga idiopatskog artritisa (JIA) i upalnih bolesti crijeva (skr. IBD, prema engl. *inflammatory bowel disease*) (8). Analiza FDA je ukazala na ukupno 48 slučajeva malignih oboljenja u razdoblju od 10 godina (1998. – 2008.) u bolesnika liječenih TNF-alfa inhibitorima. Gotovo polovica od 48 bolesnika oboljela je od limfoma (tipa Hodgkin i non-Hodgkin), a ostali su imali leukemiju, melanom i solidne tumore. Na temelju tih izvješća učinjena je metaanaliza koja je uključivala devet kliničkih studija s ukupno 3,493 bolesnika oboljelih od RA koji su bili liječeni TNF-alfa inhibitorima, lijekovima adalimumabom (skr. ADA) ili IFX. Rezultati su pokazali da je rizik za razvoj maligniteta u bolesnika liječenih tim lijekovima 3,3 puta viši nego u onih na placebu (OR 3,3; 95% CI [prema engl. *confidence interval*, interval pouzdanosti]) 1,2 – 9,1) (15). Učestalost karcinoma je bila veća u bolesnika liječenih višim dozama lijekova. Od 26 malignih bolesti registriranih u bolesnika liječenih TNF-alfa inhibitorima, njih 15 su imali solidne tumore. U kontrolnoj skupini (na placebu) zabilježen je samo jedan solidni tumor.

Protivno navedenom, druge studije su pokazale da nema povišenog rizika za razvoj malignih tumora u bolesnika oboljelih od RA liječenih TNF-alfa inhibitorima u usporedbi s konvencionalnom terapijom ili

Contrary to the aforementioned, other studies have shown that there is no increased risk for the development of malignant tumours in RA patients treated with TNF-alpha inhibitors compared to conventional therapy or the general population. The safe use of ADA in RA, PsA, AS, JIA and IBD was demonstrated in a study that included data from 71 clinical trials (16). This study included 23458 patients treated with ADA. The risk of developing tumours in patients treated with ADA, regardless of the inflammatory rheumatic disease for which they were treated, was almost the same as in the reference general population. The SIR for RA was 0.93 (95% CI, 0.82–1.06), for AS it was 0.51 (95% CI, 0.16–0.19), and for PsA it was 0.68 (95% CI, 0.22–1.59). Not a single incidence of cancer was recorded among patients with JIA. Considering the age of the affected population, JIA is certainly of particular interest when it comes to the risk of developing malignant diseases. According to data from the Swedish registry from 2019, for all cancers, regardless of their site, the HR was 1.4 (95% CI, 0.7–2.9), and for lymphoproliferative diseases the HR was 3.6 (95% CI, 1.1–11.2). The data indicate a mildly increased risk for the development of lymphoproliferative disease in patients with JIA, but not for other cancers. Also, the risk does not change depending on the treatment modality (17). In Sweden, a study was conducted in 2009 with the aim of assessing the overall risk for the development of cancer related to the use of TNFi (9). Data from the Swedish registers of biological drugs, rheumatic diseases and cancer were analysed, and the results showed that there was no difference in the risk of developing malignant diseases in patients treated with TNF-alpha inhibitors and csDMARDs (RR = 1.0; 95% CI 0.86–1.15). The study conducted on the basis of data from the Danish Registry for Biological Therapies in Rheumatology (DANBIO) in the period 2000–2008 yielded similar results (18). The data collected from 3347 RA patients who were treated with TNF-alpha inhibitors and 3812 RA patients who were not treated with biological therapy were compared, and overall, no increased risk of malignancy was found in patients treated with TNF-alpha inhibitors (RR=1.02; 95% CI 0.80–1.30). Compared to the general population, the risk of developing malignant diseases was slightly higher (SIR = 1.27; 95% CI 1.08–1.49). According to published meta-analyses and cohort studies on patients with RA, there are similar data for the drugs: abatacept, anakinra, rituximab (RTX) and tocilizumab (TCZ) (19–21). A higher incidence rate of solid or haematological neoplasm and skin cancer in patients on biological therapy compared to patients treated only with csDMARDs was not proven, except for an increased risk of developing squamous cell carcinoma with the use of abatacept (hazard ratio, (HR) was 2.12; 95% CI 1.14–3.95) (21). In a study from Finland, based on data from the national registry, the frequency of oc-

