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ORIGINAL RESEARCH PAPER ORIGINALNI ZNANSTVENI RAD

COMPARISON OF THE FREQUENCY OF NEOPLASMS AND INFECTIONS BETWEEN PATIENTS WITH RHEUMATOID ARTHRITIS AND OSTEOARTHRITIS

USPOREDBA UČESTALOSTI NEOPLAZMI I INFEKCIJA IZMEĐU BOLESNIKA S REUMATOIDNIM ARTRTISOM I OSTEOARTRITISOM

Dražen Bedeković[1,2], Ivica Bošnjak[1], Damir Kirner[1,2],Višnja Prus[3], Srđan Novak[4,5]

[1]Department of Cardiovascular Diseases, Department of Internal Medicine, University Hospital Centre Osijek / Zavod za bolesti srca i krvnih žila, Klinika za internu medicinu, KBC Osijek
[2]Department of Internal Medicine, School of Medicine in Osijek / Katedra za internu medicinu, Medicinski fakultet Osijek, Sveučilište J. J. Strossmayera, Osijek
[3]Division of Rheumatology, Clinical Immunology and Allergology, Department of Internal Medicine, University Hospital Centre Osijek / Zavod za reumatologiju, kliničku imunologiju i alergologiju, Klinika za internu medicinu, KBC Osijek
[4]Division of Clinical Immunology and Rheumatology, University Hospital Centre Rijeka / Zavod za reumatologiju i imunologiju, KBC Rijeka
[5]Department of Internal Medicine, School of Medicine in Rijeka, University of Rijeka / Katedra za internu medicinu, Medicinski fakultet Rijeka, Sveučilište u Rijeci

Corresponding author / Adresa autora za dopisivanje:
Dražen Bedeković
Department of Cardiovascular Diseases / Zavod za bolesti srca i krvnih žila
Department of Internal Medicine / Klinika za internu medicinu
University Hospital Centre Osijek / KBC Osijek
J. Huttlera 4
31000 Osijek
Croatia / Hrvatska
E-mail / e-pošta: debedekovic@yahoo.com

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ABSTRACT

Introduction: We compared the frequency of malignant diseases and infections between patients with RA and osteoarthritis (OA) over an eight-year follow-up period. *Subjects and methods:* The study was conducted as a prospective clinical observational cohort study between 2008 and 2017. The examined group included RA patients, whereas the control group was comprised of OA patients. The total number of participants included in the research was 201; 124 participants with RA and 77 participants with OA. We analysed the data collected over the eight-year follow-up period through prepared visit protocols, as well as other sources. *Results:* Out of the total of 201 participants included in the study, 124 were RA patients and 77 were OA patients. A total of 137 participants, 82 patients with RA and 55 patients with OA, completed the study, and 58 participants died. Moreover, 6 patients refused to participate in the study, or their contact info was lost (one participant with RA and five participants with OA). There was no statistically significant difference in the frequency of neoplasms between the groups, and the most common sites of neoplasms were the lungs, breasts, and kidneys. Fifteen participants with RA (12.19%) had severe infections, and 4 of them died due to the infection, while 5 of the 72 participants with OA had severe infections (9.09%) with no deaths recorded. Non-severe infections were experienced by 12 participants in the RA group and 10 in the OA group. There was no statistically significant difference in the frequency of severe or minor infections between the studied groups. There was a statistical association between the use of anti-TNF therapy and the frequency of minor infections, while the association of the use of anti-TNF therapy with the frequency of severe infections and the frequency of neoplasms was not proven. *Conclusion:* Although there was no statistically significant difference in the frequency of neoplasms, RA patients had a higher mortality rate. Severe infectious diseases did not play a significant role in morbidity and mortality in both groups.

