Psychiatria Danubina, 2021; Vol. 33, Suppl. 4, pp 625-631
Conference paper

Original article

ANTI-TNF THERAPY AND THE RISK OF MALIGNANCIES AND INFECTIONS IN INFLAMMATORY RHEUMATIC DISEASES - OUR EXPERIENCE

Mislav Pap[1], Ivana Sapina[1], Nadica Laktašić Žerjavić[1,2], Iva Žagar[1,2], Kristina Kovač Durmiš[1,2], Nataša Kalebota[1], Petra Kovačević[3], Ivan Ljudevit Caktaš[4], Vanja Dekleva[1], Duje Birkić[1], Helena Kolar Mitrović[1] & Porin Perić[1,2]

[1]University Hospital Centre Zagreb, Department of Rheumatology and Rehabilitation, Zagreb, Croatia
[2]School of Medicine, University of Zagreb, Zagreb, Croatia
[3]School of Medicine, University of Mostar, Mostar, Bosnia and Herzegovina
[4]Lječilište Topusko, Department of Physical Medicine and Rehabilitation, Topusko, Croatia

SUMMARY

Background: *Early diagnosis is the key to successful treatment of inflammatory rheumatic diseases and the use of conventional disease-modifying antirheumatic drugs (csDMARD) and biologic disease-modifying antirheumatic drugs (bDMARD) or biologics have substantially contributed to better disease control. Biological drugs have been approved for the treatment of rheumatoid arthritis (RA), juvenile arthritis (JIA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA).*

Subjects and methods: *The study involved 79 adult patients with rheumatoid arthritis (RA) and ankylosing spondylitis (AS), psoriatic arthritis (PsA) or undifferentiated spondyloarthropathy (USpA) - the last three clinical entities belong to a common group called spondyloarthropathies (SpA); receiving anti-TNF therapy at the department of Rheumatology and Rehabilitation, Clinical Hospital Center Zagreb. The duration of therapy was a minimum of 1 month, with the mean duration of 32.0±24.0 months. The infections recorded were infections that appeared during treatment or soon after the treatment was stopped.*

Results: *During the course of therapy 17 patients (21.5%) experienced an infection, with the total number of 21 infections. This resulted in an overall incidence rate (IR) of 9.9/100 patient-years. Of the patients with RA 76.5% developed an infection, which was significantly higher than for patients with SpA ($p<0.001$). The IR/100 patient-years for all infections in RA patients was 23.7 compared to 2.8 in patients with SpA. Female gender was associated with a significantly higher infection rate (70.6%, $p=0.005$). There were 8 infections that were considered serious, yielding an IR of 3.8/100 patient-years. There was only one malignancy case in our study.*

Conclusion: *Every fifth patient developed an infection during the course of anti-TNF therapy, and more than one third of all infections were serious. RA and female gender was associated with a significantly increased number of infections.*

Key words: *anti-tnf therapy - inflammatory rheumatic diseases – infections - malignancies*

* * * * *

INTRODUCTION

Rheumatic disease is an umbrella term used to describe disorders that mainly affect the joints, tendons, ligaments, muscle and bones, but also have many extra-skeletal manifestations. The characteristic symptoms are pain, stiffness and swelling of the affected areas (Hardin 1990). The topic of this paper covers rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and undifferentiated spondyloarthritis. By interfering with specific parts of the immune system and inhibiting the components of the inflammatory cascade, biological drugs increase the risk of developing infections, from mild respiratory and urinary tract infections to serious infections such as pneumonia, activation of latent tuberculosis and hepatitis B and C infection. The link between biological therapy and malignancy is not yet clear, though data from the large registries do not indicate an increased risk of malignancies that would be associated with the use of biological therapy.

