TUMOUR NECROSIS FACTOR ALPHA INHIBITORS IN RHEUMATOID ARTHRITIS THERAPY

INHIBITORY CZYNNIKA MARTWICY NOWOTWORU ALFA W TERAPII REUMATOIDALNEGO ZAPALENIA STAWÓW

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Summary: Tumour necrosis factor alpha (TNFα) is the proinflammatory cytokine that plays an important role in the pathogenesis of rheumatoid arthritis (RA). Anti-TNFα therapy is a promising method for biological RA treatment. This article summarises the role of TNFα in RA pathogenesis, the role of TNFα antagonists in RA therapy, adverse effects of TNFα inhibitors and factors that predispose patients to a positive response to anti-TNFα therapy.

Keywords: TNFα, rheumatoid arthritis, TNFα inhibitors, biological treatment

Streszczenie: Czynnik martwicy nowotworu alfa (TNFα) jest cytokiną prozapalną, która odgrywa ważną rolę w patogenezie reumatoidalnego zapalenia stawów (RZS). Terapia anty-TNFα jest obiecującą metodą biologicznego leczenia RZS. W artykule podsumowano rolę TNFα w patogenezie RZS, rolę antagonistów TNFα w terapii RZS, niekorzystne działanie inhibitorów TNFα oraz czynniki predysponujące pacjentów do pozytywnej odpowiedzi na terapię anty-TNFα.

Słowa kluczowe: TNFα, reumatoidalne zapalenie stawów, inhibitory TNFα, terapia biologiczna

Abbreviations: **ACR**–American College of Rheumatology, **DMARDs**–disease modifying anti-rheumatic drugs, **Fab**–antigen-binding fragment, **GM-CSF**–granulocyte monocyte-colony stimulating factor, HBV hepatitis B virus, **ICAM-1**–intracellular adhesion molecule 1,**IL,** interleukin, **mAbs**–monoclonal antibodies, **MHC I**–class I major histocompatibility complex, **NSAIDs**–nonsteroidal anti-inflammatory drugs, **RA**–rheumatoid arthritis, **TACE**–TNFα-converting enzyme, **TNF**–tumour necrosis factor, **TNFα**–tumour necrosis factor alpha, **TNFR1**–tumour necrosis factor receptor type 1, **TNFR2**tumour necrosis factor receptor type 2, **TNFRSF**–tumour necrosis factor receptor superfamily, **TNFSF**–tumour necrosis factor super family.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory, autoimmune disease characterised by pain, swollen and stiff of joints, synovial inflammation and deterioration of cartilage and bone. Untreated RA can lead to permanent disability and premature death. Rheumatoid arthritis affects women three times more than men[56]. Because of the chronic nature of RA, annual costs associated with treatment reach $27,000 per patient in the US and $17,400 in Europe. All treatments in total amount to $52,90 and $58 billion respectively. Over the past two decades, there have been many changes in RA treatment. Traditional therapy with synthetic drugs, such as disease modifying anti-rheumatic drugs (DMARDs) in conjunction with nonsteroidal anti-inflammatory drugs (NSAIDs), resulted in the improvement of patients' lives by reducing joint and bone damage. However, this first-line of treatment is not an option for a large portion of patients who exhibit intolerance to this therapy. Fortunately, recent discoveries in the pathogenesis of RA has led to the identification of new molecular therapeutic targets[58, 1]. The disturbance in the extremely complex, interactive network of cytokines and cells is responsible for the pathogenesis of RA. Abnormalities in molecular mechanisms lead to typical signs and symptoms of RA, such as inflammation of the synovial membrane, followed by cartilage and bone erosion. Although knowledge about RA pathogenesis is still incomplete, tumour necrosis factor alpha (TNFα) was identified as a key factor in the chronic inflammation process. TNFα, a pivotal proinflammatory cytokine, induces the activity of other cytokines in the proinflammatory cascade that lead to RA development. It has been proven that inhibition of TNFα expression can reduce the production of other proinflammatory cytokines[66]. Therefore, neutralisation of TNFα activity is now commonly used to treat RA patients[56]. In this review we described current anti-TNFα therapeutics and summarised up-to-date progress in RA therapy based on blocking TNFα.

