Tumor necrosis factor inhibitors – state of knowledge

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Abstract

Tumor necrosis factor (TNF) is considered a major proinflammatory cytokine, affecting various aspects of the immune reaction. All five TNF inhibitors currently available on the market (i.e., etanercept, infliximab, adalimumab, certolizumab and golimumab) are top sellers, although indicated only in autoimmune diseases, including rheumatoid arthritis, Crohn's disease and psoriasis. This article briefly discusses the background and place for TNF inhibitors in modern therapy. The main safety aspects of TNF inhibitor administration are described in particular, with special consideration of the available meta-analyses. Finally, perspectives on the next-generation TNF inhibitors and their use in the clinic are given.

Key words: tumor necrosis factor inhibitors, biologic agents, adverse effect, rheumatic disease.

Introduction

Tumor necrosis factor (TNF) was cloned and characterized almost 30 years ago, in 1984 [1]. It is a proinflammatory cytokine, being produced primarily by activated monocytes/macrophages [2]. TNF is synthesized as a transmembrane protein (tmTNF) and cleaved by the matrix metalloproteinase TNF converting enzyme (TACE, ADAM 17) to soluble TNF (solTNF) [3]. Both forms are biologically active. TNF is considered a major player in inflammatory reactions. Its wide range of biological effects, mediated through apoptosis [4], include antitumor and antiviral activities, as well as mediation of cachexia. However, the extreme toxicity of TNF dramatically limits its clinical use, and the human recombinant TNF tasonermin (trade name Beromun), although approved for oncological treatment, is used only in isolated limb perfusion chemotherapy [5, 6].

Much more successful, from both a clinical and a commercial perspective, was development and use of TNF antagonists. Five approved anti-TNF biologics achieved in 2008 annual sales of over 16 billion US dollars. Three TNF inhibitors, etanercept, infliximab and adalimumab, are top selling drugs of any class, with cumulated projected sales of $26.5 billion in 2012 [7] (Table I). The three anti-TNF biologics were initially developed to treat rheumatoid arthritis, but current indications also include such conditions as juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, Crohn's disease and plaque psoriasis.

Table I. Top 2012 drug sales (biologics marked in bold) [63]

Drug (active substance)	Projected sales in 2012
Humira (adalimumab)	9.3 billion $
Remicade (infliximab)	9.1 billion $
Enbrel (etanercept)	8.1 billion $
Advair (fluticasone/salmeterol)	8 billion $
Rituxan (rituximab)	7.1 billion $
Crestor (rosuvastatin)	7 billion $
Avastin (bevacizumab)	6.1 billion $
Herceptin (trastuzumab)	6.1 billion $
Lantus (insulin analog)	5.9 billion $
Abilify (aripiprazole)	5.9 billion $

TNF and TNF receptors

While both forms of TNF, i.e. solTNF and tmTNF, are biologically active, they have distinctly different roles. The transmembrane form, tmTNF, has been shown to play a crucial role in maintaining the physiological innate immune response to infections, such as tuberculosis, listeriosis and leishmaniasis, and also to provide tolerance to autoantigens [8, 9]. The broadly accepted main role of solTNF is to drive the inflammatory response. This function has been proven in animal studies showing that inhibition of solTNF causes the anti-inflammatory effect. Inhibition of tmTNF, on the other hand, results in increased sensitivity to infection and exacerbation of demyelination.

TNF acts through its receptors (TNFR). These receptors can be either constitutively expressed (TNFR1, p55) or inducible (TNFR2, p75) [10]. Both receptors are membrane glycoproteins, but they differ in expression, ligand affinity and signaling pathway activation. TNFR1 serves as the major mediator of TNF action. It can be activated by binding of either solTNF or tmTNF, but with a significant preference for solTNF. TNFR2, on the other hand, is preferentially activated by tmTNF [11]. The specific receptor expression depends on the cell type. While TNFR1 is expressed in most cell types, TNFR2 expression is limited to specific cells (i.e., oligodendrocytes, microglia and astrocytes in the CNS, endothelial cells, lymphocytes and cardiac myocytes) [12]. The two receptor types differ in their biological roles. TNFR1 is responsible for initiating inflammatory responses and mediating apoptosis, but also for protection against tuberculosis infection [13]. TNFR2 facilitates antiviral immune responses through generation of cytotoxic T-lymphocytes [14]. Current clinically approved TNF inhibitors block both solTNF and tmTNF (Table II), and this lack of ligand selectivity may be the cause of serious side effects of the therapy.

TNF antagonist structures and properties

Presently, there are five TNF inhibitors approved for the treatment of various autoimmune diseases: etanercept, infliximab, adalimumab, certolizumab and golimumab (Table III).