Tumor necrosis factor, cloned and characterized more than 20 years ago, was originally described as a macrophage-derived endogenous mediator that could induce hemorrhagic necrosis of solid tumors and destroy some tumor cell lines *in vitro*. Unfortunately, its promising use as an anticancer agent was limited by its toxicity as seen with the first clinical trials. About the same time, it was found that TNF was identical to a mediator responsible for cachexia associated with cancer and sepsis, named cachectin. This research led to the conclusion that TNF is, in fact, the main lethal mediator of sepsis, as well as the publication of articles showing that TNF inhibits the toxic effects of bacterial endotoxins, something that is now described as the systemic inflammatory response. Although clinical trials with anti-TNF in sepsis were not very successful, these studies ultimately led to the identification of TNF as a pro-inflammatory cytokine and the development of anti-TNF molecules (Sedger & McDermontt 2014). Since then, TNF-alpha has been found to play a major role in the cytokine cascade occurring in the joints of patients with RA and similar inflammatory diseases, where it stimulates the production of other inflammatory mediators and continues recruitment of immune and inflammatory cells into the joint (Scott & Kingsley 2006).

There are five anti-TNF drugs on the market today that all bind TNF-alpha: adalimumab, certolizumab pegol, etanercept, golimumab and infliximab. Adalimumab is a completely human IgG1 monocloncal antibody that blocks the interaction of TNF-alpha with TNF receptors. It also lyses cells expressing TNF-alpha in the presence of complements. Certolizumab pegol, also known as just certolizumab, is a recombinant humanized fragment antigen-binding (Fab) fragment that binds to TNF-alpha and neutralizes its activity. Etanercept, the only one of them that is a recombinant fusion protein, binds to both TNF-alpha and beta. Golimumab is also a humanized IgG1 monoclonal antibody, but it does not lyse cells expressing membrane-associated TNF-alpha like adalimumab (Katzung et al. 2012). Infliximab was the first of them to be approved by the U.S. Food and Drug Administration (FDA) in 1999 for the treatment of rheumatoid arthritis that did not respond to methotrexate (Maini 1999). Infliximab is a chimeric IgG1 monoclonal antibody possessing human constant regions and murine variable regions (Sedger & McDermontt 2014). Despite their similar mechanism of action the individual drugs can cause a different response in different patients. Some patients that do not respond or stop responding to one of the tumor necrosis factor inhibitors (TNFis) can still respond to one of the other when switched (Carmona 2008).

In the early clinical trials with infliximab it was noticed that people treated with anti-TNF therapy had higher number of infections compared to placebo. However, the safety database was regarded as small and no conclusion could be drawn. The beneficial effects of the drug were evaluated and proved to have a higher benefit then risk associated with the adverse effects. The physicians and patients where further advised to report the adverse events to assess this safety issue further. The clinical trials of etanerecept also showed some connection to risk of infection and anti-TNF use, especially upper respiratory infections (29% and 33% in the 10mg and 25mg groups respectively compared to 16% in controls). Since then, the relationship between anti-TNFs and the risk of acquiring infection has been the topic of many research papers. Opportunistic infection not common to the normal population like: Coccoidiodes immitis, Listeria spp., Histoplasma capsulatum, Aspergillus spp., Nocardia spp., mycobacteria and streptococci, have all been reported (Crum et al. 2005). The incidence of tuberculosis (TB) was the most striking and was higher than for the baseline risk of the population in some studies (Keane et al. 2001, Gomez-Reino et al. 2003). This awareness lead to new guidelines that recommends to screen for TB before commencing anti-TNF therapy, which helped to decrease the incidence of reactivation of latent TB (Ding et al. 2010). Studies conducted have showed a small but significant increased risk of serious infections (SIs) in patients treated with TNFis (Dixon et al. 2006, Galloway et al. 2010). Serious infections were here defined as either requiring hospitalization and/or IV antibiotics or leading to death. German and Swedish Biologics Registries reported similar results (Askling et al. 2007, Listing et al. 2005). These data along with other data suggest that there is a small but significant overall risk of SI. However, other studies failed to show an increased risk (Westhovens et al. 2006, Weisman et al. 2007) and it is difficult to conclude if it is the anti-TNF or other factors like the disease it self, that predispose to more SIs. Several studies have shown that people with RA compared to the general population have an almost double increased risk of infection (Atzeni et al. 2008, Doran et al. 2002, Baum 1971). This is believed to be related to the disease it self, as well as, to concomitant use of immunosuppressant drugs. A study by Favalli et al. found an increased risk associated with age, erythrocyte sedimentation rate (ESR) and the use of steroids (Favalli et al. 2009). Other studies have also found other factors to increase the risk apart from the anti-TNF therapy, making it difficult to distinguish what is attributable only to the TNFi.

