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Review

# Anti-TNF therapy: Safety aspects of taking the risk

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ABSTRACT

Rheumatoid arthritis (RA) therapy has been revolutionized in recent years following the introduction of three main anti-tumor necrosis factor-alpha inhibitors (anti-TNF) agents, infliximab, adalimumab and etanercept. Evidence in the literature indicates that patients treated with anti-TNF agents are at increased risk for bacterial infections, but it is not clear if this is a result of the treatment or of disease severity. The treatment has been recognized as a clear risk factor for reactivation of latent TB infections.

So far, observational studies have not indicated any increased overall risk of cancer in RA patients treated with anti-TNF. The overall risk of lymphoma in these patients does not appear to differ greatly from that recorded among untreated patients, but rather is associated with the degree of disease activity rather than the type of therapy.

There is a consensus in the literature that the likelihood of drug survival with infliximab is inferior to both adalimumab and etanercept, mostly due to increased risk of infection or allergic reactions. Due to the lack of head to head studies, there is no agreement as to which agent has the highest rates of treatment response and disease remission.



**Contents**



## 1. Introduction

The prognosis and well being of patients with rheumatoid arthritis (RA) have markedly improved over the last few decades due to prompt diagnosis, the systematic introduction of disease-modifying anti-rheumatic drugs (DMARDs) at an early stage of the disease, the use of DMARD combinations, and the availability of more effective anti-rheumatic agents [1–7].

The development of biologic agents during the last decade and in particular TNF alpha inhibitors (anti-TNF) represents a major breakthrough for the treatment of moderate to severe forms of RA. Until now, valid safety data has been obtained from the commercial randomized controlled trials (RCTs) and from post-marketing primarily national patient registries, which are based primarily on the three main anti-TNF drugs; infliximab, a chimeric (human/murine) IgG1 monoclonal antibody directed against TNF; adalimumab, a fully humanized IgG1 monoclonal antibody that inhibits TNF; and etanercept, a recombinant fusion protein that consists of the soluble TNF receptor (p75) linked to the Fc portion of human IgG1. However, there are growing efficacy and safety data regarding the two new commercially available agents certolizumab pegol (Cimzia, UCB)

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a human anti-TNF-alpha antibody Fab' fragment that is chemically linked to polyethylene glycol and golimumab, a human IgG1 kappa monoclonal antibody specific for human TNF-alpha that neutralizes TNF-alpha activity (Symponi, Centocor).

Similar to most active therapies, highly effective interventions raise concerns about adverse effects. Conflicting data have been published on increased rates of infections and malignancies associated with anti-TNF agents. The treatment response and remission and drug survival rates concerning this advancing mode of therapy are still under continuous investigation [8,9].

This review focuses on recent publications that evaluate the association between anti-TNF therapy and infection, malignancy and drug survival rates, in order to assess the risks of this modern mode of therapy.

## 2. Infections

The issue of anti-TNF therapy and the possibility of associated risks for infections are in debate in the literature [10]. There is mounting evidence from RCTs as well as from observational cohort studies, that patients treated with anti-TNF agents are at increased risk of bacterial infections compared to patients treated with DMARDs, especially early in the course of treatment. Curtis et al. [8] showed that over a 20-month follow-up period , the multi-variable adjusted risk of hospitalization with physician-confirmed definitive bacterial infection was about two-fold higher overall, and four-fold higher in the first six months among patients receiving anti-TNF therapy versus those receiving methotrexate (MTX) alone. Nevertheless, confounding factors must be taken in account given the fact that there is a difference in disease severity between those treated and those not treated with anti-TNF. Since severe, active disease is a criterion for treatment, patients receiving anti-TNF therapy may be more likely to be admitted to the hospital if they have an infection than are patients treated with DMARDs [10].

By going over the publications dealing with infection risks of anti-TNF treated patients Askling and Dixon [11] found out that it is highest within the first few months after therapy initiation and declines thereafter. This variation in risk is probably explained by a combination of factors. First, there will be a number of patients who are at higher baseline risk. When these individuals develop an infection, they will stop their drug and no longer contribute to the anti-TNF cohort. This results in a depletion of susceptible individuals (a healthy user effect), and so reduces the apparent risk of the drug among those who continue therapy. Additionally, there may be a true time-dependent shift in the drug safety profile. A persistent blockade of one cytokine pathway may lead to up-regulation of other immune-signaling pathways that compensate for the lack of TNF. Also as patients become established on anti-TNF therapy, their RA becomes better controlled, their dose of concomitant corticosteroids is reduced, and they become more mobile and less vulnerable to infections [12].