općom populacijom. Sigurnost primjene ADA u RA, PsA, AS, JIA i IBD prikazana je u studiji koja je obuhvatila podatke iz 71 kliničkog istraživanja (16). Obuhvaćeno je bilo 23.458 bolesnika liječenih ADA. Rizik za razvoj bilo kojeg tumora u bolesnika liječenih primjenom ADA, neovisno o upalnoj reumatskoj bolesti od koje su liječeni, bio je gotovo isti kao u referentnoj općoj populaciji. SIR za RA iznosio je 0,93 (95% CI 0,82 – 1,06), za AS je bio 0,51 (95% CI 0,16 – 0,19), a za PsA 0,68 (95% CI 0,22 – 1,59). Među oboljelima od JIA nije zabilježen ni jedan karcinom. S obzirom na dob zahvaćene populacije JIA je svakako od posebnog interesa kada je u pitanju rizik za razvoj malignih bolesti. Prema podatcima iz švedskog registra iz 2019. godine, za sve karcinome, neovisno o sijelu, HR je 1,4 (95% CI 0,7 – 2,9), a za limfoproliferativne bolesti HR iznosi 3,6 (95% CI 1,1 – 11,2). Podatci ukazuju na blaže povišen rizik za razvoj limfoproliferativne bolesti u bolesnika s JIA, no ne i za ostale karcinome. Također, rizik se ne mijenja s obzirom na modalitet liječenja (17). U Švedskoj je 2009. godine provedena studija s ciljem procjene ukupnog rizika za razvoj karcinoma vezanih uz primjenu TNFi (9). Analizirani su podatci iz švedskih registara bioloških lijekova, reumatskih bolesti i karcinoma, a rezultati su pokazali da nema razlike u riziku od obolijevanja od malignih bolesti u bolesnika liječenih TNF-alfa inhibitorima i csDMARD-ovima (RR = 1,0; 95% CI 0,86 – 1,15). Studija provedena na temelju podataka iz Danskog registra za biološku terapiju u reumatologiji (DANBIO) u razdoblju od 2000. do 2008. godine dala je slične rezultate (18). Uspoređeni su podatci 3.347 bolesnika oboljelih od RA koji su liječeni TNF-alfa inhibitorima i 3.812 bolesnika s RA koji nisu liječeni biološkom terapijom te sveukupno nije nađen povišeni rizik za malignitet u bolesnika liječenih TNF-alfa inhibitorima (RR=1,02; 95% CI 0,80 – 1,30). Uspoređujući s općom populacijom, rizik obolijevanja od malignih bolesti bio je nešto viši (SIR = 1,27; 95% CI 1,08 – 1,49). Prema objavljenim metaanalizama i kohortnim istraživanjima na bolesnicima s RA, slični su podatci za lijekove: abatacept, anakinru, rituksimab (RTX, prema eng. *rituximab*) i tocilizumab (TCZ) (19–21). Nije dokazana viša stopa incidencije solidne ili hematološke neoplazme te karcinoma kože u bolesnika na biološkoj terapiji u odnosu na bolesnike koji su liječeni samo csDMARD-ovima, izuzev povišenog rizika za razvoj karcinoma skvamoznih stanica uz primjenu abatacepta (HR [prema engl. *hazard ratio*, omjer rizika] koji je bio 2,12; 95% CI 1,14–3,95) (21). U istraživanje iz Finske, na temelju podataka iz nacionalnog registra, analizirana je učestalost pojave malignih bolesti u bolesnika oboljelih od RA liječenih TNF-alfa inhibitorima (IFX, ETN, ADA), RTX ili csDMARD-ovima (22). Stopa incidencije (IR, prema engl. *incidence rate*) malignoma bila je najviša u bole-

currence of malignant diseases in RA patients treated with TNF-alpha inhibitors (IFX, ETN, ADA), RTX or csDMARDs was analysed (22). Incidence rate (IR) of malignancy was the highest in patients treated with csDMARDs (IR = 12; 95% CI 8.6–17) and RTX (IR = 9.5; 95% CI 3.8–2.0), and the lowest in patients treated with IFX (IR = 5.8; 95% CI 2.8–11). Comparing biological drugs and csDMARDs, the risk of developing a malignant disease is lower with biological drugs, with the exception of RTX. However, as it was concluded in the study, after adjusting the data according to age and gender, no statistically significant difference was found in the rate of incidence of malignant diseases during treatment with any combination of drugs, and the only risk factor associated with the development of a malignant disease was age.

The safety of secukinumab, which is increasingly used in the treatment of SnSpA, PsA and psoriasis, has been investigated in several large studies. The 2021 study included data from 49 clinical trials that included a total of 14,519 patients whose follow-up was performed over a five-year period (23). The results showed that there is no increased risk for the development of malignant disease (SIR 0.99; 95% CI 0.82–1.19).