TNF was initially found to have a tumor necrosis action in mice and accordingly named so (Carswell et al. 1975). Therefore, it was thought that when blocking its effect, with anti-TNF drugs, that it could cause the development of cancers. However, pre-clinical and clinical studies with anti-TNF therapy on humans have failed to clearly answer if it is associated with an increased risk of malignancy. A post-marketing study from Mayo Clinic, by Bongartz et al, showed a three-fold increase in the risk of developing cancer in patients receiving infliximab or adalimumab therapy, compared to placebo (Bongartz et al. 2006). However, there was no person-year incidence rate calculated in the study and a commentary article showed the patients treated were studied for a longer time than the placebo group. When it was adjusted for time the results that Bongartz found were not statistically significant (Dixon et al. 2006). A Swedish study found that there was no overall tumor risk in treated patients, however, a proportional hazard analysis of lymphomas was done yielding a risk of 4,9 (95% CI:0,9-26,2) (Geborek et al. 2005). A subsequent analysis done later adjusted for age, gender and duration of disease did not show any significance in the risk of developing lymphoma (Askling et al. 2005). BIOBADASERs extensive study done in Spain showed no increase in rate of malignancy between exposed and non-exposed groups. Many studies have been carried out failing to provide substantial evidence. Possible explanation to this could be due to the nature of the diseases. It is known that inflammation it self is a risk factor for cancer (Coussens & Werb 2002). This means that the increased risk of cancer in patients with inflammatory diseases treated with anti-TNF could be a result of the underlying disease process and not the effect of the therapy (Simon et al. 2015).

SUBJECTS AND METHODS

Participants

This study included 79 patients treated at the department for Rheumatology and Rehabilitation at Clinical Hospital Centre Zagreb, Croatia, from 2004 to 2015. The participants gave informed consent and patient anonymity was preserved. Patients were diagnosed with RA, AS, PsA or USpA. The latter three diseases were considered as one group, SpA (seronegeative spondyloarhtropathies). Data was gathered from medical files and follow-up interviews. Patients were selected and treated according to guidelines from American Collage of Rheumatology (ACR) and Croatian Society for Rheumatology 2013 guidelines.

The patients included in the study received anti-TNF therapy with infliximab, adalimumab, etanercept, golimumab or certolizumab pegol for at least one month. The duration of the treatment was from 1 month to 109 months (9 years) with the mean duration of 32.2 months (SD±23.8). In particular, patients were excluded in the presence of any active infection after screening with the tuberculin skin test (TST), chest radiograph and hepatitis B (HBV) and C (HCV) viral markers. If patients had to pause the treatment due to side effects or infections, this time was subtracted from the main duration. Patients were also assessed for their use of DMARDs and glucocorticoids. Disease activity scores used for RA were DAS28 and HAQ, for SpA it was BASDAI and BASFI. These scores were not compared, but they were included to give the impressions of the disease activity. We used the score that was calculated before treatment.

Patients that did not respond to therapy or had severe adverse effects were taken off the therapy they were receiving and/or switched to another agent. For patients that underwent surgery therapy would be stopped for a certain period before and after. Only infections occurring during therapy or 1 month after were noted. All types of infection, both serious and non-serious, were recorded. Infections that were defined as serious were either life-threatening, requiring hospitalization, IV antibiotic therapy and/or caused death.

Due to the fact that many patients were switched between the various anti-TNF agents it would have been difficult to estimate what agent was responsible for the infection or malignancy. Therefore, we considered the anti-TNF as one group and did not analyze the risk of each single agent.

Statistical Analysis

Proportions were calculated for the demographic and clinical characteristics of all patients. For important clinical characteristics, incidence rates (IRs), defined as the number of observed events (infections) or persons with infection/100 patient-years of follow-up, were calculated, to estimate the risk of infection in the different groups. T-distribution, F-variance and Pearson-Chi Square were used to calculate the probabilities. All analyses were performed using Statistica versions 7.0.