Keywords: rheumatoid arthritis, osteoarthritis, infections, malignant diseases

SAŽETAK

Uvod: U ovom istraživanju provedena je usporedba učestalosti malignih bolesti i infekcija između bolesnika s reumatoidnim artritisom (RA) i osteoartritisom (OA) tijekom osmogodišnjeg razdoblja praćenja. *Ispitanici i metode:* Istraživanje je provedeno kao prospektivna klinička opservacijska kohortna studija u razdoblju od 2008. do 2017. godine. Ispitivanu skupinu činili su bolesnici oboljeli od RA, a kontrolnu skupinu oboljeli od OA. Ukupan broj ispitanika uključenih u istraživanje bio je 201, od čega 124 ispitanika s RA i 77 ispitanika s OA. U istraživanju smo se koristili podatcima prikupljenim tijekom osmogodišnjeg praćenja putem pripremljenih protokola na vizitama, kao i drugim izvorima. *Rezultati:* Od 201 ispitanika koji su nakon probira uključeni u istraživanje, bilo je 124 oboljelih od RA i 77 oboljelih od OA, ukupno 137 ispitanika; 82 oboljelih od RA i 55 oboljelih od OA završilo je istraživanje, 58 ispitanika je preminulo, dok je šest ispitanika odbilo sudjelovanje tijekom istraživanja ili su izgubljeni kontakti (jedan s RA i pet s OA). Ne postoji statistički značajna razlika u incidenciji neoplazme između skupina, a najčešće lokalizacije neoplazmi bile su pluća, dojka i bubrezi. Teške infekcije ispitanika s RA imalo je petnaest ispitanika (12,19%) od kojih je četvero preminulo od posljedica infekcije, dok je od 72 ispitanika s OA petero imalo teške infekcije (9,09%) bez preminulih. Lakše infekcije u skupini RA imalo je dvanaest ispitanika i deset u skupini OA. Ne postoji statistički značajna razlika u učestalosti teških infekcija između ispitivanih skupina, niti lakših infekcija. Postoji statistička povezanost između primjene anti-TNF terapije i učestalosti lakših infekcija, dok povezanost primjene anti-TNF terapije s učestalošću teških infekcija i neoplazmi nije dokazana. *Zaključak:* Iako nije bilo statistički značajne razlike u incidenciji neoplazmi, bolesnici s RA su imali višu smrtnost. Teške infektivne bolesti nisu imale značajniju ulogu u obolijevanju i smrtnosti u obje skupine.

Ključne riječi: reumatoidni artritis, osteoartritis, infekcije, maligne bolesti

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory systemic disease that primarily affects the synovial membrane, cartilage, and bone of small and medium-sized joints, leading to chronic damage and pannus formation. Large joints and internal organs such as the lungs, heart and blood vessels, hematopoietic system, kidneys, and gastrointestinal system can also be affected by the disease. The estimated frequency of rheumatoid arthritis is 1 to 2% of the general population. (1–5).

Osteoarthritis (OA) is the most common chronic joint disease and is characterized by chronic pain and joint deformation, which ultimately results in loss of joint function due to focal damage to the articular cartilage in combination with hypertrophic reaction of the subchondral bone and the formation of new bone at the edges of the joint. It typically affects people over the age of 65 (6–8).

The association between the risk of malignancy and RA has been demonstrated in numerous studies and registries and is the second most common cause of mortality in patients with rheumatoid arthritis (9, 10). Inflammatory mediators such as cytokines, chemokines and proteases synthesized by lymphocytes and macrophages can promote tumor growth and metastasis by affecting their survival, proliferation, migration and invasion into other tissues (11, 12). In a meta-analysis of 13 studies, the overall standardized frequency rate for tumors in RA was 1.05 (95% CI: 1.01–1.09) (13). According to the California Registry (approximately 400,000 patient-years) for the period from 1991 to 2002, patients with RA had a higher risk of developing malignant diseases: lymphoproliferative tumors,

UVOD

Reumatoidni artritis (RA) je kronična upalna sistemska bolest koja primarno zahvaća sinovijalnu membranu, hrskavicu i kost malih i srednje velikih zglobova dovodeći do kroničnih oštećenja i stvaranja panusa. Veliki zglobovi i unutrašnji organi poput pluća, srca i krvnih žila, hematopoetskog sistema, bubrega i gastrointestinalnog sustava također mogu biti zahvaćeni bolešću. Procijenjena prevalencija reumatoidnog artritisa je od 1 do 2% opće populacije (1–5).

Osteoartritis (OA) je najčešća kronična bolest zglobova i karakterizira je kronična bol i deformacija zgloba, što u konačnici rezultira gubitkom funkcije zgloba zbog fokalnih oštećenja zglobne hrskavice u kombinaciji s hipertrofičnom reakcijom subhondralne kosti i formiranjem nove kosti na rubovima zgloba. Tipično pogađa osobe starije od 65 godina (6–8).

Povezanost rizika za pojavu maligne bolesti i RA pokazana je u brojnim istraživanjima i registrima i drugi su najčešći uzrok mortaliteta u bolesnika s reumatoidnim artritisom (9, 10). Medijatori upale poput citokina, kemokina i proteaze koje sintetitiraju limfociti i makrofagi mogu pospješiti rast tumora i pojavu metastaza djelujući na njihovo preživljavanje, proliferaciju, migraciju i invaziju u druga tkiva (11,12). U metaanalizi trinaest studija, ukupna standardizirana stopa incidencije za tumore u RA je iznosila 1,05 (95% CI: 1,01 – 1,09) (13). Prema Kalifornijskom registru (oko 400 000 bolesničkih godina) za razdoblje od 1991. do 2002. bolesnici s RA imali su veći rizik za razvoj maligne bolesti: limfoproliferativnih tumora, tumora pluća, jetre, jednjaka, prostate, dojke, jajnika, maternice i cerviksa, od 15 do 57% u usporedbi s općom populacijom (12).

tumors of the lung, liver, esophagus, prostate, breast, ovary, uterus and cervix, ranging from 15 to 57% compared to the general population (12). The high risk of lymphoma in RA was first noted in a study conducted approximately thirty years ago (14). The risk of developing non-Hodgkin lymphoma increases with higher inflammatory disease activity over time and in patients with high-positive RF test, as well as in patients with extra-articular manifestations such as Felty's syndrome and secondary Sjögren's syndrome (15). A rare form of leukemia that can occur in patients with RA is T-cell large granular lymphocytic (T-LGL) leukemia which is a chronic and rarely aggressive disease in most cases (16). The risk of developing lung cancer was 43% higher in RA in an American study compared to the general population, but this study did not include data on other risks, such as the intensity and duration of smoking (17).