RISK FOR THE DEVELOPMENT OF HAEMATOLOGICAL MALIGNANCIES

Data on the association between TNF-alpha inhibitors and the risk of developing haematological malignancies in patients suffering from systemic inflammatory rheumatic diseases, especially lymphoma, are different. Some authors believe that chronic inflammation, and not its treatment, is associated with an increased risk of lymphoma in RA patients (24). Thus, data from the South Swedish Arthritis Treatment Group indicate a possible increased risk for the development of lymphoma (25). For the development of any malignant disease with the use of TNF-alpha inhibitors (ETN and IFX) the SIR was 1.1 (95% CI 0.6–1.8), and for the control group treated with csDMARDs it was 1.4 (95% CI 1.1–1.8). For lymphoma in the group treated with TNF-alpha inhibitors the SIR was 11.5 (95% CI 3.7–26.9), which is a significantly different result compared to the SIR for the group treated with csDMARDs, which was 1.3 (95 % CI 0.2–4.5). The previously mentioned retrospective cohort study in Sweden conducted on RA patients, which included more than 50,000 subjects, showed that RA patients have an increased risk of developing lymphoma (SIR 1.9) and leukaemia (SIR 2.1) compared to the general population (24). Data collected from the Swedish national registries of patients with AS and PsA in the period 2001–2011 did not show an increased risk for the development of lymphoma in patients with AS compared to the general population (HR 0.9; 95% CI 0.5 – 1.6),

snika liječenih csDMARD-ovima (IR = 12; 95% CI 8,6 – 17) i RTX (IR = 9,5; 95% CI 3,8 – 2,0), a najniža u bolesnika liječenih IFX (IR = 5,8; 95% CI 2,8 – 11). Usporedivši biološke lijekove i csDMARD-ove, rizik za razvoj maligne bolesti niži je uz biološke lijekove, izuzev RTX-a. Ipak, kako je u studiji zaključeno, nakon prilagodbe podataka prema dobi i spolu, nije nađena statistički značajna razlika u stopi incidencija malignih bolesti tijekom liječenja bilo kojom kombinacijom lijekova te je jedini čimbenik rizika povezan s razvojem maligne bolesti bila dob.

Sigurnost primjene sekukinumaba, koji se sve više koristi u liječenju SnSpA, PsA te psorijaze, ispitivana je u nekoliko velikih studija. Studija iz 2021. godine obuhvatila je podatke 49 kliničkih studija koje su uključivale ukupno 14.519 bolesnika praćenih u petogodišnjem razdoblju (23). Rezultati su pokazali da nema povišenog rizika za razvoj maligne bolesti (SIR 0,99; 95% CI 0,82 – 1,19).

RIZIK ZA RAZVOJ MALIGNIH HEMATOLOŠKIH BOLESTI

Podatci koji govore o povezanosti TNF-alfa inhibitora i riziku za razvoj malignih hematoloških bolesti u bolesnika oboljelih od sistemskih upalnih reumatskih bolesti, posebice limfoma, različiti su. Neki autori smatraju da je kronična upala, a ne njezino liječenje, povezana s povišenim rizikom od nastanka limfoma u oboljelih od RA (24). Tako, podatci iz regionalnog registra u južnoj Švedskoj (eng. *The South Swedish Arthritis Treatment Group*) upućuju na mogući povišeni rizik za razvoj limfoma (25). SIR za razvoj bilo koje maligne bolesti uz primjenu TNF-alfa inhibitora (ETN i IFX) bio je 1,1 (95% CI 0,6 – 1,8), a za kontrolnu skupinu liječenu csDMARD-ovima iznosio je 1,4 (95% CI 1,1 – 1,8). SIR za limfom u skupini liječenih TNF-alfa inhibitorima bio je 11,5 (95% CI 3,7 – 26,9), što je značajno različit rezultat u odnosu na SIR za skupinu liječenu csDMARD-ovima koji je iznosio 1,3 (95% CI 0,2 – 4,5). Ranije spomenuto retrospektivno kohortno istraživanje u Švedskoj provedeno na oboljelima od RA, koje je uključivalo više od 50.000 ispitanika, pokazalo je da bolesnici oboljeli od RA imaju povišen rizik za razvoj limfoma (SIR 1,9) i leukemije (SIR 2,1) u usporedbi s općom populacijom (24). Prikupljeni podatci iz švedskih nacionalnih registara oboljelih od AS i PsA u razdoblju od 2001. do 2011. godine nisu pokazali povišeni rizik za razvoj limfoma u bolesnika s AS u odnosu na opću populaciju (HR 0,9; 95% CI 0,5 – 1,6), dok je u oboljelih od PsA nađen blago povišeni rizik (HR 1,2; 95% CI 0,9 – 1,7) (26). Uspoređujući oboljele od PsA liječene TNF-alfa inhibitorima s bolesnicima liječenim MTX-om ili sulfasalazinom, rizik je bio nešto viši uz konvencionalnu terapiju (HR 1,7; 95% CI 1,0 – 3,1).

while a slightly increased risk was found in patients with PsA (HR 1.2; 95 % CI 0.9–1.7) (26). By comparing PsA patients treated with TNF-alpha inhibitors to patients treated with MTX or sulfasalazine, it was revealed that the risk was slightly higher with conventional therapy (HR 1.7; 95% CI 1.0–3.1).