RESULTS

Data provided in table 1 show the baseline demographics of the study group (Table 1).

There were 56 patients with SpA (33 AS, 16 PsA and 7 USpA) and 23 with RA. The mean age of patients with RA and SpA was 50.5±11.8 and 44.8±10.7 years, respectively, showing a statistical significant difference in age between the patients of each group ($p<0.04$). In total 58% of the study candidates were male and 43% female. There were significantly more females with RA compared to SpA (Pearson Chi-square 27.2, df 1, $p<0.0001$ and t-value -2.1, df 77, $p<0.05$ respectively). Between the two groups there was no statistically significant difference in duration of disease or duration of therapy,

Table 1. Baseline demographics and clinical data

	All patients 79	RA 23 (29.1%)	SpA 56 (70.8%)	p-value
Age (years)	46.4±11.2	50.5±11.8	44.8±10.7	0.04
Age beginning of therapy	43.9±11.8	46.7±13.0	42.8±11.2	ns
Females	33 (41.7%)	20 (86.9%)	13 (23.2%)	<0.0001
Males	46 (58.2%)	3 (13.0%)	43 (76.8%)	<0.0001
Disease duration (years)	11.4±8.9	12.6±7.2	10.9±9.6	ns
Therapy duration (months)	32.0±24.0	37.2±24.2	30.2±23.6	ns
DMARD therapy	35 (44.3%)	15 (65.2%)	20 (35.7%)	0.016
Corticosteroid therapy	51 (64.6%)	19 (82.6%)	32 (57.1%)	0.032
DAS28	-	6.2±0.9	-	-
HAQ	-	1.8±0.6	-	-
BASFI	-	-	6.58±1.73	-
BASDAI	-	-	6.56±1.42	-

DAS28 = Disease activity score; HAQ = Health Assessment Questionnaire; DMARDs = Disease-modifying anti-rheumatic drugs
Continuous variables expressed as mean values±S.D. ns: not statistically significant

with the total average of 11.4±8.9 years and 32.0±24.0 months respectively. In total 44.3% of all patients were receiving or had previously been receiving DMARDs, and 64,5% had been treated with oral corticosteroids. A greater percentage of subjects in the RA group were receiving DMARDs and glucocorticoids compared to SpA. For the patients with RA an average DAS28 score was 6.2±0.9 and HAQ 1.8±0.6. Average BASFI and BASDAI for the SpA group was, 6.58±1.73 and 6.56±1.42, respectively.

Baseline demographics of patients that developed an infection are depicted in Table 2.

Table 2. Baseline demographics and clinical data of patients with infection

	Patients with infection	p value
Total	17 (21.5%)	
RA	13 (76.5%)	<0.001
SpA	4 (23.5%)	<0.001
Age	47.6±10.2	ns
Age beginning of therapy	43.0±11.1	ns
Female	12 (70.6%)	0.005
Male	5 (29.4%)	0.005
Duration of disease (months)	12.9±7.2	ns
Duration of therapy	40.1±26.7	ns
DMARDs	8 (47.0%)	ns
Corticosteroids	10 (58.8%)	ns
DAS28 (RA)	6.1±1.0	ns

DAS28 = Disease activity score; HAQ = Health Assessment Questionnaire; DMARDs = Disease-modifying anti-rheumatic drugs. Continuous variables expressed as mean values±SD; ns: not statistically significant

At least one infection was detected in 17 patients (21.5%) had at least one infection, with the total number of infections being 21. The total incidence rate (IR) of patients that developed an infection was 8.0 per 100 patient-year. The mean age of the patients with infections was 47.6, which did not differ much from the mean age of the patients without an infection (47.5 years). Our study showed that two factors were associated with an increased risk of developing and infection, and this was the type of inflammatory rheumatic disease and gender. We noticed a much higher number of infections in RA patients treated with anti-TNF therapy compared to patients with SpA (13 (76.5%) vs 4 (23.5%) respectively, p<0.001). From our basic calculation this showed us that more than half (56.5%) of patients that suffered from RA developed an infection, compared 7.1% of patients with SpA (Risk ratio (RR) 7.9). Female gender was also greatly associated with the development of an infection (p<0.005). More than one third of all women developed an infection (36.4%), compared to 10.8% of males (RR 3.4).