RHEUMATOID ARTHRITIS

Rheumatoid arthritis is the one of the most common, chronic, autoimmune diseases, that affects 0.5% to 1.0% of the global population. It is characterised by joint synovium inflammation (synovitis), followed by joint, cartilage and bone destruction, resulting in functional disability. Patients affected by RA have a higher rate of morbidity and mortality. Although the exact trigger of the autoimmune response is still undetermined, it is commonly known that a complex, interactive network of cells and proinflammatory cytokines are involved in the pathogenesis of RA[66]. Synovitis is characterised by cellular proliferation and activation and

infiltration of various inflammatory cells, including macrophages, plasma cells, endothelial cells, CD4+ T cells, B cells and neutrophils. All cells that infiltrate the synovial membrane, secrete great amounts of proinflammatory cytokines including TNFα, interleukin-1 (IL-1), interleukin-6 (IL-6) and proteases. All these factors are triggers for macrophages and fibroblasts activation, which results in the secretion of other inflammatory factors. This proinflammatory cascade results in the formation of synovitis, followed by pannus formation. The pannus triggers joint destruction, followed by cartilage and bone erosion. Bone erosion is the result of osteoclasts differentiation and proliferation. Even though activated cells secrete large amounts of many different inflammatory factors, TNFα plays a key role in this complex, interactive network, therefore becoming a critical target in RA treatment[12].

TNFα

TNFα is a member of the tumour necrosis factor super family (TNFSF) which consist of at least 20 different peptides [18]. To date, it has been demonstrated that there are over 35 specific ligand-receptor pairs between TNFSF and members of tumour necrosis factor receptor superfamily (TNFRSF). Although there are many TNFSF representatives, TNFα appears to be a central inflammatory cytokine that demonstrates pleiotropic effects on various cell types [73].

The human TNFα coding gene is located on chromosome 6 and the cytokine is initially generated as a precursor peptide called transmembrane TNFα because it is displayed on the plasma membrane of many cell types. Newly synthesised transmembrane TNFα consist of 233 amino acid residues and lacks a classic signal peptide. Subsequently, the TNFα precursor peptide is cleaved by TNFα-converting enzyme (TACE) into a soluble, mature 17-kDa protein, consisting of 157 amino acid residues [37, 69]. TACE belongs to a class of membrane-associated enzymes that consist of disintegrin and matrix metalloprotease domains. Even though the TACE substrates are not completely understood, it appears that the biological functions of TACE are not exclusively limited to TNFα processing [18]. Knock-out of the TACE gene was developmentally lethal in a mouse model, while TNFα gene knock out had no significant influence on the development, growthand reproduction of animals[51]. This observation indicates that TACE enzyme is also crucial for the processing of the other regulatory proteins[18]. Soluble TNFα, as well as transmembrane TNFα, are homotrimers composed of three identical subunits that can interact with type 1 and type 2 tumour necrosis factor receptors (TNFR1 and TNFR2). Peptide binding to the receptor causes many biological effects such as apoptosis, cell proliferation and cytokine production [12, 18, 37].

The biological activity of TNFα is very broad. However, the cytotoxicity of TNFα to tumour cell lines was the first TNFα activity discovered. In the 1970s, Lloyd Old, along with his colleagues, had identified a substance derived from macrophages that induced haemorrhagic necrosis of solid tumours[18]. This observation led to the discovered product being named tumour necrosis factor (TNF). TNFα is produced primarily by macrophages and monocytes, but also by other immune cells (B-cells, T-cells, eosinophils, basophils, neutrophils, natural killer cells, dendritic cells and mast cells). Many of the non-immune cells such as fibroblasts, astrocytes, glial cells, granuloma cells, keratinocytes, neurons, osteoblasts, retinal pigment epithelial cells, smooth muscle cells and tumour cells also produce TNFα. Even though the biological activity of TNFα is very comprehensive, the most important in terms of RA pathogenesis is its ability to promote and support the process of chronic inflammation.