There is no evidence that anti-TNF-α therapy further increases the risk of neoplasm development, except for the increased incidence of melanoma and non-melanoma skin tumors (18).

Patients with RA have an increased risk of infections, which correlates with disease activity and severity. Additional risk factors include age, pulmonary, and cardiovascular comorbidity (19). Medications, such as glucocorticoids, certain anti-TNF-α drugs, and other immunosuppressive drugs may further increase this risk (20). EULAR recommendations include vaccination of patients with autoimmune inflammatory rheumatic diseases against influenza, COVID-19, and pneumococcus to reduce the risk of these infections (21, 22). The most common infection sites are the respiratory system, urinary system, skin and soft tissues, joints and bones, and are usually caused by the bacteria: Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus and Gram-negative bacteria (23). According to a 2011 study conducted by Galloway JB, anti-TNF therapy doubles the risk of developing septic arthritis (24). The risk of tuberculosis in patients with RA is increased in those treated with biologics (25, 26).

The objectives of this study are to compare the frequency of malignant and infectious diseases between the experimental (RA) and control groups (OA) during an eight-year follow-up period.

PARTICIPANTS AND METHODS

The study was conducted in the period from 2008 to 2017 as a prospective clinical observational cohort study. The experimental group consisted of patients with RA, and the control group consisted of patients with OA from five counties in Eastern Croatia. The total number of participants included in the study was 201; 124 with RA and 77 with OA. The study used data

Veliki rizik za pojavu limfoma kod RA prvo je uočen u studiji prije tridesetak godina (14). Rizik razvoja od ne-Hodgkinovih limfoma raste s višom upalnom aktivnošću bolesti tijekom vremena i u onih s visokopozitivnim RF, kao i kod bolesnika s ekstraartikularnim manifestacijama kao što su Feltyev sindrom i sekundarni Sjögrenov sindrom (15). Rijedak oblik leukemije koji se može pojaviti kod bolesnika s RA jest velika granulocitna T-limfatična leukemija, koja je najčešće kronična i rijetko agresivna (16). Rizik razvoja karcinoma pluća bio veći za 43% kod RA u američkoj studiji u usporedbi s općom populacijom, ali u ovoj studiji nisu bili poznati podatci o drugim rizicima, kao o intenzitetu i duljini pušenja (17).

Nema dokaza da anti-TNF-α terapija dodatno povećava rizik od razvoja neoplazme, osim povećane incidencije melanoma i nemelanomskih tumora kože (18).

Bolesnici s RA imaju povećan rizik od infekcija, koji korelira s aktivnosti i težinom bolesti. Dodatni čimbenici rizika su dob, plućni i kardiovaskularni komorbiditet (19). Lijekovi dodatno mogu povisiti taj rizik poput glukokortikoida, određenih anti-TNF-α lijekova i drugih imonosupresivnih lijekova (20). EULAR-ove smjernice preporučuju cijepljenje bolesnika s autoimunim upalnim reumatskim bolestima protiv gripe, COVID-19 i pneumokoka kako bi se smanjio rizik od tih infekcija (21, 22). Najčešća mjesta infekcija jesu respiratorni sustav, mokraćni sustav, koža i meka tkiva, zglobovi i kosti, a obično su uzrokovane bakterijama: *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus* i gram-negativnim bacilima (23). Prema studiji Gallowaya iz 2011. godine anti-TNF terapija udvostručuje rizik od razvoja septičkog artritisa (24). Rizik od tuberkuloze u bolesnika s RA povećan je u onih liječenih biološkom terapijom (25, 26).

Cilj ovog istraživanja jest usporedba učestalosti malignih i infektivnih bolesti između ispitivane (RA) i kontrolne skupne (OA) tijekom osmogodišnjeg praćenja.