Infliximab, adalimumab and golimumab are bivalent IgG monoclonal antibodies, but only adalimumab and golimumab are fully human. Adalimumab is a humanized bivalent mouse IgG1 monoclonal antibody. It binds specifically to TNF and neutralizes the biological function of TNF by blocking its interaction with both TNFR1 and TNFR2 receptors. Golimumab forms high-affinity

Table II. Approved TNF inhibitors

Inhibitor	Trade name	Specificity	Developer/ date of approval	MAH	Route of administration
Etanercept	Enbrel	sol TNF, tmTNF, lymphotoxin A	Amgen, Wyeth, Takeda FDA – 1998 EMA – 2000	Pfizer Ltd.	Subcutaneous injection
Infliximab	Remicade	sol TNF, tmTNF	Centocor Schering-Plough 1998 – FDA 1999 – EMA	Janssen Biologics B.V.	Intravenous injection
Adalimumab	Humira	sol TNF, tmTNF	Abbot 2005 – FDA 2003 – EMA	AbbVie Ltd	Subcutaneous injection
Certolizumab	Cimzia	sol TNF, tmTNF	UCB 2008 – FDA 2009 – EMA	UCB Pharma S.A.	Subcutaneous injection
Golimumab	Symponi	sol TNF, tmTNF	Centocor, Schering-Plough 2009 – FDA 2009 – EMA	Janssen Biologics B.V.	Subcutaneous injection

FDA – Food and Drug Administration, EMA – European Medicines Agency, MAH – Marketing Authorization Holder

Table III. Approved indications of TNF inhibitors

Inhibitor	Indications
Etanercept	Rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, plaque psoriasis, pediatric plaque psoriasis
Adalimumab	Rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, axial spondyloarthritis ankylosing spondylitis, psoriatic arthritis, psoriasis, Crohn's disease, pediatric Crohn's disease, ulcerative colitis
Infliximab	Rheumatoid arthritis, adult Crohn's disease, pediatric Crohn's disease, ulcerative colitis, pediatric ulcerative colitis, ankylosing spondylitis, psoriatic arthritis, psoriasis
Certolizumab	Rheumatoid arthritis
Golimumab	Rheumatoid arthritis, ankylosing spondylitis (AS), psoriatic arthritis

complexes with both solTNF and tmTNF, preventing their binding to receptors.

Infliximab is a chimeric bivalent IgG1 human-murine protein containing about 25% mouse-derived amino acids. It binds with high affinity to both soluble and transmembrane forms of TNF, but not to lymphotoxin α (TNF_{β}). Certolizumab is the Fab' fragment of a recombinant, humanized antibody against both solTNF and tmTNF. It does not contain the Fc region.

Etanercept is a genetically engineered fusion protein, and consists of the Fc domain of human IgG1 fused to a dimer of the extracellular ligand-binding domain of human TNFR2/p75. It binds with high affinity to both soluble and transmembrane forms of TNF. It is worth noting that etanercept is the only clinically approved TNF inhibitor which binds also to lymphotoxin α (TNF_{β}) [15]. The unique structure of etanercept is probably responsible for its properties. Compared to infliximab and adalimumab, etanercept exerts significantly lower complement-dependent cytotoxicity and outside-to-inside signals (apoptosis/cell cycle arrest) through the transmembrane TNF. This feature may also be the cause of its inefficacy in the treatment of granulomatous diseases such as Crohn's disease and Wegener's granulomatosis [16].

All the inhibitors competitively inhibit the binding of TNF to its receptors. However, they differ in both the pharmacokinetic and pharmacodynamic properties, leading to significant differences in their clinical efficacy and indications. For example, it has been shown that approximately one-third of patients with rheumatoid arthritis (RA) were primary non-responders to the anti-TNF therapy [17]. The observed heterogeneity in the treatment responsiveness may also be associated with genetic factors. Namely, different polymorphic variants of the TNF gene have recently been linked to autoimmune diseases [18].

Approved indications of TNF inhibitors

The European Medicines Agency has approved several indications for each of the five TNF inhibitors described above, as summarized in Table III.

Rheumatoid arthritis (RA)

Adalimumab, infliximab, etanercept, certolizumab and golimumab are currently indicated in the treatment of:

- Moderate to severe, active rheumatoid arthritis in adult patients, who did not respond adequately to disease-modifying anti-rheumatic drugs including methotrexate;
- Severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate;
- Rheumatoid arthritis in case of intolerance to methotrexate or if continued treatment with methotrexate was ineffective.

The effects of TNF blockade have been summarized by Feldmann and Maini (2010), and they include: 1) normalization of IL-6 level in serum within a few hours of anti-TNF treatment, 2) reduction of chemokine and adhesion molecule expression in joints, 3) restoration of osteoprotegerin levels and reduction of matrix metalloproteinase levels in cartilage and bone, and 4) slowing bone destruction.

Ankylosing spondylitis (AS)

Adalimumab, infliximab, etanercept, certolizumab and golimumab are all indicated in the treatment of:

- Severe active ankylosing spondylitis that had an inadequate response to the conventional therapy;
- Severe axial spondyloarthritis without radiographic evidence of AS but with objective signs of inflammation (elevated CRP and/or MRI), in patients who have had an inadequate response to, or are intolerant of, nonsteroidal anti-inflammatory drugs.

Adalimumab is also approved for the treatment of active polyarticular juvenile idiopathic arthritis in combination with methotrexate, in children and adolescents aged 2 to 17 years who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs.

Psoriasis and psoriatic arthritis (PsA)

Adalimumab, infliximab and etanercept are approved for the treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to, or who have contraindications to, or are intolerant to, other systemic therapies such as cyclosporine, methotrexate or PUVA.

Adalimumab, infliximab, etanercept and golimumab are approved for the treatment of active and progressive psoriatic arthritis in adults with an inadequate response to previous disease-modifying anti-rheumatic drug therapy.

Inflammatory bowel disease (IBD)

Adalimumab and infliximab are approved for treatment of moderately to severely active Crohn's disease, in adult patients who have not responded to a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant, or who are intolerant to or have medical contraindications for such therapies.