TNFα CONTRIBUTION TO RA PATHOGENESIS

Physiologically, TNFα plays a crucial role in both innate and acquired immunity in the response to inflammation. In the condition of homoeostasis, there is a close balance between pro- and anti-inflammatory cytokines, which allows immunity to perform its complex functions effectively. Unfortunately, sometimes the balance is disturbed in favour of the proinflammatory response. An uncontrolled proinflammatory response leads to inappropriate TNFα synthesis and release, and by extension, the overproduction of other proinflammatory cytokines. This proinflammatory cascade, with TNFα playing a key role, is one of the characteristic attributes of RA.

TNFα is overproduced in the serum and the synovial tissue in many patients with RA[47, 74, 68, 64, 54]. TNFα gene expression can be induced by various biological, chemical and physical factors and stimuli. In RA pathogenesis, the primary trigger of an uncontrolled immune response is unknown, but TNFα expression can be stimulated by viruses, bacterial or parasitic products, tumour cells, ischaemia, trauma, irradiation and many other stimuli [18]. TNFα is a potent autocrine stimulator and a paracrine inducer of other proinflammatory cytokines. It stimulates cells to secrete interleukins (IL-1, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, IL-18), granulocyte monocyte-colony stimulating factor (GM-CSF) and adhesion molecules such as intracellular adhesion molecule 1 (ICAM-1) [12, 18]. Macrophages are the primary source of TNFα in the synovial membrane. Clinical outcomes correlate with an increased number of infiltrating macrophages and overproduction of TNFα [64]. Another study demonstrated that pro-arthritic effects of TNFα can be mediated by local interactions between TNFα ligands (soluble and transmembrane) and its receptors [74]. In RA, TNFα mediates the most

critical events in the acute and chronic synovial membrane inflammation, inducing multiple proinflammatory cytokines and chemokines, expression of adhesion molecules and elevated levels of class I major histocompatibility complex (MHC I) determinants. TNFα triggers cartilage and bone erosion by inducing synovial fibroblasts to synthesise and release proteases and prostaglandin E2 [14, 15]. Taking all the data into consideration, TNFα is a key component in the cascade of cytokines induced in RA, therefore the reduction of excess TNFα in inflammation sites was expected to be promising in RA therapy.

LIGAND-RECEPTOR BINDING AND NATURAL TNFα INHIBITION

TNFα, as a key mediator of proinflammatory cascade induced in RA, exerts its influence on target cells through binding to TNFR1 and TNFR2. TNFR1 is expressed on almost all cell types that contain a nucleus, whereas TNFR2 is mostly expressed on endothelial and hematopoietic cells[18, 37]. There were several models for the molecular events between TNFα and its receptors discussed by researchers, but the model of molecular-switch is the most preferred. The molecular-switch model assumes that signal transduction is a direct effect of conformational changes within the cytoplasmic domain of the receptor[29]. Both TNFα receptors are transmembrane proteins, but they can also be produced naturally as soluble molecules in the process of proteolytic cleavage of extracellular domains. Soluble receptors are natural inhibitors of TNFα action because they compete with transmembrane receptors for binding to TNFα. The binding of TNFα to a soluble receptor has no biological effect, therefore TNFα action is blocked[22]. Understanding molecular events underlying TNFα's mechanism of action permits researchers to develop novel strategies for RA treatment. These novel strategies are based on biological agents that mimic naturally occurring mechanisms of TNFα inhibition. To date, biological agents licensed for the treatment of RA can be divided in two major types. One type is a group of monoclonal antibodies against TNFα and the second type is a group of recombinant soluble fusion proteins [66].

STRUCTURE OF TNFα ANTAGONISTS

Biological agents responsible for the inhibition of TNFα activity, by interfering with TNFα-TNFR binding, are called TNFα antagonists or inhibitors. To date, five different TNFα antagonists are licensed for clinical use as therapeutics for RA: infliximab, etanercept, adalimumab, certolizumab and golimumab[67].