A study from Japan conducted on a sample of 5,573 patients analysed the safety profile of TCZ in the treatment of patients suffering from inflammatory rheumatic diseases (27). In analysing the number of recorded malignancies, it was revealed that only the incidence of lymphoma was significantly increased in patients treated with TCZ compared to the general population (SIR = 3.13; 95% CI 1.82–5.39). The incidence of leukaemia was not higher compared to the general population (SIR 0.54; 95% CI 0.08–3.83).

A study was conducted in the USA based on data available from the National Databank for Rheumatic Diseases (5). Separate research revealed that neither IFX nor ETN were associated with an increased risk for lymphoma.

The RATIO registry in France was established with the aim of collecting data on all cases of opportunistic infections and lymphomas associated with the treatment with TNF-alpha inhibitors regardless of the underlying disease, and to identify risk factors and compare the risk among different biological drugs (28). Based on the analysis of data collected from 2004–2006 a case control was conducted in which 38 cases of lymphoma (29 non-Hodgkin lymphomas, 5 Hodgkin lymphomas and 2 Hodgkin-like lymphomas) were recorded in patients suffering from inflammatory rheumatic diseases treated with TNF-alpha inhibitors. The risk of developing lymphoma in these patients was elevated compared to the general population (SIR 2.4; 95% CI 1.7–3.2), almost the same as in those who were not treated with drugs of this group. Thus, the study failed to demonstrate an increased risk for the development of lymphoma in patients suffering from inflammatory rheumatic diseases treated with TNF-alpha inhibitors.

RISK FOR THE DEVELOPMENT OF SOLID MALIGNANT TUMOURS

Most of the extensive studies published so far, mostly meta-analyses, which examined the safety of TNF-alpha inhibitor use, did not show a significantly increased risk for the development of solid tumours (5,29). In 20–50% of cases the risk is increased for cancers related to smoking and in 70% of cases there is an increased risk for all skin cancers except melanoma. In contrast, a reduced risk of developing breast cancer by 20% and colorectal cancer by 25% is reported, which was explained in the aforementioned part of the paper.

Furthermore, according to BSRBR-RA data (the British Society for Rheumatology Biologics Register

Studija iz Japana na uzorku od 5,573 pacijenata analizirala je sigurnosni profil TCZ-a u liječenju bolesnika oboljelih od upalnih reumatskih bolesti (27). Analizirajući sijela zabilježenih malignih bolesti, samo je učestalost limfoma bila znatno povišena u bolesnika liječenih TCZ-m u usporedbi s općom populacijom (SIR = 3,13; 95% CI 1,82 – 5,39). Učestalost leukemije nije bila veća u usporedbi s općom populacijom (SIR 0,54; 95% CI 0,08 – 3,83).

U SAD-u je provedeno istraživanje na temelju podataka dostupnih iz Nacionalnog registra za reumatske bolesti (5). Promatrano zasebno, niti IFX niti ETN ne povezuju se s povišenim rizikom za limfom.

Registar RATIO u Francuskoj osnovan je s ciljem da se skupe podatci o svim slučajevima oportunističkih infekcija i limfoma povezanih s liječenjem TNF-alfa inhibitorima neovisno o osnovnoj bolesti, te da se identificiraju rizični čimbenici i usporedi rizik među različitim biološkim lijekovima (28). Na temelju analize podataka prikupljenih od 2004. do 2006. godine provedeno je istraživanje parova (engl. *case-control)* u kojem je zabilježeno 38 slučajeva limfoma (29 non-Hodgkin limfoma, pet Hodgkin limfoma i dva limfoma slična Hodgkinovom) u bolesnika oboljelih od upalnih reumatskih bolesti liječenih TNF-alfa inhibitorima. Rizik za razvoj limfoma u ovih bolesnika bio je povišen u odnosu na opću populaciju (SIR 2,4; 95% CI 1,7 – 3,2), gotovo isti kao i u onih koji nisu liječeni lijekovima te grupe. Dakle, studija nije uspjela dokazati povišen rizik za razvoj limfoma u bolesnika oboljelih od upalnih reumatskih bolesti na terapiji TNF-alfa inhibitorima.

RIZIK ZA RAZVOJ SOLIDNIH MALIGNIH TUMORA

Većina do sada objavljenih opsežnih studija, pretežito metaanaliza, koje su ispitivale sigurnost primjene TNF-alfa inhibitorima nije pokazala značajno povišen rizik za razvoj solidnih tumora (5,29). U 20–50% slučajeva rizik je povišen za karcinome povezane s pušenjem te čak 70% povišen rizik za sve kožne karcinome osim melanoma. Nasuprot tomu, navodi se sniženi rizik za razvoj karcinoma dojke za 20%, a za kolorektalni karcinom 25%, što je objašnjeno ranije u tekstu.