ISPITANICI I METODE

Istraživanje je provedeno kao prospektivna klinička opservacijska kohortna studija koja se provodila u razdoblju od 2008. do 2017. godine. Ispitivanu skupinu čine bolesnici oboljeli od RA, a kontrolnu skupinu čine bolesnici oboljeli od OA s područja pet županija istočne Hrvatske. Ukupan broj ispitanika uključenih u istraživanje bio je 201, od toga 124 s RA i 77 s OA. U istraživanju smo se koristili podatcima prikupljenim tijekom osmogodišnjeg praćenja, kao i drugim izvorima (povijestima bolesti, ambulantnim listovima iz pismohrana i računalne baze podataka Zavoda za reumatologiju, kliničku imunologiju i alergologiju i Zavoda za fizikalnu medicinu i rehabilitaciju KBC-a Osijek, podatcima dobivenim od liječnika obiteljske medicine,

collected during the eight-year follow-up period, as well as other sources (case histories, outpatient archived forms and computer database records obtained from the Department of Rheumatology, Clinical Immunology and Allergology and the Department of Physical and Rehabilitation Medicine of the University Hospital Center in Osijek, data obtained from family physicians, as well as data obtained from the regional centers of the Croatian Institute of Public Health).

The criteria for the inclusion of patients in the study were the following:

1. Diagnosis of rheumatoid arthritis or osteoarthritis made by a rheumatologist in accordance with the current 1987 American College of Rheumatology (ACR) classification criteria for rheumatoid arthritis, or ACR criteria for osteoarthritis.
2. Signed informed consent to participate in the study, which the patient must confirm by signing the informed consent.
3. Registered continuous permanent residence in one of the 5 counties of Eastern Croatia during the course of the study.

The criteria for the exclusion of patients in the study were the following:

1. Patients with diagnosed cardiovascular disease, primary cardiomyopathy, severe uncorrected valvular disease or symptomatic heart failure before the first visit.
2. Failure to meet inclusion criteria.
3. Patient's refusal to further participate in the study after the first study visit.
4. Permanent cessation of residence in one of the 5 counties of Eastern Croatia during the course of the study; migration within the region is not an exclusion criterion.
5. Non-white race.
6. Inability to get in touch with the patient after the first study visit.

Clinical and laboratory methods include a detailed history, completion of a pre-prepared questionnaire, physical examination (including blood pressure measurement three times at 10-minute intervals with the average value recorded as the final value), anthropometric measurements; assessment of general health status, assessment of pain intensity, completion of the DAS28-CRP form (RA patients), completion of the AUSCAN Osteoarthritis Hand Index form (OA patients) (27), completion of the Lequesne Hip Osteoarthritis Index form (OA patients) (28), completion of the Lequesne Knee Osteoarthritis Index form (OA patients) (28), completion of the Croatian translation of the Health Assessment Questionnaire (HAQ) (RA and OA patients) (29), recording of a 12-lead ECG and venous blood sampling for laboratory analysis. In case of

kao i podatcima iz regionalnih centara Zavoda za javno zdravstvo).

Kriteriji za uključivanje bolesnika u istraživanje bili su:

1. dijagnosticiran reumatoidni artritis ili osteoartritis od strane reumatologa prema važećim klasifikacijskim kriterijima za reumatoidni artritis American College of Rheumatology (ACR) iz 1987., odnosno kriterijima ACR-a za osteoartritis
2. informirani pristanak za sudjelovanje u studiji koje bolesnik treba potvrditi potpisom
3. prijavljeno prebivalište / trajni boravak u jednoj od pet županija istočne Hrvatske neprekidno tijekom trajanja studije.

Kriteriji za isključivanje bolesnika iz ispitivanja bili su:

1. bolesnici s dijagnosticiranim kardiovaskularnim bolestima, primarnom kardiomiopatijom, teškom nekorigiranom valvularnom bolesti ili simptomatskim srčanim zatajivanjem prije prve vizite
2. neispunjavanje uključnih kriterija
3. odbijanje daljnjeg sudjelovanja bolesnika nakon prve vizite istraživanja
4. trajni prestanak boravka na području jedne od pet županija istočne Hrvatske tijekom perioda studije, migracija unutar regije nije isključni kriterij
5. pripadnost ne-bijeloj rasi
6. nedostupnost bolesnika nakon prve vizite istraživanja.

Kliničke i laboratorijske metode uključuju detaljnu analizu povijesti bolesti, popunjavanje unaprijed pripremljenog upitnika, fizikalni pregled (uz mjerenje krvnog tlaka tri puta u razmaku od deset minuta uz uzimanje prosječne vrijednosti za konačnu analizu), antropometrijske mjere, procjenu općeg zdravstvenog stanja, procjenu intenziteta boli, popunjavanje obrasca DAS28-CRP (RA bolesnici), popunjavanje obrasca AUSCAN indeksa za *osteoartritis* šake (OA bolesnici) (27), popunjavanje obrasca Lequesne indeksa za *osteoartritis* kuka (OA bolesnici) (28), popunjavanje obrasca Lequesne indeksa za *osteoartritis* koljena (OA bolesnici) (28), popunjavanje hrvatskog prijevoda Health Assessment Questionnaire (HAQ) (RA i OA bolesnici) (29), snimanje 12-kanalnog EKG-a i uzimanje venske krvi za laboratorijsku analizu. Za ispitanike koji su preminuli evidentirani su uzrok i vrijeme smrti kao i poznati komorbiditeti.