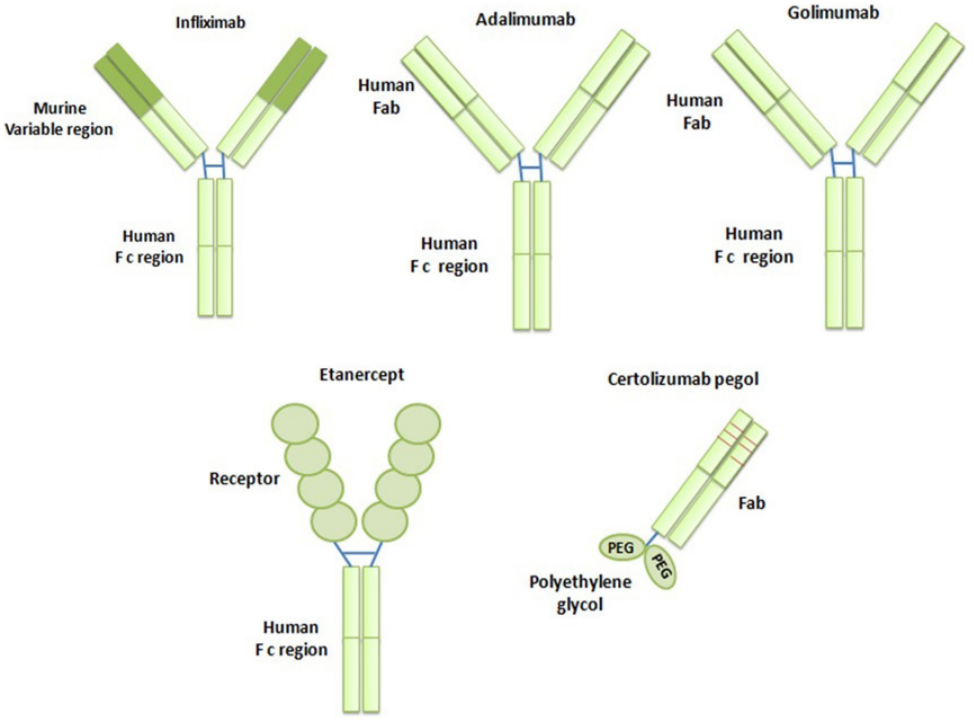

FIGURE 1. Schematic representation of the molecular structures of all five TNFα inhibitors licensed for the RA treatment. Infliximab is a chimeric human-mouse mAb. Adalimumab and golimumab are fully human mAbs. Etanercept is a fusion protein that consists of two recombinant, soluble TNFα receptors fused with the Fc region of human IgG. Certolizumab is a humanised IgG mAb fragment, without an Fc region

RYCINA 1. Schematyczne przedstawienie struktur molekularnych wszystkich pięciu inhibitorów TNFα zarejestrowanych w terapii RZS. Infliksymab jest chimerycznym ludzko-mysim przeciwciałem. Adalimumab i golimumab są w pełni ludzkimi przeciwciałami. Etanercept jest białkiem fuzyjnym, które składa się z dwóch rekombinowanych, rozpuszczalnych receptorów TNFα połączonych z regionem Fc ludzkiej IgG. Certolizumab jest humanizowanym fragmentem przeciwciała IgG bez regionu Fc

Schematic structures of these therapeutics, with their similarities and differences, are shown in **figure 1**. Infliximab, adalimumab, certolizumab and golimumab are monoclonal antibodies (mAbs) or monoclonal antibody fragments[58]. Infliximab, adalimumab and golimumab are full-length IgG mAbs, whereas certolizumab is a humanised antigen-binding fragment (Fab) covalently conjugated to polyethylene glycol. Etanercept is a soluble fusion protein[67].