Nadalje, prema podatcima BSRBR-RA (engl. *British Society for Rheumatology Biologics Register for Rheumatoid Arthritis*) nema povišenog rizika za solidne tumore u bolesnika liječenih TNFi u usporedbi s bolesnicima koji nikad nisu primili biološku terapiju (HR 0,83; 95% CI 0,64 – 1,07) (30). Studija je obuhvatila 11.767 bolesnika s RA liječenih TNF-alfa inhibitorima i 3.249 bolesnika s RA koji su liječeni csDMARD-ovima. Studija iz 2015. godine koju su proveli švedski istraživači nije našla povišeni rizik za razvoj solidnih malignih tumora. U kliničkoj studiji koja je trajala 11

for Rheumatoid Arthritis) there is no increased risk for solid tumours in patients treated with TNFi compared to patients who were never treated with biological drugs (HR 0.83; 95% CI 0.64–1.07) (30). The study included 11,767 RA patients treated with TNF-alpha inhibitors and 3,249 RA patients treated with csDMARDs. A 2015 study by Swedish researchers found no increased risk for developing solid malignancies. In a clinical trial that lasted 11 years, a follow-up was performed on the population of RA patients treated with RTX. The aim of the trial was to determine the possible long-term consequences of this therapy. The most common solid tumour was breast cancer (0.14/100 patient-years; 95% CI 0.08–0.22) (31). The SIR for breast cancer was 0.63 (95% CI 0.79–0.90) suggesting no increased risk compared to previous epidemiological studies of the safety of RTX in RA (SIR = 0.84; 95% CI 0.79–0.90) (32).

RISK FOR THE DEVELOPMENT OF SKIN CANCER AND MELANOMA

Research conducted so far has shown an increased risk for the development of non-melanoma skin cancer (NMSC) in patients suffering from RA (33,34). According to the study results, the use of TNF-alpha inhibitors and prednisone increases the risk of developing NMSC, which is confirmed by the results of a recent meta-analysis from 2020 which included 123,031 patients (35). It is emphasized that there is a statistically significantly higher risk for the development of squamous cell carcinoma (SCC) in RA patients treated with TNF-alpha inhibitors. In contrast, a British study that analysed data from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR-RA) from 2001–2008 did not show an additional increased risk for NMSC when using drugs from the group of TNF-alpha inhibitors (36). The results of the study showed that the risk of developing basal cell carcinoma (BCC) and SCC is increased in RA patients compared to the general population, regardless of whether they were treated with TNF-alpha inhibitors (SIR 1.72; 95% CI 1.43–2.04) or csDMARDs (SIR 1.83; 95% CI 1.30–2.50). The previously mentioned systematic literature review and meta-analysis based on the data collected from various databases (MEDLINE, EMBASE, Cochrane Database of Systematic Reviews) and from the data published by rheumatology societies yielded very comprehensive results on the risk of treatment with TNF-alpha inhibitors and skin cancers (27). The results of 4 studies involving over 28,000 patients showed that patients treated with TNF-alpha inhibitors have a higher risk of developing BCC and SCC (RR 1.45; 95% CI 1.15–1.76). In addition to that, the study presented data for the development of invasive melanoma, according

godina praćena je populacija oboljelih od RA liječenih RTX-om. Cilj studije bio je ustanoviti eventualne dugoročne posljedice terapije. Najčešći solidni tumor bio je karcinom dojke (0,14/100 bolesnik-godina; 95% CI 0,08 – 0,22) (31). SIR za karcinom dojke iznosio je 0,63 (95% CI 0,79 – 0,90), što govori da nema povišenog rizika u usporedbi s prethodnim epidemiološkim istraživanjima sigurnosti RTX-a kod RA (SIR = 0,84; 95% CI 0,79 – 0,90) (32).