Table 3. Frequency and seriousness of each infection

Infection	Category	Count
Non-serious	URT	6
	Bronchitis	2
	Herpes Zoster	2
	UTI	2
	Enterocolitis	1
Total		13
Serious	Abscess in extremity	1
	Abscess in liver	1
	Necrotizing pneumonia	1
	Osteomyelitis	1
	Phlegmona- extremity	1
	Pyoarthros	1
	Sepsis	1
	Tuberculos pleuritis	1
Total		8
All total		21

URT=Upper Respiratory Tract, UTI=Urinary tract infection

We performed Pearson Chi-Square to assess whether there was any significance in the subjects with infection and the use of DMARDs or corticosteroids, however, no significance was shown (DMARDs Chi-square: 0.26 p=0.61; corticosteroids Chi-square: 0.28, p=0.59).

We did a t-distribution on the mean DAS28 score between subjects with RA that developed an infection compared to the subjects with RA that did not, (t-value: 0.82, df: 19, p=0.42), without revealing any significance.

Table 3 depicts the different types of infections and separates them into serious and non-serious (Table 3).

A total of 21 infections were detected (61.9% non-serious and 38% SIs), and three was the maximum number of infections per person. Nearly one third of all infections were serious, this is a higher than what is expected to be normal.

URT were the most common type of infections the patients presented with including: sinusitis, rhinitis and throat infections. We calculated an IR/100 patient-years of 3.8 for the serious infections (SIs) and 9.0 for total number of infections. One patient died as a result of the infection, this patient developed sepsis after multiple abscesses in the abdomen.

Malignancy

One of the 79 patients developed a malignancy throughout the duration of the study. This shows a calculated risk if 1,25% of developing malignancy. The patient was a 55-year old male that developed hepatocellular carcinoma and died as a result of its complications. The results were regarded as not significant due to the small sample size. No further calculations were therefore carried out in relation to malignancy and anti-TNF therapy.

DISCUSSION

We observed an IR/100 patient-years of 3.8 for the serious infections (SIs) and 9.9 for all infections in total. A study performed by Atzeni et al. showed similar results to our study (IR/1000 patient-years 31.8 equivalent to 3.2 per 100 patient-years), however, it was only conducted in patients with RA and lacked a control group (Atzeni et al. 2012).

Due to the lack of a control group in our study, we used other studies and their results as a comparison to be able to draw any conclusion as to whether anti-TNF agents are associated with an increased risk of infection. A study conducted by Salliot et al. found that the risk of SI and overall infection was 3.4 and 9.3 (IR/100 patient-years) respectively in subjects before they received any therapy with TNFis (Salliot et al. 2007). Comparing our results to their study we see that we have the same rate of infection, after anti-TNF therapy, as they had before this therapy. This would mean that if Salliot et al. findings are correct then our results do not show an increased risk of infection above what is expected in patients with inflammatory rheumatic disease. Another study conducted by Grijalva et al., from a US-multi-institutional collaboration, found the IR for SIs in the comparison group, that was not treated with TNFi, to be 7.78 and 5.37 for RA and SpA respectively (Grijalva et al. 2011). What more, this study found that the incidence rate of infections after therapy with a TNFi was 8.16 and 5.41, for RA and SpA respectively. This yielded an adjusted hazard ratio of 1.05 for both groups and was not statistically significant. We calculated our IR for SIs in RA and SpA subjects separately and the result was 8.4 (6 cases on 71.4 patient-years) and 1.4 (2 cases on 140.8 patient-years) respectively. When comparing to the group from Grijalva et al. that was not recieving anti-TNF therapy we calculated an incidence rate ratio (IRR) of 1.07 for RA and 0.26 for SpA. This would again indicate that our study does not show any increased risk of SI in inflammatory rheumatic diseases when receiving anti-TNF therapy. To further assist in the discussion, a study found an IR of 9.6 per 100 patient-years for patients with RA not receiving TNFi, with a hazard ratio of 1.9 compared to normal matched controls (Doran et al. 2002). This study included infections requiring hospitalization in RA patients, a criteria of a SI, and since our rate for RA is lower it further strengthens the fact that we can not say that anti-TNF therapy increases the risk of infection. However, since we did not assess the different characteristics of the study candidates between our study and the other studies, it is not possible to use this discussion to draw any conclusion. Salliot et al. further found that after his subjects were treated with TNFis the IR increased (10.5 and 54.1 for SIs and all infections, respectively) and they showed an almost doubling of risk. Many other studies conducted have found an increased risk of infection with anti-TNF therapy. The German study RABBIT showed an IR of 6.4 and 6.1 for etanercept and infliximab, respectfully (Listing et al. 2005) and Dixon et al. 5.3 per 100 patient-years (Dixon et al. 2006). Our result showed just slightly lower values than in the studies above.