Infliximab is a chimeric human-mouse mAb (75% human, 25% mouse) which binds to TNFα with high specificity and affinity. Infliximab binds to both soluble and transmembrane TNFα and inhibits the biological effects of TNFα by blocking

TNFα-TNFRs interactions. It is also cytotoxic to cells which express TNFα [56]. Adalimumab and golimumab are fully human mAbs that also bind to soluble and transmembrane TNFα with high affinity. Certolizumab is a humanised IgG mAb fragment, without an Fc region, and therefore lacks effector functions. Instead of an Fc region, the hinge region of certolizumab is modified and covalently conjugated to two chains of polyethylene glycol [67]. One of the TNFα inhibitors is not structurally a mAb, but a recombinant, soluble TNFα receptor. Etanercept is a fusion protein that consists of two recombinant, soluble TNFα receptors fused with the Fc region of human IgG. The dimeric structure of etanercept significantly influences its efficiency to neutralise TNFα. Dimeric, soluble TNFα receptors are approximately 1000 times more efficient in inhibiting TNFα than monomeric TNFα receptors. Etanercept prevents interactions between TNFα and its receptor by binding to the cytokine. The mechanism of action of etanercept mimics the naturally occurring process of TNFα inhibition.

Despite the structural differences between individual TNFα inhibitors, the primary mechanism of action of these biologics is to neutralise TNFα activity. In many randomised clinical trials, all TNFα antagonists exhibit a high efficiency in reducing clinical signs of chronic inflammation in RA patients. A large portion of patients, in which disease modifying anti-rheumatic drugs (DMARDs) failed, appear to be responsive to treatment with TNFα inhibitors To date, unfortunately, only few comparative clinical trials have been performed comparing individual TNFα inhibitors, thus the determination of the most effective agent is still impossible[1].

TNFα INHIBITORS EFFICIENCY AND SAFETY

The efficiency of clinical outcomes during treatment with TNFα inhibitors is calculated based on the American College of Rheumatology (ACR) score. The ACR score is a set of seven disease activity outcomes used to measure changes in RA symptoms. Different degrees of improvement are referred to as ACR20, ACR50 and ACR70. ACR20 means that there is 20% improvement in tender or swollen joint counts, as well as 20% improvement in three of the other five criteria. ACR50 and ACR70 correspond to 50% and 70% improvements, respectively[58]. The additional measure of TNFα antagonists' efficiency is disease activity score 28 (DAS28). The DAS28 is a weighted score of tender and swollen joint counts, overall patient assessment of disease activity and acute phase reactants[1]. The data of efficacy and safety of anti-TNFα agents, from randomised clinical trials, have shown that TNFα inhibitors are effective in reducing clinical signs of inflammation in RA patients[40, 45, 43, 72, 33, 34, 55, 60, 35]. Many of the RA patients, in which DMARDs therapy failed, achieved ACR20 and DAS28

scores[25-28]. Furthermore, in these clinical trials, a significant number of patients also achieved improvement on the ACR50 and ACR70 level[43, 72, 33, 34, 55, 60, 35]. Moreover, TNFα antagonists exhibited their efficiency in reducing radiographic progression[33, 55, 35]. The results of the ARMADA trial showed that adalimumab was effective in most patients treated with a TNFα inhibitor, taking concomitant methotrexate [72]. In the GO-FORWARD clinical trial, the efficacy and safety of golimumab were estimated after five years of treatment. This trial confirmed both efficacy and safety of subcutaneous administration of golimumab to RA patients [35]. Similar outcomes were reported in previous, independent studies of other TNFα inhibitors[8].The most recent data confirms previous reports regarding safety and efficacy of TNFα inhibitors. Long-term safety and effectiveness of adalimumab were confirmed during the 3-year treatment period [28]. Similar clinical responses to golimumab in different doses were reported through week 120[65]. Several recent studies confirm the advantage of using TNFα inhibitors compared to the traditional therapies. Treat-to-target study conducted in regions with limited biologic access have shown that combination of etanercept and DMARD is more effective in maintenance of remission than DMARDs therapy alone [49]. The C-OPERA clinical trial evaluated efficacy and safety of combination therapy using certolizumab pegol and methotrexate, compared to using methotrexate alone. This study showed that combination therapy was superior to methotrexate alone, bringing clinical benefit for further 2 years, even after certolizumab withdrawal[75, 4]. Although, most of the data supports the use of biologic agents after failure of methotrexate monotherapy in RA, one study reports an evidence that a combination of conventional therapies can be more effective than TNFα inhibitors [50].