RIZIK ZA RAZVOJ KARCINOMA KOŽE I MELANOMA

Do sada provedena istraživanja pokazala su povišen rizik za razvoj nemelanomskih tumora kože (NMSC, prema engl. *non-melanoma skin cancer*) u bolesnika koji boluju od RA (33,34). Prema rezultatima studija, primjena TNF-alfa inhibitora i prednizona povećava rizik za razvoj NMSC-a, što potvrđuju i rezultati novije metaanalize iz 2020. godine koja je obuhvatila 123.031 bolesnika (35). Ističe se kako je statistički značajno viši rizik za razvoj karcinoma skvamoznih stanica (SCC, prema engl. *squamous cell carcinoma*) u bolesnika s RA liječenih TNF-alfa inhibitorima. Suprotno tomu, britanska studija koja je analizirala podatke iz britanskog registra biološke terapije za bolesnike oboljele od RA (BSRBR-RA) od 2001. do 2008. godine nije pokazala dodatni povišeni rizik za NMSC pri primjeni lijekova iz skupine TNF-alfa inhibitora (36). Rezultati studije pokazali su da je rizik za razvoj bazocelularnog karcinoma (BCC, prema engl. *basal cell carcinoma*) i SCC-a povišen u bolesnika oboljelih od RA u usporedbi s općom populacijom, nevezano jesu li liječeni TNF-alfa inhibitorima (SIR 1,72; 95% CI 1,43 – 2,04) ili csDMARD-ovima (SIR 1,83; 95% CI 1,30 – 2,50). Ranije spomenuti sistematski pregled literature i meta-analiza na temelju podataka koji su prikupljeni iz raznih baza podataka (*MEDLINE, EMBASE, Cochrane Database of Systematic Reviews*) te iz podataka koje su objavila reumatološka društva dali su vrlo iscrpne rezultate o riziku liječenja TNF-alfa inhibitorima i kožnih karcinoma (27). Rezultati četiriju studija koje su uključivale više od 28.000 bolesnika pokazali su da bolesnici koji su liječeni TNF-alfa inhibitorima imaju viši rizik za razvoj BCC-a i SCC-a (RR 1,45; 95% CI 1,15 – 1,76). Osim toga, studija je prikazala podatke i za razvoj invazivnog melanoma, prema kojima je viši relativni rizik za njihov razvoj u bolesnika liječenih TNF-alfa inhibitorima (RR = 1,79; 95% CI 0,92 – 2,67). Europska agencija za lijekove (EMA; prema engl. *European Medicines Agency*) zatražila je u svrhu boljeg prepoznavanja nuspojava liječenja TNF-alfa inhibitorima da se provedu istraživanja o mogućim štetnim učincima. Provedena je metaanaliza podataka 74 randomizirane kliničke studije o TNF-alfa inhibitorima koja je

to which the relative risk for their development is higher in patients treated with TNF-alpha inhibitors (RR = 1.79; 95% CI 0.92–2.67). The European Medicines Agency (EMA) requested that research be conducted on possible adverse effects in order to better recognize the side effects of treatment with TNF-alpha inhibitors. A meta-analysis of data from 74 randomized clinical trials on TNF-alpha inhibitors was conducted, which included 15,418 patients. The results showed a significantly increased risk for the development of skin cancer in patients treated with TNF-alpha inhibitors (RR = 2.02; 95% CI 1.11–3.95) (37). The study of the Danish Registry for Biological Therapies in Rheumatology (DANBIO) compared data for 3347 patients treated with TNF-alpha inhibitors and 3812 patients who were not treated with biological drugs. Patients suffering from RA, PsA and AS were included in the study. The data showed that there is no significantly increased risk for the development of skin cancer in patients treated with TNF-alpha inhibitors compared to patients treated with csDMARDs (HR = 1.10; 95% CI 0.69–1.76), while the risk compared to the general population was still increased (SIR = 1.92; 95% CI 1.42–2.59) (18). A large prospective cohort study conducted in Sweden, in the period from 2001–2010, which included patients with RA, studied the risk of developing skin melanoma (38). In patients who did not receive biological therapy, 113 cases of invasive melanoma were recorded (HR 1.2; 95% CI 0.9–1.5). In the group of patients treated with TNF-alpha inhibitors, 38 cases of melanoma were recorded (HR 1.5; 95% CI 1.0–2.2), which indicates an increased risk for the development of invasive melanoma. The authors of the study conclude that patients with RA who were not treated with TNF-alpha inhibitors are not at a significant risk for developing invasive melanoma compared to the general population, while patients treated with TNF-alpha inhibitors are exposed to a 50% higher risk for developing invasive melanoma.

RISK FOR THE DEVELOPMENT OF NEW MALIGNANCIES IN PATIENTS WITH PREVIOUSLY DIAGNOSED MALIGNANCIES

There are numerous studies whose goal was to determine whether there is an increased risk of developing another malignant tumour in RA patients with a previously diagnosed malignant disease if they are treated with biological drugs. The lack of data on this group of patients could not produce significant results, which is understandable because these patients are at an exceptional risk (5). In Great Britain, based on the data collected from the BSRBR-RA, a study was conducted that dealt with this very issue (39). This study included 14,000 patients with RA, and 293 of these patients suffered from primary cancer. In the group of patients

uključivala 15.418 bolesnika. Rezultati su pokazali značajno povećan rizik za razvoj karcinoma kože u bolesnika liječenih TNF-alfa inhibitorima (RR = 2,02; 95% CI 1,11 – 3,95) (37). Studija danskog registra DANBIO usporedila je podatke za 3.347 bolesnika na terapiji TNF-alfa inhibitora i 3.812 bolesnika koji nisu liječeni biološkim lijekovima. U studiju su uključeni bolesnici oboljeli od RA, PsA i AS. Podatci su pokazali da nema značajno povišenog rizika za razvoj karcinoma kože u bolesnika liječenih TNF-alfa inhibitorima u odnosu na bolesnike liječene csDMARD-ovima (HR = 1,10; 95% CI 0,69 – 1,76), dok je rizik u odnosu na opću populaciju ipak bio povišen (SIR = 1,92; 95% CI 1,42 – 2,59) (18). Velika prospektivna kohortna studija provedena u Švedskoj u razdoblju od 2001. do 2010. godine, koja je uključivala bolesnike oboljele od RA, proučavala je rizik za razvoj melanoma kože (38). U bolesnika koji nisu primali biološku terapiju zabilježeno je 113 slučaja invazivnog melanoma (HR 1,2; 95% CI 0,9 – 1,5). U skupini koja je primala TNF-alfa inhibitore zabilježeno je 38 slučajeva melanoma (HR 1,5; 95% CI 1,0 – 2,2), što ukazuje na povišen rizik za razvoj invazivnog melanoma. Autori studije zaključuju da bolesnici oboljeli od RA koji nisu liječeni TNF-alfa inhibitorima nisu pod značajnijim rizikom za razvoj invazivnog melanoma u usporedbi s općom populacijom, dok su bolesnici liječeni TNF-alfa inhibitorima izloženi 50% većem riziku za razvoj invazivnog melanoma.