Teška infekcija definirana je kao infekcija koja je zahtijevala hospitalizaciju ili intravensko antibiotsko liječenje.

Ovo istraživanje je provedeno u skladu s Helsinškom deklaracijom, a odobreno od strane etičkog povjerenstava KBC-a Osijek (br: 602-04/21-08/07).

participants who died, the cause and time of death as well as known comorbidities were recorded.

Severe infection was defined as an infection that required hospitalization or intravenous antibiotic treatment.

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the University Hospital Center in Osijek (No. 602-04/21-08/07).

Informed consent for participation: a written informed consent was obtained from all participants.

Statistical methods

Descriptive statistics were used to describe and summarize the study data. Inferential statistics were used to test hypotheses. The Independent Samples T-Test method was used to test the significance of mean differences. The Chi-Square Test of Independence was used to analyze the relationship between qualitative variables. Fisher's exact test was used when the assumptions for the Chi-Square Test were not met. The significance level was set at $p < 0.05$. The SPSS version 17 was used for the analysis.

RESULTS

Demographic data

Out of the total of 201 participants who were included in the study after screening, 124 patients were RA patients and 77 were OA patients. A total of 137 participants, 82 RA patients and 55 OA patients, completed the study after 8 years and 4 months. A total of 58 participants died; 41 RA patients and 17 OA patients; and 6 refused to further participate in the study (1 RA patient and 5 OA patients). Cardiovascular disease was the leading cause of death in both groups, accounting for 39 of the 58 deaths.

Table 1 shows the demographic data of the experimental and control groups at baseline and follow-up.

At the baseline visit, OA participants were significantly older than RA participants (t=2.98, p=0.004), the average duration of RA was 12.2 years (0.1–47) and in OA it was 5.64 years (0.1–31), which represents a statistically significant difference between the groups (t=-4.72, p=0.001).

The prevalence of former and current smokers at baseline was 46.77% and 21.77% for RA and 27.27% and 14.28% for OA (p=0.41; p=0.84) patients. RA inflammatory activity measured by the DAS28 score was moderately high during the course of the study with a significant decrease in inflammatory activity at the end of the study (p=0.001).

A total of 15 participants received anti-TNF therapy during the course of the study (18.29%), and in three cases therapy was discontinued (two patients died and

Informirani pristanak za sudjelovanje: pisani informirani pristanak dobiven je od svih sudionika.

Statističke metode

Deskriptivna statistika korištena je za opisivanje i sažimanje podataka studije. Za testiranje hipoteza primijenjena je diferencijalna statistika. Za provjeru značajnosti srednjih razlika korišten je t-test za neovisne uzorke. Za analizu odnosa između kvalitativnih varijabli primijenjen je hi-kvadrat test neovisnosti. Fisherov egzaktni test korišten je kada pretpostavke za hi-kvadrat test nisu bile ispunjene. Razina značajnosti postavljena je na $p < 0,05$. Za analizu je upotrijebljen računalni program SPSS verzija 17.

REZULTATI

Demografski podatci

Od 201 ispitanika koji su nakon probira uključeni u istraživanje (124 oboljelih od RA i 77 oboljelih od OA, ukupno 137 ispitanika), 82 oboljelih od RA i 55 oboljelih od OA završilo je istraživanje nakon osam godina i četiri mjeseca. Ukupno 58 ispitanika je preminulo (41 s RA i 17 s OA), a njih šest je odbilo sudjelovanje u istraživanju tijekom istraživanja (jedan s RA i pet s OA). Kardiovaskularne bolesti bile su vodeći uzrok smrtnosti u obje skupine, ukupno 39 od 58 preminulih.

Tablica 1. prikazuje demografske podatke ispitivane i kontrolne skupine na početnoj i završnoj viziti.

U početnoj viziti OA ispitanici su značajno stariji od RA ispitanika (t = 2,98, p = 0,004), prosječno trajanje RA bilo je 12,2 godine (0,1 – 47), a OA 5,64 godine (0,1 – 31), što predstavlja statistički značajnu razliku između skupina (t = -4,72, p = 0,001).

Prevalencija bivših i sadašnjih pušača na početnoj viziti bila je za RA 46,77% i 21,77%, dok je za OA bila 27,27% i 14,28% (p = 0,41; p = 0,84). Upalna aktivnost RA mjerena DAS28 skorom bila je tijekom istraživanja umjereno visoka sa značajnim smanjenjem upalne aktivnosti na kraju istraživanja (p = 0,001).

Ukupno je petnaest ispitanika primilo anti-TNF terapiju tijekom istraživanja (18,29%), trojica su prekinula (dva su preminula i jedan je imao nuspojave) dok je njih dvanaest primalo anti-TNF terapiju na završnoj viziti (14,63%).