Another aspect of long-term clinical outcome of TNFα is the patients' reaction to drug dose reduction or withdrawal. The main goal of dose tapering or drug withdrawal is to optimise the treatment by decreasing the risk of adverse effects and to lower the treatment costs. The authors of DRESS trial published results of the 3-year study, in which a long-term outcomes of TNFα inhibitors dose reduction were assessed. It has been proven that safety and efficacy of disease activity guided TNFα inhibitors dose reduction were maintained for up to 3 years, with a significant reduction of TNFα inhibitors use [6]. These reports have been confirmed by the results of other, independent studies[75, 31]. Tapering of TNFα inhibitors by 33% does not cause any loss of clinical response[31]. The C-OPERA clinical trial demonstrated that withdrawal of certolizumab pegol has no negative impact on radiographic progression or clinical benefits[75]. The most recent PREDICTRA study aim to generate data on patient and disease characteristics that may predict the clinical course of fixed dose-reduction regimen with adalimumab. This clinical trial hasbegun in February 2018 and is still ongoing[19].

The last aspect of clinical outcome of biologic therapy is to evaluate how individual TNFα inhibitors differ from each other in terms of efficacy and safety. To date, there are still only few studies tackling this issue[30, 36, 61]. Golimumab appeared to be effective and well-tolerated in patients who had shown inadequate response to DMARDs or other anti-TNFα agents[30, 36].The results of head-to-head comparison of certolizumab pegol versus adalimumab demonstrated equivalence of these drugs, simultaneously showing that switching from one to another TNFα inhibitor is safe and effective[36].

In summary, all five clinically licensed anti-TNFα therapeutics have been evaluated in a series of randomised, controlled clinical trials. All TNFα inhibitors were effective and safe for most of the patients. The therapeutic effect was manifested by a reduction of chronic inflammation and erosive damage, which was visualised by radiography. Additionally, the quality of life of RA patients was improved. However, a large portion of RA patients were non-responsive to anti-TNFα treatment and did not achieve ACR20. For this reason, in the future, it would be helpful to identify some predictors for anti-TNFα therapy response [71].

SAFETY, IMMUNOGENICITY AND EFFICACY OF BIOSIMILAR DRUGS

Biosimilar agents are similar versions of an original biological substance already licensed for clinical use as therapeutics. Access to effective biologicals, due to the high cost, is restricted only to certain patients and countries. However, biosimilars can remove that inequality by reducing cost and making the treatment more accessible. To date, there are few phase III clinical trials comparing original TNFα inhibitors and biosimilar agents. The infliximab was compared to the biosimilar SB2 product in terms of its efficacy, safety, immunogenicity and pharmacokinetics[44]. The results of this study demonstrated bioequivalence of these drugs. After approval of biosimilar SB2, the agent has been examined in terms of switching from infliximab to SB2 [62]. The goal of this transition period was to compare results in RA patients who switched from infliximab to biosimilar SB2 with those who continue receiving infliximab or biosimilar SB2. The results have shown no significant differences between groups up to week 78, therefore suggesting that the clinical profile of SB2 is comparable with originator infliximab, even when administrated long term. The SB4 and LBEC0101 are etanercept biosimilar agents. The SB4 clinical profile was evaluated in two different phase III studies [19, 20]. In the first study, the efficacy and safety of SB4 were evaluated at week 24, and in the second up to week 52. The results of both studies have demonstrated similarities in clinical profile between SB4 and etanercept. Last

year, the other etanercept biosimilar- LBEC0101 was also evaluated in phase III, multicentre, double-blind, randomised, parallel-group study [42]. As a result, the clinical efficacy of LBEC0101 and its similarity to etanercept reference products were proven. SB5 is a biosimilar agent to adalimumab and likewise SB2 and SB4 was evaluated in two phase III randomized clinical trials [36, 23]. The first study assessed the clinical profile of SB5 at week 24. The second study evaluated patients who switched from adalimumab to SB5 or who maintained treatment with SB5 or adalimumab up to 52 weeks. In both studies the SB5 was well tolerated and had comparable safety profile to adalimumab.