RIZIK ZA RAZVOJ NOVIH MALIGNOMA U BOLESNIKA S RANIJE DIJAGNOSTICIRANIM MALIGNOMOM

Brojna su istraživanja kojima je cilj bio utvrditi postoji li u osoba oboljelih od RA s već dijagnosticiranom malignom bolešću povećan rizik od nastanka nekog drugog malignog tumora ako primaju biološku terapiju. Manjak podataka o toj skupini bolesnika nije mogao iznjedriti značajnije rezultate, što je i razumljivo jer su ti bolesnici pod iznimnim rizikom (5). U Velikoj Britaniji na osnovi podataka prikupljenih u BSRBR-RA provedena je studija koja se bavila upravo tom problematikom (39). U studiju je bilo uključeno 14.000 bolesnika s RA, od kojih je njih 293 imalo primarni karcinom. U grupi liječenih TNF-alfa inhibitorima bolesnici koji su već od ranije bolovali od melanoma češće su razvili novi karcinom (3 od 17 osoba, 18%) u usporedbi s bolesnicima na terapiji csDMARD-ovima u kojih nije zabilježen razvoj niti jednoga novog karcinoma. Prema ovoj studiji nema povišenog rizika za primjenu TNF-alfa inhibitora u oboljelih od RA i maligne bolesti, iako je potreban velik oprez. Autori zaključuju da je moguće da rezultati nisu reprezentativni zbog pogreške prilikom određi-

treated with TNF-alpha inhibitors, patients who already suffered from melanoma developed a new cancer more frequently (3 out of 17 people, 18%) than patients treated with csDMARDs in whose case no incidence of new cancer was recorded. According to this study, there is no increased risk for the use of TNF-alpha inhibitors in patients with RA and malignant disease, although great caution is required in the use of this therapy. The authors conclude that it is possible that the results are not representative due to an error when determining the criteria for the inclusion of patients in the clinical trial and thus the selection of patients. Future studies will reveal whether a diagnosis of melanoma in itself represents an increased risk for the development of another malignancy.

Although the data from the existing studies are actually few, they still indicate that the use of TNF-alpha inhibitors does not affect the prognosis in patients who develop cancer during treatment. Another Swedish study found no difference in the risk of cancer progression or death in cancer patients, whether treated with TNF-alpha inhibitors or csDMARDs (RR = 1.1; 95% CI 0.8–1.6) (40).

SMALL MOLECULES, INFLAMMATORY RHEUMATIC DISEASES AND THE RISK OF DEVELOPING MALIGNANCIES

Although the main purpose of this paper was to analyse the risk for the development of malignancies in patients with inflammatory rheumatic diseases treated with biological DMARDs, we shall briefly review the conventional therapy with targeted synthetic tsDMARDs that is commonly used today. Janus kinase inhibitors (JAKi), baricitinib, upadacitinib, tofacitinib and filgotinib (the latter is not yet registered in the Republic of Croatia) and the phosphodiesterase-4 inhibitor, apremilast, are used in the treatment of inflammatory rheumatic diseases. According to the data published so far in the available medical literature, adjusted for age, gender, other demographic data and anamnestic specifics, no increased signals for the risk of developing malignant diseases were detected compared to biological drugs (41–44). More detailed analysis of the mentioned literature goes beyond the scope of this paper.

CONCLUSION

The introduction of biological therapy as a standard treatment modality for inflammatory rheumatic diseases significantly improved the quality of life of patients and the functional status of patients. The study included 14,000 patients with RA. Numerous epidemiological studies were conducted that investigated the safety of the use of biological drugs in patients with various inflammatory rheumatic diseases, precisely in

vanja kriterija za uključivanje bolesnika u kliničko ispitivanje i samim time odabira bolesnika. Buduće studije pokazat će predstavlja li dijagnoza melanoma sama za sebe povišen rizik za razvoj nekog drugog malignoma.