Adalimumab and infliximab are registered for the treatment of severe active Crohn's disease in pediatric patients (6 to 17 years of age) who have had an inadequate response to conventional therapy including primary nutrition therapy, a corticosteroid, and an immunomodulator, or who are intolerant to or have contraindications for such therapies.

Infliximab and adalimumab are approved for treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

Off-label indications of TNF inhibitors

Beside the approved therapies, TNF inhibitors are also used in off-label indications. Even though in most of these cases large, controlled studies are still lacking, case reports indicate their efficacy in selected conditions (Table IV).

Granulomatous diseases – sarcoidosis

Sarcoidosis is a granulomatous inflammatory disease of unclear etiology. TNF, produced by macrophages, plays a key role in the pathology of the disease, and is responsible for the formation of granulomas and progression of the disease. A systematic review of the literature together with the analysis of the Spanish registry of biological therapies BIOBADASER, which evaluates safety, efficacy and effectiveness of infliximab and etanercept,

Table IV. Effective, selected off-label uses of TNF inhibitors [63–65]

Disease	TNF inhibitor	Type of proof
Granuloma annulare	Infliximab, etanercept	Case reports
Necrobiosis lipoidica	Infliximab, etanercept	Case reports
Hidradenitis suppurativa	Infliximab	Double-blind, placebo-controlled study
Pyoderma gangrenosum	Infliximab, etanercept, adalimumab	Case reports
Sweet's syndrome	Etanercept	Case reports
Subcorneal pustular dermatosis	Infliximab, etanercept	Case reports
Systemic lupus erythematosus	Infliximab	Case reports
Scleroderma	Infliximab	Case reports
Dermatomyositis	Infliximab, etanercept	Open-label trial, case reports
Behcet's disease	Infliximab, etanercept, adalimumab	Case reports
Acute/chronic graft versus host disease	Etanercept	Retrospective study
Pityriasis rubra pilaris	Infliximab, etanercept, adalimumab	Case reports
Sjogren's syndrome	Infliximab	Double-blind, placebo-controlled study
Wegener's granulomatosis	Etanercept	Double-blind, placebo-controlled study
Polymyalgia rheumatica	Infliximab	Double-blind, placebo-controlled study
Dermatomyositis	Infliximab, etanercept	Open-label trial
Pyoderma gangrenosum	Infliximab	Case reports

has not found sufficient evidence ensuring their effectiveness in sarcoidosis. However, the authors conclude that infliximab can cause moderate improvement of selected signs of the disease [19]. Adalimumab has been shown to be less effective than infliximab, and a phase II trial of etanercept in the treatment of stage II or III progressive pulmonary sarcoidosis was terminated due to lack of efficacy [20]. Paradoxically, there are reports describing cases of new onset sarcoidosis-like diseases in patients treated with etanercept, infliximab and adalimumab [21]. This phenomenon clearly shows that the data to support a role of TNF in sarcoidosis are insufficient.

Ophthalmic indications

Uveitis can have a wide range of clinical presentations, as it refers to ocular inflammation of the iris, choroid and ciliary body. Treatment of uveitis is dependent on the location and severity of inflammation. Whereas there are no TNF inhibitors approved for the treatment of uveitis, they are being used off-label [22]. One of the best studied is ocular inflammation in Behcet disease. Behcet disease is a chronic, relapsing inflammatory disease, and ocular inflammation is one of the most common and severe signs of the disease. Infliximab has been shown to induce a rapid clinical remission with an improvement in visual acuity. Other studies showed fewer recurrences and a lower number of attacks in patients treated with infliximab versus standard treatment [23]. In a recent, double-blind, randomized, placebo-controlled trial, infliximab was shown to cause significant improvement of visual acuity in the treatment of diabetic macular edema [24].

Skin disorders

Acne inversa (*hidradenitis suppurativa*) is a chronic inflammatory condition that affects mainly young females. As acne inversa may coexist with Crohn's disease and spondyloarthropathy, it is suggested that dysfunction of the immune system may play a role in the pathogenesis of the disease. The efficacy of infliximab, adalimumab and etanercept in the treatment of acne inversa has been shown in many case-report studies [25]. Promising results have also been obtained in the treatment of multicentric reticulohistiocytosis, pityriasis rubra pilaris, eosinophilic fasciitis, panniculitis, necrobiosis lipoidica diabeticorum and cicatricial pemphigoid [23, 26].

Safety profile of TNF inhibitors

Safety concerns are the most important reason for the withdrawal of a drug from the market. Due to their relatively short presence on the market, all reports concerning TNF inhibitors, as belonging to the class of biologics, are very thoroughly analyzed by government authorities, such as the Food and Drug Administration (FDA) and the European Medicines Agency. If medical research studies indicate that the drug carries a significant risk of serious, or even life-threatening, adverse effects, the "black box" warning is issued. It is the strongest warning that the FDA requires. It is so named for the black border that usually surrounds the text of the warning, appearing on the labeling of the prescription drug, or in the literature describing it.

For TNF inhibitors, three warnings have been issued: 1) increased risk for developing serious infections (including tuberculosis (TB), histoplasmosis, listeriosis, *Pneumocystis pneumonia*) that may lead to hospitalization or death (2008); 2) increased risk of developing lymphoma and other malignancies, some fatal, in children and adolescent patients (2009), and 3) post-marketing cases of fatal hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma (2011; for more details, see Table V). Moreover, safety alerts are released in case of any new important safety data. All the safety alerts issued for TNF antagonists are summarized in Table VI. Also, drug information, such as *Core Company Data Sheets* and *Summary of Product Characteristics*, is updated regularly (Table VII).