Our study found a significant correlation between development of infection and type of inflammatory rheumatic disorder ($p<0.0001$). Subjects with RA had a greater risk than the subjects with SpA with more than half of patients with RA developing an infection. The IR/100 patient-years for all infections in the RA and SpA group was 24.1 and 2.9 respectively (IRR 8.3). There seems to be few studies comparing the different infection risk between these two groups, however, as mentioned in the introduction RA is associated with a higher baseline risk of infection while this risk seems to be low for SpA (Fouqué-Aubert et al. 2010). Therefore, it would be natural to expect that there were more infections in RA patients also after anti-TNF therapy. We must be careful, however, to conclude that anti-TNF therapy causes more infections in RA patients than in SpA patients. Many studies did not find any significant difference in risk of developing an infection in RA and SpA patients receiving anti-TNF (Germano et al. 2014, Grijalva et al. 2011, Salliot et al. 2007). Normally patients with SpA, especially AS, are younger and this would be abatable to bias. In our study we did have significant difference between the ages in the two groups that could be at least partially responsible for this variation.

The second factor that seemed to increase the risk of infections in patients receiving TNFis was their gender. More than one third of the females developed an infection. Female to male IRR was 2.8 (IR/100 patient-years being 12.3 and 4.4 respectively). Germano et al. showed a similar result with more than one third increased risk for females. This was also observed in other studies (Lacaille et al. 2008, Au et al. 2011). Germano et al. suspected that the reason for the increased risk was because of uro-genital tract infections (UTIs), which are known to occure more frequently in women. However, in our study there were only 2 UTIs, which could not account for the higher number of infections that was observed in females. The preponderance of women with RA compared to SpA is a probable cause of these results. We did show that there was a much higher number of infections in the RA group and 86.9% of the subjects with RA were women. Whether RA or female gender are predisposing factors to increased rate of infections is debatable, and one would need to adjust for the gender difference or have similar subject distribution in the two groups. Our study was limited when it came to that. Since other studies also found an association between gender and infection risk in anti-TNF treated persons, we could speculate that maybe genetic factors connected to the female sex are

responsible for these increased risks regardless of the type of inflammatory rheumatic disease. There should be a focus on finding out if there is any difference between infection risk and gender, if so the therapy regimes could be changed and more caution given to women that are treated with TNFis.

In the basic statistical analysis of the two groups, showed in table 1, we see that the use of DMARDs and corticosteroids in the RA group are significantly higher (p=0.016 and 0.032 respectively). When adjusted for presence of infection we did not find any statistical significance between the development of infections and the use of DMARDs or corticosteroids. However, other studies have found that concomitant use of these medications increases the risk of infection (Germano et al. 2014, Atzeni et al. 2012). The weakness of our analysis when addressing this association was that it was not known whether the patients were receiving steroids or DMARDs during the therapy with anti-TNF or if they had been receiving them sometime in the past. Possibly resulting in patients being falsely labeled as being treated with these medications during the study when in fact they were not.

The small sample size of this study (79 patients in total) makes it difficult to extract any significant data regarding infections and especially malignancies that occur at a very low rate. In addition, there is no other group to compare the results too. The ideal would be to have a cohort study with a larger sample size with one group receiving therapy and the other not, but that both groups have similar characteristics.