Among patients treated with anti-TNF, the most common infections are bacterial and viral [13] and the most common site organs are the respiratory system (including pneumonia), cutaneous and soft tissues and the urinary tract [14–17]. According to Dixon et al. [9,10], there is a four-fold increased risk of skin and soft tissue infections in anti-TNF treated patients, suggesting an important physiological role of TNF in host defense of the skin and soft tissues beyond that in other tissues.

While TNF is a central cytokine in the synovial inflammation of RA, it also has an important role in the host defense mechanism against intra-cellular bacterial infections [18–20]. TNF blockade in RA patients, therefore, has the potential to lead to an increased rate of those types of infections. Dixon et al. [10] could not provide any conclusive comments regarding non-Mycobacterial intracellular infections due to the small number of patients in their registry. However, such infections have previously been reported to occur in RA patients treated with anti-TNF. It also raises issues of public health and primary prevention regarding *Listeria* (foods made from unpasteurized milk), and *Salmonella* (undercooked eggs, meat) infections. Hence, advising patients to avoid high-risk foods at initiation of anti-TNF therapy may reduce the incidence of these emerging infections.

In contrast, results from many short-term RCTs of selected RA patients suggest that TNF antagonists increase the risk of infection minimally, if at all [10,21–24]. Reports have shown that the incidence of serious infections was not increased in anti-TNF treated patients compared with the DMARD-treated cohort. Indeed, mortality related to serious infections may have been reduced in the anti-TNF cohort. It is possible that this represents a genuine protective effect, since TNF plays a central role in the pathogenesis of inflammation and sepsis. Alternatively, as mentioned earlier, patients receiving anti-TNF therapy may be more likely to be admitted to the hospital if they have an infection than are DMARD-treated patients, resulting in a lower mortality rate [9,10].

TNF-alpha has a central role in the initial host response to infection. In tuberculosis (TB), it results in macrophage activation, cell recruitment, granuloma formation, and maintenance of granuloma integrity. Treatment with anti-TNF has been recognized as a risk factor for active TB in patients with immune-mediated inflammatory diseases, including RA, ankylosing spondylitis (AS), Crohn's disease, psoriatic arthritis, and psoriasis [8,20,25–29]. Most cases of TB develop soon after treatment initiation and correspond to reactivation of a latent TB infection [20,27].

Treatment with all three available TNF antagonists has been associated with an increased incidence of TB. However, there may be a difference between drugs in the incidence of TB. Tubach et al. [30] investigated 69 cases of TB (40 with RA) collected over three years that clearly demonstrated a difference in the risk of TB between patients receiving anti-TNF mAb (infliximab and adalimumab) therapy and those receiving sTNFR (etanercept). They observed a higher risk for patients receiving anti-TNF mAb therapy than for those receiving sTNFR, with a 7 to 17-fold difference in risk. In some studies, it appears that the risk of TB may be increased in patients treated with infliximab compared to those treated with adalimumab and etanercept; and others showed that the risk of TB attributable to adalimumab was substantially greater than that for etanercept, and similar to the risk attributable to infliximab [30,31].

About 85% of TB in the general population is pulmonary in origin. Estimates of the frequency of extra-pulmonary TB in patients treated with anti-TNF therapy have ranged from 28 to 75%. In addition, there is a greater risk for extra-pulmonary disease with the anti-TNF mAb [20,31].

Herpes zoster, a neurocutaneous disease characterized by a painful vesicular dermatomal rash resulting from reactivation of the Varicella zoster virus (VZV), is one of the most common adverse events reported in clinical trials of anti-TNF agents. Also, patients with RA, systemic lupus erythematosus, or noninflammatory musculoskeletal disorders are at increased risk for herpes zoster compared to the general population [32,33]. In a retrospective study, Smitten et al. [34] analyzed a US claims database and the UK general practitioner database and found adjusted hazard ratios (HRs) of 1.91 (95% CI: 1.8–2.03) and 1.65 (95% CI: 1.57–1.75), respectively, for herpes zoster in patients with RA compared with patients without RA.

Strangfeld et al. [35] analyzed data from the German biologics register RABBIT, which is an ongoing nationwide prospective cohort study that included all patients with RA who started new treatment with either infliximab, adalimumab or etanercept, and patients who changed their DMARD treatment after at least one DMARD failure (control group) from January 2001 to December 2006 (5040 patients in total). Significantly higher crude incidence rates of herpes zoster were demonstrated in patients receiving anti-TNF treatment, especially those who were treated with the monoclonal antibodies, infliximab or adalimumab, compared to conventional DMARD