THE ADVERSE EFFECTS OF TNFα INHIBITORS

There are several adverse effects of TNFα inhibitors that were identified during administration of the biological therapy. The most common adverse effects were: allergic reactions directly related to the administration of the drug as an infusion, skin reactions after injections and various types of infections. The less common adverse effects were: idiopathic pulmonary fibrosis, optic neuritis, multiple sclerosis intensification, hepatomegaly, and aplastic anaemia[21].

TNFα is a key factor that is synthesised and secreted by cells as a part of immune response to various kinds of infections. Therefore, inhibiting TNFα synthesis can increase the potential risk of serious infections [70]. Other factors can also influence the increased risk of infections after TNFα inhibitors administration: the advanced age of the patient, administration of corticosteroids, especially at medium and high doses, advanced disease activity, and comorbidities such as diabetes, chronic lung diseases or kidney failure[63, 17].There are three types of infections that were identified during administration of TNFα inhibitor therapy: bacterial, viral and opportunistic. The most frequent were bacterial infections of the upper respiratory tract, urogenital system and skin and soft tissues [38]. Due to the increased risk of pneumococcal infection, it is recommended that RA patients receive a pneumococcal vaccine before biological therapy begins [59]. Patients with RA are also at high risk for viral infections. Scientists reported an increased frequency of herpes zoster infection, with a high percentage of hospitalisation, especially after therapy with monoclonal antibodies [10]. As a result, it is also recommended that RA patients receive a vaccine for herpes zoster before biological therapy administered [59]. Patients infected with the hepatitis B virus are at risk of reactivation of the infection, and therefore hepatitis B virus (HBV) serology should be determined before the implementation of TNFα inhibitor therapy [7]. In the case of negative HBV serology, vaccination is recommended. No contraindications to biological therapy were identified in the case of hepatitis C virus infections [59]. Opportunistic infections did not cause disease in a healthy host

with a normal, functioning immune system. However, RA patients that undergo therapy with TNFα inhibitors are at a serious risk of opportunistic infections, especially Mycobacterium tuberculosis infection. In RA patients, tuberculosis developed within the first month of biological therapy implementation. There is a significant difference between classic and biological therapy-related tuberculosis. The reported cases of tuberculosis infection induced by TNFα inhibitor treatment involved extrapulmonary sites of infection and were life threatening[24]. The extrapulmonary sites of a tuberculosis infection suggest a latent form of the disease. Due to previous observations, there is a recommendation that tests for the latent form of tuberculosis be performed before TNFα inhibitors are administered. Testing for the latent form of tuberculosis would significantly reduce the number of life-threatening cases[10, 26].

The relationship between implementing TNFα inhibitor therapy and the risk of cancer is still unclear. To date, some data shows that RA patients that undergo biological therapy are at an increased risk for cancer compared to the general population [5].In a clinical trial for RA patients, biological therapy has not been associated with an increased risk of malignancy compared with other DMARDs or placebo[39]. Other studies on the incidence of solid malignancies also show a minor increase of cancer risk in RA patients treated with TNFα antagonists compared to non-biological DMARDs [3, 11]. No evidence of a higher incidence of lymphoma and leukaemia in TNFα antagonists-treated patients was found[2]. A few studies showed an increased risk of skin cancer, especially non-melanoma cancers, although other studies found no significant difference [52, 53]. Moreover, prolonged administration of TNFα inhibitors has not been associated with an increased risk of cancer. Also, there is no evidence of a correlation between malignancies following biological therapy and worse post-cancer survival rates[52]. Nevertheless, therapy with TNFα inhibitors is not recommended in RA patients with a medical history of cancer, except for treated solid malignancies in remission over five years [59].