Neoplazme

Od 123 ispitanika s RA ukupno je jedanaest (8,94%) razvilo neoplazmu tijekom razdoblja praćenja, od kojih je šest ispitanika bilo živo na završnoj viziti, dok je od 72 ispitanika s OA njih osam (6,94%) razvilo neoplazmu, od kojih je šest bilo živo na završnoj viziti. Nije dokazana značajna razlika između učestalosti neoplazme i

one had side effects) while 12 participants were receiving anti-TNF therapy at the final visit (14.63%).

Neoplasms

Out of the total of 123 participants with RA, a total of 11 (8.94%) developed a neoplasm during the follow-up period. Out of these 11 patients, 6 participants were alive at the final visit. Out of the total of 72 participants with OA, 8 (6.94%) patients developed a neoplasm. Out of these 8 patients, 6 were alive at the final visit. There was no significant difference between the frequency of neoplasm and the type of arthritis (χ^2=0.77, p=0.38). The most common sites of neoplasms were the lungs, breasts and kidneys.

Infections

Out of the total of 123 participants with RA, 12.19% of patients had severe infections, including sepsis, pneumonia, hepatitis B and C, and tuberculosis, while out of the total of 72 participants with OA, 9.09% of patients had severe infections. Table 2 shows the number of cases and deaths due to severe and minor infections. There was no difference between the frequency of severe infections and the type of arthritis (χ^2=0.7, p=0.4), nor between minor infections and the type of arthritis (χ^2=1.13, p=0.29).

There is an association between the use of anti-TNF therapy and the frequency of minor infections (χ^2= 09.05 p=0.007), while the association between the use of anti-TNF therapy and the frequency of severe infections (χ^2=1.05, p=0.59) and the frequency of neoplasms has not been proven (χ^2=0.013, p=0.99).

DISCUSSION

The demographic characteristics of our participants in both groups are consistent with the epidemiological data from published studies and include: higher prevalence in women for RA and OA, older age for OA, longer disease duration for RA and higher prevalence of smokers in RA, earlier onset of RA and the association of BMI with OA as well as the association of RA with smoking (30).

A smaller number of participants developed neoplasms during the follow-up period (8.94% of RA patients and 6.94% of OA patients) without significant differences between the groups, while the most common sites of neoplasms were the lungs and breasts. Although only a small number of participants were treated with anti-TNF therapy, the association between its use and the frequency of neoplasms is not proven. Only a small number of participants died due to neoplasms: 5 participants out of the total of 123 (4.1%) from the RA group and 2 participants out of the total of 72 from the OA (2.8%) group. They are the second

Table 1. Demographic data of the experimental and control groups at baseline and final visits

Tablica 1. Demografski podatci ispitivane i kontrolne skupine na početnoj i završnoj viziti

	Initial visit Početna vizita 2009	Final visit Završna vizita 2017
Total number of participants (N) Ukupni broj ispitanika (N)	201	137
Rheumatoid arthritis (N) Reumatoidni artritis (N)	124	82
Osteoarthritis (N) Osteoartritis (N)	77	55
Male patients with RA (N) Muškarci RA (N)	25	16
Female patients with RA (N) Žene RA (N)	99	66
Male patients with OA (N) Muškarci OA (N)	11	10
Female patients with OA (N) Žene OA (N)	66	45
Average life expectancy of RA patients (years, min. and max) Prosječna životna dob RA (godine, min. i max)	59.78 (37-81)	65.5 (45-90)
Average life expectancy of OA patients (years min. and max.) Prosječna životna dob OA (godine, min. i max.)	64.23 (27-80)	71.2 (36-89)
DAS28 CRP (min. and max.) DAS28 CRP (min. i max.)	4.94 (1.46-8.04)	4.08 (1.38-6.04)

vrste artritisa (χ^2 = 0,77, p = 0,38). Najčešće lokalizacije neoplazmi bile su pluća, dojka i bubrezi.

Infekcije

Od 123 ispitanika s RA ukupno je teške infekcije koje uključuju sepsu, upalu pluća, hepatitis B i C i tuberkulozu imalo 12,19% ispitanika, dok je od 72 ispitanika s OA 9,09% imalo teške infekcije. Tablica 2 prikazuje brojeve slučajeva i preminulih od težih i lakših infekcija. Nije utvrđena razlika između učestalosti teških infekcija i vrste artritisa (χ^2 = 0,7, p = 0,4), kao ni između lakših infekcija i vrste artritisa (χ^2 = 1,13, p = 0,29).