An important part of the safety profile of a drug is interactions with other products. It is worth stressing that TNF inhibitors very rarely cause drug interactions. In clinical trials, no interactions have been reported when etanercept or certolizumab was administered with glucocorticoids, salicylates (excluding sulfasalazine), nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics, or methotrexate. For infliximab, even though no systematic studies have been performed, single reports suggest a possibility of interactions with methotrexate and immunomodulatory drugs. According to the *Summary of Product Characteristics*, it is not recommended to use TNF inhibitors with anakinra and abatacept.

An important safety concern for the use of TNF inhibitors is the risk of inducing antidrug antibodies. Immunogenicity may result in serious clinical consequences, such as reduction in efficacy of the drug and infusion or injection site reactions. Chimeric antibodies have been shown to be more immunogenic than humanized or human antibodies. One of the studies of patients with RA found anti-infliximab antibodies in more than 40% of patients [27].

All of the available clinical trials bring new information about potentially harmful effects of TNF inhibitors. Most of the effects result from the direct inhibition of TNF. However, valuable conclusions can be made only based on meta-analyses. This

Table V. Summarized black-box warnings for TNF inhibitors issued by FDA

Inhibitor	Black-box warning
Etanercept Adalimumab Infliximab Certolizumab Golimumab	Patients treated with *Trade name* are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. *Trade name* should be discontinued if a patient develops a serious infection or sepsis. Reported infections include: • Active tuberculosis, including reactivation of latent tuberculosis. Patients with tuberculosis have frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent tuberculosis before *Trade name* use and during therapy. Treatment for latent infection should be initiated prior to *Trade name* use. • Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Empiric anti-fungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness. • Bacterial, viral, and other infections due to opportunistic pathogens, including *Legionella* and *Listeria*. The risks and benefits of treatment with *Trade name* l should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with *Trade name*, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy. **Malignancies** Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, including *Trade name*.
Adalimumab Infliximab	Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including *Trade name*. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases has occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all these patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants.

relatively new tool is used often, for example, by Health Technology Agencies. Conclusions drawn from meta-analyses that suggest an increased risk for serious infections, malignancy, autoimmune disorders, and congestive heart failure in patients treated with TNF inhibitors are presented below.

Serious infections

As all five TNF inhibitors that are currently available on the market non-selectively block TNF, thus affecting the immune system and impairing host defense mechanisms, they may also result in an increased risk of serious infections, such as pneumonia, tuberculosis, sepsis, osteomyelitis and progressive multifocal leukoencephalopathy. The analysis of serious infections in head-to-head studies and randomized controlled trials with placebo or disease-modifying agents showed increased incidence with certolizumab, compared to adalimumab, etanercept, golimumab, infliximab and placebo. Compared to control groups, the risk of serious infections was increased in patients treated with adalimumab, certolizumab, golimumab and infliximab, but not with etanercept [28]. The most common infections include lower respiratory tract and skin infections. Tuberculosis was shown to be the most common opportunistic infection. Observational studies showed increased risk of tuberculosis during treatment with TNF antagonists, with the estimated incidence of 52.5 cases per 100 000 patient-years [29]. The risk of tuberculosis appeared to be increased with adalimumab and infliximab when compared with etanercept [30]. In a very elegant paper by Tubach *et al.*, summarizing data of the RATIO registry, the risk of developing tuberculosis was shown to be higher in patients treated with adalimumab and infliximab, compared to etanercept. The proposed mechanisms include a critical role of tmTNF in the host defense against *Mycobacterium tuberculosis* infection. Antagonizing the tmTNF action by anti-TNF monoclonal antibodies may lead to inhibition of granuloma formation, which is a protective reaction for host defense [31]. Among other reported opportunistic infections were: candidiasis, listeriosis, *Pneumocystis carinii*, and herpes zoster. Some studies also suggest an increased risk of herpes zoster infection in patients treated with TNF antagonists, except for etanercept [32].

Table VI. Safety alerts released by FDA for TNF inhibitors

Year	TNF inhibitor	Alert
2001	Infliximab	Potential serious adverse effects of Remicade in patients with CHF. Preliminary results of an ongoing phase 2 trial in patients with moderate to severe CHF demonstrated higher incidences of mortality and hospitalization for worsening heart failure in patients treated with Remicade, especially those treated with the higher dose of 10 mg/kg.
2001	Infliximab	Cases of tuberculosis and other serious opportunistic infections, including histoplasmosis, listeriosis, and pneumocystosis reported in both the clinical research and post-marking surveillance settings. Some of these infections have been fatal.
2004	Infliximab	Cases of severe hepatic reactions, including acute liver failure, jaundice, hepatitis and cholestasis reported in postmarketing data in patients receiving Remicade. Autoimmune hepatitis has been diagnosed in some of these cases. Severe hepatic reactions occurred between 2 weeks to more than a year after initiation of Remicade. Some of these cases were fatal or necessitated liver transplantation.
2004	Infliximab	More cases of lymphoma observed among patients receiving the agents than among control group patients. Malignancies have also been observed in open-label, uncontrolled clinical studies at a rate several-fold higher than expected in the general population. Patients with Crohn's disease or rheumatoid arthritis, particularly patients with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several fold) than the general population for the development of lymphoma.
2000	Etanercept	Post-marketing reports of adverse events of rare cases of nervous system disorders including demyelinating disorders such as multiple sclerosis, myelitis, and optic neuritis have been reported in patients with rheumatoid arthritis who have received Enbrel therapy.
2004	Adalimumab	Serious infections with the combined use of Humira (adalimumab) and anakinra, hypersensitivity reactions, including anaphylaxis, and hematologic events, including pancytopenia and aplastic anemia.