Iako su podatci iz postojećih studija zapravo malobrojni, oni ipak ukazuju da primjena TNF-alfa inhibitora ne utječe na prognozu u bolesnika koji razviju karcinom tijekom liječenja. Prema još jednom istraživanju provedenom u Švedskoj nije nađena razlika u riziku za napredovanje stadija karcinoma ili smrti u oboljelih od karcinoma, bilo da su liječeni TNF-alfa inhibitorima ili csDMARD-ovima (RR = 1,1; 95% CI 0,8 – 1,6) (40).

MALE MOLEKULE, UPALNE REUMATSKE BOLESTI I RIZIK ZA RAZVOJ MALIGNOMA

Iako je glavna namjena ovog rada bila analizirati rizik za razvoj malignoma u bolesnika s upalnim reumatskim bolestima na biološkim DMARD-ovima, kratko se osvrćemo na danas već standardnu terapiju ciljanim sintetskim tsDMARD-ovima. U liječenju upalnih reumatskih bolesti koriste se inhibitori janus kinaza (JAKi), baricitinib, upadacitinib, tofacitinib i filgotinib (potonji još nije registriran u RH) te inhibitor fosfodiesteraze-4, apremilast. Prema do sada objavljenim podatcima u dostupnoj medicinskoj literaturi, prilagođeno za dob, spol, ostale demografske podatke i anamnestičke specifičnosti, nisu detektirani pojačani signali za rizik od razvoja malignih bolesti u usporedbi s biološkim lijekovima (41–44). Detaljnije analize navedene literature nadilaze opseg ovoga rada.

ZAKLJUČAK

Uvođenjem biološke terapije kao standardnog modaliteta liječenja upalnih reumatskih bolesti značajno se poboljšala kvaliteta života bolesnika i funkcionalni status bolesnika. Provedene su brojne epidemiološke studije koje su istraživale sigurnost primjene bioloških lijekova u oboljelih od različitih upalnih reumatskih bolesti upravo u kontekstu rizika za razvoj maligniteta. Najviše je studija dostupnih u literaturi provedeno za TNF-alfa inhibitore, budući da su to lijekovi koji su najduže u primjeni. Rezultati su različiti ovisno o tome koji je biološki lijek korišten i koje je sijelo maligne bolesti promatrano. Prema navedenim istraživanjima postoji određen rizik za obolijevanje od hematološke bolesti, kožnih tumora te razvoja nove maligne bolesti u bolesnika s već ranije dijagnosticiranim malignom. Međutim, vrlo je važno naglasiti da tumačenju rezultata treba pristupati oprezno, te između ostalog u obzir uzeti vrstu istraživanja (npr. deskriptivna studija, kohortna studija, randomizirana studija itd.), način prikupljanja podataka, veličinu uzorka i moguću pogrešku u uzorkovanju. Pitanje je potrebe sustavnog probira

the context of the risk of developing malignancy. Most of the studies available in the literature were conducted on TNF-alpha inhibitors, given that these are the drugs that have been in use the longest. The results are different depending on which biological drug was used and which site of the malignant disease was observed. According to the aforementioned research, there is a certain risk of developing a haematological disease, skin tumours, and the development of a new malignant disease in patients with a previously diagnosed malignant disease. However, it is particularly important to highlight the fact that the results of these studies should be interpreted very cautiously, taking into account, among other things, the type of research (e.g., descriptive study, cohort study, randomized trial, etc.), the method of data collection, sample size and possible sampling error. The question is the need for systematic screening for malignant diseases in patients with rheumatic diseases, for which there are currently no clear, i.e., generally accepted, guidelines. Bearing in mind the previously mentioned tumour diseases, it is possible to screen patients with an increased risk once a year (for example, ultrasound of the abdomen and lymph nodes, serum protein electrophoresis and serum immunofixation test, examination by a dermatologist). Considering that it is a matter of risk assessment on an individual level, it is the duty of the treating physician to adapt the diagnostic procedure depending on that risk. The effectiveness and good safety profile of biological drugs are unquestionable if they are used according to the guidelines of the national rheumatology societies, and thus the risks associated with their use are minimized.

Conflict of interest statement: The authors declare no conflict of interest.

na maligne bolesti u reumatoloških bolesnika, o čemu za sada nema jasnih, tj. općeprihvaćenih smjernica. Imajući u vidu ranije spomenute tumorske bolesti, u obzir dolazi jednom godišnje učiniti probir u bolesnika s povišenim rizikom (primjerice, ultrazvučni pregled abdomena i limfnih čvorova, elektroforezu serumskih proteina i imunofiksaciju, pregled dermatologa). Budući da je riječ o procjeni rizika na individualnoj razini, zadaća je ordinarijusa da ovisno o tom riziku prilagodi dijagnostički postupak. Učinkovitost i dobar sigurnosni profil bioloških lijekova nedvojbeni su ako se primjenjuju prema smjernicama nacionalnih reumatoloških društava te su samim time rizici povezani s njihovom primjenom minimizirani.

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

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LIST OF REVIEWERS **POPIS RECENZENATA**

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