CONCLUSION

This is clearly a small sample of patients compared to other larger studies done with the same scope of interest. Compared to other similar studies the rate of SIs from our study was slightly lower, nevertheless, more than one third of the infections recorded were serious, which is believed to be high. Patients with RA and females that were treated with anti-TNFs had a significantly higher risk of overall and serious infections compared to patients with SpA and males. This study serves as a basis for further bDMARDs safety monitoring in our Department. It is necessary to increase the sample size and continue follow up to before making any definite conclusions.

Acknowledgements: *None.*

Conflict of interest: *None to declare.*

Contribution of individual authors:

All authors reviewed and discussed the manuscript draft and contributed to the final manuscript and all authors give final approval of the version to be submitted.

References

1. *Askling J, Fored CM, Baecklund E, Brandt L, Backlin C, Ekbom A et al.: Heamatopoetic malignancies in rheumatoid arthritis: lymphoma risk and characteristics after exposure to tumor necrosis factor antagonists. Ann Rheum Dis 2005; 64:1414-20*
2. *Atzeni F, Bendtzen K, Bobbio-Pallavicini F, Conti F, Cutolo M, Montecucco C et al.: Infections and treatment of patients with rheumatic diseases. Clin Exp Rheumatol 2008; 26:S67–73*
3. *Atzeni F, Sarzi-Puttini P, Botsios C, Carletto A, Cipriani P, Favalli EG, Frati E et al.: Long-term anti-TNF therapy and the risk of serious infections in a cohort of patients with rheumatoid arthritis: Comparison of adalimumab, etanercept and infliximab in the GISEA registry Autoimmunity Reviews 2012; 12:225–229*
4. *Au K, Reed G, Curtis JR, Kremer JM, Greenberg JD, Strand V et al.: High disease activity is associated with an increased risk of infection in patient with rheumatoid arthritis. Ann Rheum Dis 2011; 70:785-791*
5. *Baum J: Infections in rheumatoid arthritis. Arthritis Rheum 1971; 14:135–7*
6. *Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V: Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA 2006; 295:2275-85*
7. *Carmona L: Switching between anti-TNFs: Is it always justifiable? Reumatol Clin 2008; 4:87-9*
8. *Carswell EA, Old LJ, Kaassel RL, Green S, Fiore N, Williamson B: An endotoxin-induced serum factor that causes necrosis of tumors. Immunology 1975; 72:3666-70*
9. *Coussens LM & Werb Z: Inflammation and cancer. Nature 2002; 420:860–867*
10. *Crum NF, Lederman ER, Wallace MR: Infections associated with tumor necrosis factor-alpha antagonists. Medicine (Baltimore) 2005; 84:291-302*
11. *Ding T, Ledingham J, Luqmani R, Westlake S, Hyrich K, Lunt M et al.: BSR and BHPR rheumatoid arthritis guidelines on safety of anti-TNF therapies. Rheumatology 2010; 49:2217-9*
12. *Dixon WG, Watson K, Lunt M, Hyrich KL, Silman AJ, Symmons DP et al.: Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-TNF therapy. Arthritis Rheum 2006; 54:2368-76*
13. *Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE: Frequency of infection in patients with rheumatoid arthritis compared with controls. A population- based study. Arthritis Rheum 2002; 46:2287–93*
14. *Favalli EG, F Desiati F, F Atzeni F, Sarzi-Puttini P, Caporali R, Pallavicini FB et al.: Serious infections during anti-TNF alpha treatment in rheumatoid arthritis patients. Autoimmun Rev 2009; 8:266-73*
15. *Fouqué-Aubert A, Jette-Paulin L, Combescure C, Basch A, Tebib J, Gossec L: Serious infections in patients with ankylosing spondylitis with and without TNF blockers: a systematic review and meta-analysis of randomised placebo-controlled trials. Ann Rheum Dis 2010; 69:1756-61*
16. *Galloway JB, Hyrich KL, Mercer LK, Dixon WG, Fu B, Ustianowski AP et al.: Anti-TNF therapy is associated*

with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. Rheumatology (Oxford) 2010; 50:124-31