Table VII. Contraindications for use of TNF inhibitors

Inhibitor	Contraindications
Etanercept	Hypersensitivity to the active substance or to any of the excipients. Sepsis or risk of sepsis. Initiation of treatment in patients with active infections, including chronic or localized infection.
Adalimumab Infliximab Certolizumab Golimumab	Hypersensitivity to active substance or to any of the excipients of the product. Tuberculosis or other severe infections such as sepsis, abscesses, and opportunistic infections. Moderate or severe heart failure (NYHA class III/IV). Infusion reactions (only infliximab).

Malignancy

Originating in the basic mechanism of TNF action, TNF inhibitors were expected to cause an imbalance in antitumor mechanisms. Although TNF was originally discovered as an anti-tumor cytokine, recombinant TNF is used in clinical practice only in the treatment of irresectable soft tissue sarcoma of the limbs, due to serious untoward effects resulting from systemic administration. Moreover, experiments revealed pro-tumor actions of TNF. Namely, malignant cell-derived TNF has been proven to enhance the growth and spread of tumors of the skin, ovary, pancreas, pleural cavity and bowel, although the underlying mechanisms of these phenomena are not fully understood. It has been postulated that most pro-tumor actions are mediated through the TNFR1 receptor, which is present on tumor and stromal cells [33, 34].

Some studies showed increased risk of non-melanoma skin cancer associated with the use of adalimumab, etanercept and infliximab. In 2009, the FDA issued a warning about the potential risk of malignancy in children. A systematic review of 25 clinical trials showed the varying risks of malignancy in patients with psoriatic arthritis treated with etanercept, infliximab or adalimumab [35]. However, two other meta-analyses, of etanercept alone [36], and adalimumab, infliximab and etanercept, performed on more than 26 000 patients, did not prove a statistically significant increase in the risk of malignancy [37]. Similarly, no increase was indicated with certolizumab and golimumab [38, 39]. In addition, no increase in risk of solid tumors was detected in patients treated with adalimumab, etanercept and infliximab.

A meta-analysis of 33 double-blind randomized controlled trials in adult rheumatoid arthritis pa-

tients, performed by Moulis *et al.*, revealed no excessive risk of malignancy in therapy with any of five TNF inhibitors during up to two years of treatment. However, a tendency to an increased rate of non-melanoma skin cancers (NMSC) was found [40, 41]. A meta-analysis of observational studies by Mariette *et al.* showed a significantly increased risk of developing NMSC as well as melanoma in patients with rheumatoid arthritis treated with TNF inhibitors. However, there was no evidence of increased risk of lymphoma between patients with RA treated with TNF inhibitors and classic disease-modifying antirheumatic drugs (DMARD) [42].

TNF inhibitors were shown to increase the risk of non-melanoma skin cancers. The meta-analysis published in 2011 and based on 74 trials (including only those that lasted at least 4 weeks, but with various doses and ways of administration) showed a statistically significant increase in the risk of non-melanoma skin cancers [26]. Due to the limitations of the analysis that are a result of potentially dissimilar conditions of the individual studies, transferability of the results to clinical practice may be limited.

Autoimmune disorders

TNF is considered one of the major players in the pathology of multiple sclerosis (MS). The evidence includes reports of elevated TNF concentrations in the CSF and serum of MS patients, and increased expression of TNF in MS plaques [43, 44].

Moreover, it has been shown that there is increased secretion of TNF from monocytes shortly before the exacerbation of the disease symptoms, suggesting the role of TNF in the pathomechanisms of demyelinating disorders [45, 46].

Based on this evidence, the effects of TNF inhibitors were investigated in MS patients. Unfortunately, lenercept's phase II clinical trial had to be halted because of the unexpected increase in the frequency of MS attacks, accompanied by a tendency for an increase in the duration and severity of attacks [47]. Lupus-like symptoms have been reported with each of the TNF inhibitors adalimumab and infliximab [48–50]. Recently, alopecia areata was reported to be associated with treatment with infliximab, adalimumab, etanercept and certolizumab [51]. Finally, an increased risk of psoriasis was reported in a retrospective cohort study of rheumatoid arthritis patients treated with TNF inhibitors [52].

Congestive heart failure

Reports also suggest a potential risk for congestive heart failure as a result of treatment with TNF inhibitors. However, there are several inconsistencies among the individual analyses of these particular adverse effects. Namely, one retrospective cohort study showed a statistically significant increase in the risk of hospitalization due to congestive heart failure in patients treated with TNF inhibitors, compared with those treated with methotrexate [53]. Conversely, another study [54] could not detect any significant differences between TNF biologics and other treatments of rheumatoid arthritis.