Generally, RA patients have an increased risk for cardiovascular disease when compared to the general population. The increased risk of cardiovascular disease is associated with chronic inflammation, which is the hallmark of RA [41, 25]. However, there are no significant differences in the risk of acute myocardial infarction between RA patients that undergo biological treatment and patients receiving traditional DMARDs. Interestingly, some data indicates that treatment with TNFα inhibitors reduces the risk of all cardiovascular events [16]. These observations are most likely the result of TNFα inhibitors' activity. TNFα, as a proinflammatory cytokine, plays an important pathological role in thrombotic mechanisms, leading to the increased risk of cardiovascular events in RA patients. TNFα inhibitors by blocking TNFα, suppress these pathological mechanisms, therefore reducing the cardiovascular risk associated with RA. In contrast, patients with a history of cardiovascular

disease have an increased risk for heart failure when treated with TNFα inhibitors[41]. Therefore, patients with a history of cardiovascular disease should not receive TNFα antagonists. It is worth drawing attention to the fact that some of the patients enrolled in the study, who experienced cardiac insufficiency, received greater than standard dosage of TNFα inhibitors [9, 13]. In conclusion, more clinical data is needed to correctly assess the cardiovascular risk associated with TNFα inhibitors therapy.

Many of the adverse events described to date are affected by various skin reactions, including autoimmune diseases. The main pathological conditions induced by TNFα inhibitors treatment are: vitiligo, spot baldness, cutaneous lupus erythematosus, cutaneous vasculitis, relapsing polychondritis and various psoriasis-like skin lesions. The large number of cutaneous adverse events reported to date indicate that skin is the target organ for adverse effects of the TNFα inhibitor therapy.

THE THERAPEUTIC RESPONSE TO TNFα INHIBITORS − THE EFFECTS OF GENE POLYMORPHISMS IN THE TUMOUR NECROSIS FACTOR

Among RA patients, there is a substantial heterogeneity in the clinical response to TNFα inhibitors. Considering the high costs of biological therapy, there is a serious need to find the predictors of treatment response. Such predictors would be useful in the selection of the appropriate agents. To date, few studies show that polymorphisms in TNFα influence the clinical response to TNFα inhibitors. Most of the studies were focused on the polymorphism at position -308 in the TNFα gene promoter. A study in France examined whether the G-to-A polymorphism at position -308 in the TNFα gene promoter has any influence on the clinical response to infliximab. They found that patients with TNFα-308G/G genotype respond better to infliximab compared to patients with A/A or A/G genotypes [46]. A similar study was performed concerning the response to etanercept, where two groups of patients were compared: -308 A/G genotype and -308 G/G genotype [27]. Similar to the results of the study by Guis et al. patients with TNF-308G/G genotype respond to the biological therapy better than patients with a -308 A/G genotype. These results were confirmed by a study conducted recently, in which the authors demonstrated the impact of the same polymorphism on responsiveness of RA patients to three TNFα inhibitors: infliximab, etanercept and adalimumab[57]. In this study, they also proved that patients with a TNF-308G/G genotype are better responders to anti-TNFα therapy than those with A/A or A/G genotypes. In addition, a study conducted in Sweden revealed that the combination of two polymorphisms: -308G/G in TNFα gene promoter and -1087G/G in the interleukin 10 gene was associated with good response of RA patients to etanercept[48]. The impact of C-to-T polymorphism at the position -857 of the TNFα gene pro-

moter on responsiveness to etanercept therapy was demonstrated in another study [32]. The results demonstrated that RA patients with the TNFα-857C/T genotype respond better to etanercept therapy than homozygotes for the C allele. This single nucleotide polymorphism can become another useful predictor of etanercept treatment. In conclusion, the presented results indicate that TNFα gene promoter is an important determinant of biological treatment response.

CONCLUSION

Anti-TNFα therapy is a promising therapeutic method for the treatment of RA. Although this therapy is relatively safe in many patients, various adverse events can occur during treatment. Prevention of toxicity and other adverse effects of this therapy requires a better understanding of the molecular mechanisms and pathways involved in the toxicity of these drugs. The search for biomarkers that predispose patients to a positive response to anti-TNFα therapy will be the primary focus of research in the coming years. These studies may enable the identification of patients who are most likely to respond to treatment with anti-TNFα inhibitors. At present, we should search for new TNFα inhibitors that may enable safer and more effective treatment of RA.

AUTHOR CONTRIBUTIONS

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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