17. *Geborek P, Bladstrom A, Turesson C, Gulfe A, Petersson IF, Saxne T et al.: Tumor necrosis factor blockers do not increase overall tumor risk in patients with rheumatoid arthritis, but may be associated with an increased risk of lymphomas. Ann Rheum Dis. 2005; 64:699-703*
18. *Germano V, Cattaruzza MS, Osborn J, Tarantino A, Di Rosa R, Salemi S et al.: Infection risk in Rheumatoid Arthritis and Spondyloarthropathy patients under treatment with DMARDs, Journal of Translational Medicine 2014; 12:77*
19. *Gómez-Reino JJ, Carmona L, Valverde VR, Mola EM, Montero MD; BIOBADASER Group: Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: A multicenter active-surveillance report. Arthritis & Rheumatism 2003; 48:2122-27*
20. *Grijalva CG, Chen L, Delzell E, Baddley JW, Beukelman T, Winthrop KL et al.: Initiation of Tumor Necrosis Factor-α Antagonists and the Risk of Hospitalization for Infection in Patients With Autoimmune Diseases. JAMA 2011; 306:2331-9*
21. *Hardin JG: Rheumatic Pain. In Walker HK, Hall WD, Hurst JW (eds): Clinical Methods, 3rd edition: The History, Physical, and Laboratory Examinations, 753-756. Boston: Butterworths-Heinemann, 1990*
22. *Katzung BG, Masters SB, Trevor AJ: Basic and clinical pharmacology twelfth edition. International edition, 636-650. McGraw-Hill, 2012*
23. *Keane J, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, Schwieterman WD et al.: Tuberculosis Associated with Infliximab, a Tumor Necrosis Factor α–Neutralizing Agent. N Engl J Med 2001; 345:1098-1104*
24. *Lacaille D, Guh DP, Abrahamowicz M, Anis AH, Esdaile JM: Use of non biologic disease-modifying antirheumatic drugs and risk of infection in patients with rheumatoid arthritis. Arthritis Rheum 2008; 59:1074-81*
25. *Listing J, Strangefeld A, Kary S, Rau R, von Hinueber U, Stoyanova-Scholz M et al.: Infections in patients with rheumatoid arthritis treated with biologic agents. Arthritis Rheum 2005; 52:3403-12*
26. *Maini R , EW St Clair, F Breedveld, D Furst, J Kalden, J Smolen et al.: Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. The Lancet 1999; 354:1932–1939*
27. *Salliot C, Gossec L, Ruyssen-Witrand A, Luc M, Duclos M, Guignard S et al.: Infections during tumour necrosis factor-α blocker therapy for rheumatic diseases in daily practice: a systematic retrospective study of 709 patients. Rheumatology 2007; 46:327-334*
28. *Scott DL and Kingsley GH: Tumor necrosis factor inhibitors for rheumatoid arthritis. NEJM 2006; 355:704-12*
29. *Sedger LM and McDermontt MF: TNF and TNF-receptors: From mediators of cell death and inflammation to therapeutic giants – past, present and future. CGFR 2007; 25:453-72*
30. *Simon TA, Thompson A, Gandhi KK, Hochberg MC, Suissa S: Incidence of malignancy in adult patients with rheumatoid arthritis: a meta-analysis. Arthritis Res Ther 2015; 17:212*
31. *Weisman MH, Paulus HE, Burch FX, Kivitz AJ, Fierer J, Dunn M et al.: A placebo-controlled, randomized, double blinded study evaluating the safety of etanercept in patients with rheumatoid arthritis and concomitant comorbid diseases. Rheumatology 2007; 46:1122-1125*
32. *Westhovens R, Yocum D, Han J, Berman A, Strusberg I, Geusens P et al.: The safety of infliximab, combined with background treatments, among patients with rheumatoid arthritis and various comorbidities: a large, randomized, placebo-controlled trial. Arthritis Rheum 2006; 54:1075-1086*

Correspondence:

Mislav Pap, MD
University Hospital Centre Zagreb, Department of Rheumatology and Rehabilitation
Kišpatićeva 12, 10 000 Zagreb, Croatia
E-mail: mislav.pap@gmail.com