Safety of TNF inhibitors in pregnancy

Thus far, only one study has been published concerning the safety of TNF inhibitors during pregnancy. No evidence for an increased risk of adverse pregnancy outcomes was detected in a study describing 131 cases of exposure to infliximab for the treatment of Crohn's disease during pregnancy (104 patients completed the study) [55]. There are single reports showing pregnancy outcomes of women treated with infliximab and etanercept. The anomalies described for infliximab-exposed fetuses included tetralogy of Fallot (1 case), intestinal malrotation (1 case), teratoma (1 case), and cases of unspecified anomalies of the following systems and organs: cardiac (3 cases), musculoskeletal (4 cases), reproductive (3 cases), eye (2 cases), nervous (1 case) and digestive system (1 case). Two cases of fetal anomalies in women treated with etanercept included one case of trisomy 18 and one case of VACTERL (i.e., vertebral, anal, cardiac, tracheal, esophageal, renal or limb anomalies) [56].

Analysis of data on adverse events in pregnant patients with rheumatoid arthritis treated with anti-TNF therapy collected by the British Society for Rheumatology Biologics Register showed an association between spontaneous abortion and the duration of pregnancy. Moreover, exposure to anti-TNF therapy at the time of conception was associated with the highest rate of spontaneous abortion [57]. However, the data are sparse and, although TNF inhibitors are classified as B-category drugs (i.e., animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women), the potential risk of a harmful effect must be kept in mind.

Future strategies for TNF inhibitors

The spectrum of TNF actions and the extent of its roles in pathology of various systems and organs suggest that the indications for its use will be expanded in the near future. As TNF exerts pleiotropic effects on the CNS, various studies have been carried out to examine possible clinical applications in models of stoke [58], Parkinson's disease [59] and Alzheimer's disease [60]. However, the problem of undesirable effects that may ac-

company a therapy with TNF inhibitors is still open. The quest for means to avoid them has resulted in studies leading to the development of second-generation TNF inhibitors. For example, specific TACE inhibitors, which are believed to block formation of solTNF and thereby decrease the risk of tuberculosis infection and autoimmune reactions, are currently in pre-clinical and clinical phase II trials [61].

Conclusions

Due to the unique role of TNF in the initiation and maintenance of inflammatory reactions, TNF inhibitors constitute an important and promising group of modern drugs with prospects of implementation in various diseases whose pathogenesis is linked to the immune system. The usage in approved indications, such as rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, ulcerative colitis and plaque psoriasis, has confirmed their efficacy. Although the therapy is associated with undesirable effects, the overall safety profile of this class should be considered positive. There are many preclinical and clinical data showing that TNF inhibitors may also be beneficial in many other inflammatory diseases, including CNS disorders. Cases of successful or non-successful usage of TNF inhibitors in a variety of off-label indications, described in Table IV, indicate the potential directions of future studies. Presently, based only on current data, it is extremely difficult to specify potential new indications. Each disease with an established role of TNF in the pathology may be a target. Based on pre-clinical research, showing the critical role of TNF in the trigeminal system [62], temporomandibular disorder or trigeminal neuralgia might be of interest for future clinical trials on efficacy of TNF inhibitors.

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References

1. Pennica D, Nedwin GE, Hayflick JS, et al. Human tumor necrosis factor: precursor structure, expression and homology to lymphotoxin. Nature 1984; 312: 724-9.
2. Pappa S, Hatzistilianou M, Kouvatsi A, et al. Tumour necrosis factor gene polymorphisms and migraine in Greek children. Arch Med Sci 2010; 6: 430-7.
3. Mielczarek-Palacz A, Kondera-Anasz Z, Sikora J. Higher serum levels of tumour necrosis factor and its soluble receptors are associated with ovarian tumours. Arch Med Sci 2012; 8: 848-53.
4. Yildiz Y, Yayllm-Eraltan I, Arikan S, Ergen A, Küçücük S, Isbir T. Is there any correlation between TNF-related apoptosis-inducing ligand (TRAIL) genetic variants and breast cancer? Arch Med Sci 2010; 6: 932-6.
5. Hayes AJ, Neuhaus SJ, Clark MA, Thomas JM. Isolated limb perfusion with melphan and tumor necrosis factor for advanced melanoma and soft- tisssue sarkoma. Ann Surg Oncol 2007; 14: 230-8.
6. http://www.emea.europa.eu/docs/en_GB/document_library/EPAR__Scientific_Discussion/human/000206/WC500052375.pdf
7. No authors listed. Biologic drugs set to top 2012 sales. Nature Medicine 2012; 18: 636.
8. Alexopoulou L, Kranidioti K, Xanthoulea S, et al. Transbembrane TNF protects mutant mice against intracellular bacterial infections, chronic inflammation and autoimmunity. Eur J Immunol 2006; 36: 2768-80.
9. Tansey MG, Szymkowski DE. The TNF superfamily in 2009: new pathways, new indications, and new drugs. Drug Discov Today 2009; 14: 1082-8.
10. Buks J, Wilczak M, Rzymski P, Opala T. Do soluble p55 and p75 TNF- receptor concentrations play a role in women with primary sterility? Arch Med Sci 2010; 6: 264-9.
11. Grell M. Tumor necrosis factor (TNF) receptors in cellular signaling of soluble and membrane-expressed TNF. J Inflamm 1995; 47: 8-17.
12. Grell M, Wajant H, Zimmermann G, Scheurich P. The type I receptor (CD 120a) is the high-affinity receptor for soluble tumor necrosis factor. Proc Natl Acad Sci USA 1998; 95: 570-5.
13. Naude PJW, den Boer JA, Luiten PG, Eisel LM. Tumor necrosis factor receptor cross-talk. FEBS J 2011; 278: 888-98.
14. Kafrouni MI, Brown GR, Thiele DL. The role of TNF-TNFR2 interactions in generation of CTL responses and clearance of hepatic adenowirus infection. J Leukoc Biol 2003; 74: 564-71.
15. Tracey D, Klareskog L, Sasso EH, Salfeld JG, Tak PP. Tumor necrosis factor antagonist mechanism of action: a comprehensive review. Pharmacol Therap 2008; 117: 244-79.
16. Mitoma H, Horiuchi T, Tsukamoto H, et al. Mechanisms for cytotoxic effects of anti-tumor necrosis factor agents on transmembrane tumor necrosis factor-expressing cells. Arth Rheum 2008; 58: 1248-57.
17. Feldmann M, Maini RN. Anti-TNF therapy from rationale to standard of care: what lesson has it taught us? J Immunol 2010; 185: 791-4.
18. Prajapati R, Plant D, Barton A. Genetic and genomic predictors of anti-TNF response. Pharmacogenomics 2011; 12: 1571-85.
19. Maneiro JR, Salgado E, Gomez-Reino JJ, Carmona L. Efficacy and safety of TNF antagonists in sarcoidosis: data from the Spanish registry of biologics BIOBADASER and a systematic review. Semin Arthitis Rheum 2012; 42: 89-103.
20. Utz JP, Limper AH, Kalra S, et al. Etanercept for the treatment of stage II and III progressive pulmonary sarcoidosis. Chest 2003; 124: 177-85.
21. Tong D, Manolios N, Howe G, Spencer D. New onset sarcoid-like granulomatosis developing during anti-TNF therapy: an under-recognised complication. Int Med J 2012; 42: 89-94.
22. Rifkin LM, Birnbaum AD, Goldstein DA. TNF inhibition for ophtalmic indications: current status and outlook. BioDrugs 2013; 27: 347-57.