Table 2. Number of cases and deaths due to severe and mild infections
Tablica 2. Brojevi slučajeva i preminulih od težih i lakših infekcija

	Final visit in 2017 Završna vizita 2017.
Frequency of severe RA infections (N) Učestalost teških infekcija RA (N)	15
Deceased due to severe RA infections (N) Preminuli zbog teških infekcija RA (N)	4
Frequency of severe OA infections (N) Učestalost teških infekcija OA (N)	5
Deceased due to severe OA infections (N) Preminuli zbog teških infekcija RA (N)	0
Frequency of minor RA infections(N) Učestalost lakših infekcija RA (N)	12
Frequency of minor OA infections (N) Učestalost lakših infekcija OA (N)	10

most common cause of death among the participants, after cardiovascular diseases. Although previous studies have described an increased risk of neoplasms in RA, such as the Finnish study conducted on 604 RA patients and 447 control groups from the general population (31) or the California registry (12), this was not demonstrated in this study, even though the follow-up period of our participants lasted over eight years. Similarly, a high frequency of lymphoproliferative diseases was not demonstrated, although it was described in previous studies, while the remaining sites of neoplasms were in accordance with the previous studies (15–17, 32–34). The association of the use of anti-TNF therapy with the occurrence of neoplasms was also not proven, which is in accordance with the previous relevant studies (18).

Patients with RA have an increased risk of infections due to a number of contributing factors: high inflammatory activity and severity of the disease, age, pulmonary and cardiovascular comorbidity (5, 19), but patients with OA also have an increased risk of infectious diseases due to: age (they are usually older than RA patients), comorbidity and exposure to the risk of infections during alloarthroplasty (24). In our study, there was no significant difference in the frequency of severe infections between the groups, 15 (12.19%) participants with RA and 5 (9.09%) participants with OA, while mortality due to infections was higher in the RA group; 4 patients died as a result of an infection, while there were no deaths recorded in the OA group during the follow-up period. When it comes to the severe infections, pneumonia and sepsis were the leading ones, which is in line with the previous studies (20). Although the frequency was similar in both groups, the

Postoji povezanost između primjene anti-TNF terapije i incidencije lakših infekcija (χ^2 = 09,05, p = 0,007), dok povezanost primjene anti-TNF terapije s incidencijom teških infekcija (χ^2 = 1,05, p = 0,59) i incidencijom neoplazmi nije dokazana (χ^2 = 0,013, p = 0,99).

RASPRAVA

Demografska obilježja naših ispitanika u obje skupine u skladu su s epidemiološkim podatcima objavljenih studija i uključuju veću prevalenciju kod žena za RA i OA, višu dob kod OA, dulje trajanje bolesti za RA, veću prevalenciju pušača kod RA, raniji početak RA te povezanost BMI s OA, kao i povezanost RA s pušenjem (30).

Manji broj ispitanika tijekom razdoblja praćenja razvio je neoplazmu (8,94% RA i 6,94% OA) bez značajne razlike među skupinama, dok su najčešća mjesta neoplazmi bila pluća i dojka. Iako je tek manji broj ispitanika bio liječen anti-TNF terapijom, povezanost njezine primjene i učestalosti neoplazmi nije dokazana. Tek manji broj ispitanika preminuo je od neoplazmi, pet ispitanika od 123 (4,1%) iz RA skupine i dva ispitanika od 72 (2,8%) iz OA skupine. Na drugom su mjestu po uzrocima smrti ispitanika, iza kardiovaskularnih bolesti. Iako dosadašnja istraživanja opisuju povećan rizik od pojave neoplazmi kod RA, poput finske studije s 604 RA pacijenta i 447 kontrola iz opće populacije (31) ili Kalifornijskog registra (12), u ovom istraživanju to nije pokazano iako je razdoblje praćenja naših ispitanika bilo dulje od osam godina. Isto tako, visoka prevalencija limfoproliferativnih bolesti nije pokazana iako je opisana u ranijim studijama, dok su ostala sijela neoplazmi u skladu s ranijim istraživanjima (15–17, 32–34). Povezanost primjene anti-TNF terapije s pojavom neoplazmi također nije dokazana, što je u skladu s ranijim relevantnim istraživanjima (18).

Pacijenti s RA imaju povećan rizik od infekcija zbog brojnih čimbenika koji tome pridonose: visoka upalna aktivnost i težina bolesti, dob, plućni i kardiovaskularni komorbiditet (5, 19), no i pacijenti s OA imaju također povišen rizik od infektivnih bolesti zbog dobi (obično su stariji od RA bolesnika), komorbiditeta i izloženosti riziku od infekcija prilikom aloartoplastika (24). U našem istraživanju nije bilo značajne razlike u učestalosti teških infekcija između skupina: petnaest ispitanika (12,19%) s RA i pet (9,09%) s OA, dok je smrtnost od infekcija kod RA bila veća: četvero je preminulo od posljedica infekcije, dok kod OA skupine nije bilo preminulih tijekom praćenja. Od težih infekcija vodeće su bile upala pluća i sepsa, što je u skladu s ranijim studijama (20). Iako je incidencija bila podjednaka u obje skupine, rizik od smrtnog ishoda bio je veći za RA. Povezanost primjene anti-TNF terapije s pojavom teških infekcija nije dokazana, dok je primjena glukokortikoida u RA skupini bila prisutna tijekom