23. Karampetsou MP, Liossis SNC, Sfikakis PP. TNF antagonists beyond approved indications: stories of success and prospects for the future. QJMed 2010; 103: 917-28.
24. Sfikakis PP, Grigoropoulos V, Emfietzoglou I, et al. Infliximab for diabetic macular edema refractory to laser photocoagulation: a randomized, double-blind, placebo-controlled, crossover, 32-week study. Diabetes Care 2010; 33: 1523-8.
25. Haslund P, Lee RA, Jemec GB. Treatment of hidradenitis suppurativa with tumor necrosis factor inhibitors. Acta Derm Venerol 2009; 89: 595-600.
26. Patel R, Cafardi JM, Patel N, Sami N, Cafardi JA. Tumor necrosis factor biologics beyond psoriasis in dermatology. Expert Opin Biol Ther 2011; 11: 1341-59.
27. Wolbink GJ, Vis M, Lems W, et al. Development of antiinfliximab antibodies and relationship to clinical response in patients with rheumatoid arthritis. Arthritis Rheum 2006; 54: 711-5.
28. Singh JA, Wells GA, Christensen R, et al. Adverse effects of biologics: a network meta-analysis and Cochrane overview. Cochrane Database Syst Rev 2011; 2: CD008794.
29. Wolfe F, Michaud K, Anderson J, Urbansky K. Tuberculosis infection in patients with rheumatoid arthritis and the effect of infliximab therapy. Arthritis Rheum 2004; 50: 372-9.
30. Brassard P, Kezouh A, Suissa S. Antirheumatic drugs and the risk of tuberculosis. Clin Infect Dis 2006; 43: 717-22.
31. Tubach F, Salmon D, Ravaud P, et al. Risk of tuberculosis is higher with anti-tumor necrosis factor monoclonal antibody therapy than with soluble tumor necrosis factor receptor therapy. Arth Rheum 2009; 60: 1884-94.
32. Strangfeld A, Listing J, Herzer P, et al. Risk of herpes zoster in patients with rheumatoid arthritis treated with anti-TNF-alpha agents. JAMA 2009; 301: 737-44.
33. Balkwill F. Tumor necrosis factor and cancer. Nat Rev Cancer 2009; 9: 361-71.
34. Balkwill F, Mantovani A. Cancer and inflammation: implications for pharmacology and therapeutics. Clin Pharmacol Ther 2010; 87: 401-6.
35. Rodgers M, Epstein D, Bojke L, et al. Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis: a systematic review and economic evaluation. Health Technol Assess 2011; 15: 1-329.
36. Baecklund E, Ekbom A, Sparen P, Feltelius N, Klareskog L. Disease activity and risk of lymphoma in patients with rheumatoid arthritis: nested case-control study. BMJ 1998; 317: 180-1.
37. Askling J, Fahrbach K, Nordstrom B, Ross S, Schmid CH, Symmons D. Cancer risk with tumor necrosis factor alpha (TNF) inhibitors: meta-analysis of randomized controlled trials of adalimumab, etanercept, and infliximab using patient level data. Pharmacoepidemiol Drug Saf 2011; 20: 119-30.
38. Ruiz Garcia V, Jobanputra P, Burls A, et al. Certolizumab pegol (CDP870) for rheumatoid arthritis in adults. Cochrane Database Syst Rev 2011; 2: CD007649
39. Singh JA, Noorbaloochi S, Singh G. Golimumab for rheumatoid arthritis. Cochrane Database Syst Rev 2010; 1: CD008341.
40. Moulis G, Sommet A, Bene J, et al. Cancer risk of anti-TNF at recommended doses in adult rheumatoid arthritis: a meta-analysis with intention to treat and per protocol analyses. PLOS One 2012; 7: 1-7.
41. Moulis G, Sommet A, Lapeyre-Mestre M. Mortality rates among patients with rheumatoid arthritis treated with tumor necrosis factor inhibitors: comment on the article by Simard et al. Arthitis Rheum 2013; 65: 1670-1.
42. Mariette X, Matucci-Cerinic M, Pavelka K, et al. Malignancies associated with tumor necrosis factor inhibitors in registries and prospective observational studies: a systematic review and meta-analysis. Ann Rheum Dis 2011; 70: 1895-904.
43. Sharief MK, Hentges R. Association between tumor necrosis factor-alpha and disease progression in patients with multiple sclerosis. N Eng J Med 1991; 325: 467-72.
44. Hofman FM, Hinton DR, Johnson K, Merrill JE. Tumor necrosis factor identified in multiple sclerosis brain. J Exp Med 1989; 170: 607-12.
45. Rieckmann P, Albrecht M, Kitze B, et al. Tumor necrosis factor messenger RNA expression in patients with relapsing-remmiting multiple sclerosis is associated with disease activity. Ann Neurol 1995; 37: 82-8.
46. Rieckmann P, Albrech M, Kitze B, et al. Cytokine mRNA levels in mononuclear blood cells from patients with multiple sclerosis. Neurology 1994; 44: 1523-6.
47. Arnason BG. TNF neutralization in MS: results of a randomized placebo-controlled multicenter study. Neurology 1999; 53: 457-65.
48. Schiff MH, Burmester GR, Kent JD, et al. Safety analyses of adalimumab (HUMIRA) in global clinical trials and US postmarketing surveillance of patients with rheumatoid arthritis. Ann Rheum Dis 2006; 65: 889-94.
49. Schaible TF. Long term safety of infliximab. Can J Gastroenterol 2000; 14: 29-32.
50. Aringer M, Smolen JS. Therapeutic blockade of TNF in patients with SLE-promising or crazy? Autoimmun Rev 2012; 11: 321-5.
51. Bene J, Moulis G, Auffret M, Fessier C, Lefevre G, Gautier S. Tumor necrosis factor antagonists and alopecia: a case/non case in a Nationwide Pharmacovigilance Database. Arthitis Rheum 2012; 64: S788.
52. Harrison MJ, Dixon WG, Watson KD, et al. Rates of new-onset psoriasis in patients with rheumatoid arthritis receiving anti-tumour necrosis factor alpha therapy: results from the British Society for Rheumatology Biologics Register. Ann Rheum Dis 2009; 68: 209-15.
53. Setoguchi S, Schneeweiss S, Avorn J, et al. Tumor necrosis factor-(alpha) antagonist use and heart failure in elderly patients with rheumatoid arthritis. Am Heart J 2008; 156: 336-41.
54. Curtis JR, Kramer JM, Martin C, et al. Heart failure among younger rheumatoid arthritis and Crohn's patients exposed to TNF-alpha antagonists. Rheumatology 2007; 46: 1688-93.
55. Katz JA, Antoni C, Keenan GF, Smith DE, Jacobs SJ, Lichtenstein GR. Outcome of pregnancy in women receiving infliximab for the treatment of Crohn's disease and rheumatoid arthritis. Am J Gastroenterol 2004; 99: 2385-92.
56. Yaser AM, Kuriya B, Orozco C, Cush JJ, Keystone EC. Can tumor necrosis factor inhibitors be safely used in pregnancy? J Rheumatol 2010; 37: 9-17.
57. Verstappen SMM, King Y, Watson KD, Symmons DPM, Hyrich KL. Anti-TNF therapies and pregnancy: outcome of 130 pregnancies in the British Society for Rheumatology Biologics Register. Ann Rheum Dis 2011; 70: 823-6.
58. Hallenbeck JM. The many faces of tumor necrosis factor in Stoke. Nat Med 2002; 8: 1363-8.
59. Mogi M, Harada M, Riederer P, Narabayashi H, Fujita K, Nagatsu T. Tumor necrosis factor alpha increases both in the brain and in the cerebrospinal fluid form parkinsonian patients. Neurosci Lett 1994; 165: 208-10.
60. Mehlhorn G, Hollborn M, Schliebs R. Induction of cytokines in glial cells surrounding cortical beta-amyloid

plaques in transgenic Tg2576 mice with Alzheimer pathology. Int J Dev Neurosci 2000; 18: 423-31.
61. Moss ML, Sklair-Tavron L, Nudelmann R. Drug insight: tumor necrosis factor- converting enzyme as a pharmaceutical target for rheumatoid arthritis. Nat Clin Pract Rheumatol 2008; 4: 300-9.
62. Bałkowiec-Iskra E, Vermehren-Schmaedick A, Balkowiec A. Tumor necrosis factor-alpha increases brain-derived neurotrophic factor expression in trigeminal ganglion neurons in an activity-dependent manner. Neuroscience 2011; 180: 322-33.
63. Biologic drugs set to top 2012 sales. Nat Med 2012; 18: 636.
64. Karampetsou MP, Liossis SNC, Sfikakis PP. TNF antagonists beyond approved indications: stories of success and prospects for the future. QJM 2010; 103: 917-28.
65. Patel R, Cafardi JM, Patel N, Sami N, Cafardi JA. Tumor necrosis factor biologics beyond psoriasis in dermatology. Expert Opin Biol Ther 2011; 11: 1341-59.