risk of death was higher in the RA group. The association of anti-TNF therapy with the occurrence of serious infections was not proven, while the use of glucocorticoids was present in the RA group throughout the entire follow-up period (74.2% at baseline and 76.8% at the end of the study; p = 0.332). The effect of glucocorticoids on the occurrence of infections is somewhat contradictory, often described in observational studies while not proven in randomized clinical trials (35). The incidence of minor infections (not requiring hospital treatment) was also similar in both groups; 12 participants in the RA group and 10 participants in the OA group. An association between the use of anti-TNF therapy and a higher incidence of minor infections (predominantly respiratory viral and bacterial infections) has been demonstrated, which is in accordance with the published data (20, 36, 37). Although the risk of tuberculosis and hepatitis B and C is increased (38, 39) in the case of RA, during a period of over eight years of follow-up, only one case of tuberculosis and 2 cases of hepatitis B were recorded, while no case of hepatitis C was recorded, and no cases of these diseases were recorded in the control group. Published studies describe a slightly increased risk of tuberculosis and hepatitis B in RA patients, which they associate with the use of DMARDs and biologics (38–41). The risk of infection in the control OA group is related to the general condition of the patient and to orthopedic procedures (24). In our study, we did not record any serious infections after orthopedic procedures.

In conclusion, neoplastic diseases play a significant role and are in second place in mortality of both groups of participants, although the number of patients and deaths caused by these diseases is incomparably lower than the number of patients who suffer and die from cardiovascular diseases. Although there was no statistically significant difference in the incidence of neoplasms, RA patients live significantly shorter than OA patients, and cardiovascular diseases and neoplastic diseases contribute to their shorter life span. Possible causes for this are the inflammatory nature of RA, especially in uncontrolled high inflammatory activity, but also the use of specific drugs that increase the risk of neoplastic diseases. Severe infections did not play a significant role in morbidity and mortality in either group in this study, which is largely due to disease prevention and patient education, timely detection, and treatment of infections, while the occurrence of milder infections is expected, especially in patients with RA receiving biological therapy.

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cijelog razdoblja praćenja (74,2% na početku, a 76,8% na kraju istraživanja; p = 0,332). Utjecaj glukokortikoida na pojavu infekcija donekle je kontradiktoran; često je opisivan u opservacijskim studijama, dok u randomiziranim kliničkim studijama nije dokazan (35). U obje skupine također je bila podjednaka incidencija lakših infekcija (koje ne zahtijevaju bolničko liječenje): dvanaest ispitanika u RA skupini i deset u OA skupini. Dokazana je povezanost primjene anti-TNF terapije i viša incidencija lakših infekcija (predominantno respiratorne virusne i bakterijske infekcije), što je u skladu s objavljenim podatcima (20, 36, 37). Iako je rizik od tuberkuloze i hepatitisa B i C povećan (38, 39) kod RA, tijekom više od osam godina praćenja zabilježen je samo jedan slučaju tuberkuloze i dva slučaja hepatitisa B, dok nije zabilježena pojava hepatitisa C, a kod kontrolne skupine nije zabilježen niti jedan slučaj ovih bolesti. Objavljene studije opisuju kod RA pacijenata blago povećan rizik za pojavu tuberkuloze i hepatitisa B, što povezuju s primjenom DMARD-ova i biološke terapije (38-41). Rizik od infekcije kod kontrolne OA skupine odnosi se na opće stanje bolesnika i na ortopedske zahvate (24). U našem istraživanju nismo zabilježili niti jednu ozbiljnu infekciju nakon ortopedskog zahvata.

Zaključno, neoplastične bolesti imaju značajnu ulogu i na drugom su mjestu smrtnosti ispitanika u obje skupine, iako je broj oboljelih i preminulih od istih neusporedivo manji nego od kardiovaskularnih bolesti. Iako nije bilo statistički značajne razlike u pojavnosti neoplazmi, RA pacijenti žive značajno kraće u odnosu na OA pacijente, čemu uz kardiovaskularne bolesti doprinose i neoplastične bolesti. Mogući uzroci tomu su upalna priroda RA, osobito kod nekontrolirane visoke upalne aktivnosti, ali i primjena specifičnih lijekova koji povećavaju rizik od neoplastičnih bolesti. Teške infekcije nisu imale značajniju ulogu u obolijevanju i smrtnosti u obje skupine u ovom istraživanju, čemu najviše pridonosi prevencija i edukacija pacijenata, pravovremeno otkrivanje i liječenje infekcija, dok je pojava lakših infekcija očekivana osobito kod bolesnika s RA koji primaju biološku terapiju.

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