

Infectious Complications with Anti-TNF Therapy in Rheumatic Diseases: A Review

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Abstract: TNF plays a pivotal role not only in the inflammatory process but also in the normal response against pathogens and therefore, interfering with this cytokine may increase the risk of infection. TNF antagonists are commonly used in daily clinical practice for the treatment of inflammatory rheumatic diseases including rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and juvenile idiopathic arthritis since the beginning of 2000. The spectrum of pathogens giving infectious disease in patients under anti-TNF therapies ranges from common bacteria to more opportunistic organisms such as *Mycobacterium tuberculosis*. The infections which were described with TNF inhibitors may have a benign course or may be a serious, life threatening disease, and may be localized or disseminated. These TNF inhibitors related infections were described in the randomized clinical trials, and were then declared to post-marketing surveillance systems and special registries. Tuberculosis (TB) is the most frequent opportunistic infection which has been reported with TNF antagonists and the highest risk appears to be associated with infliximab, and at a lesser extent with etanercept. Currently available data and recent patents on the risk of TB with adalimumab are not sufficient to conclude, but TB cases were also reported with this agent. The description of TB infections with TNF inhibitors led to the establishment of new guidelines for screening patients at high risk of developing TB. These data highlight the importance of post-marketing surveillance and special registries for accurately evaluating the safety profile and particularly the infectious risk of this very effective class of drug in inflammatory rheumatic diseases.

Keywords: TNF antagonists - Tuberculosis - Opportunistic infections - Serious bacterial infections.

INTRODUCTION

Inflammatory rheumatic diseases are chronic and disabling conditions responsible for pain, joint swelling and/or spinal inflammation with specific radiological features and extra-articular manifestations. These diseases chiefly include rheumatoid arthritis (RA), seronegative spondylarthropathies (SpA) such as ankylosing spondylitis (AS), psoriatic arthritis (PsA), and juvenile idiopathic arthritis (JIA). The therapeutic management of these diseases includes symptomatic treatments such as non-steroidal anti-inflammatory drugs, and second line treatments or disease modifying antirheumatic drugs (DMARDs). Many DMARDs have been used for treating RA, producing in general, a mild response, excepting methotrexate or leflunomide which are considered effective in RA. In SpA, second line treatments are restricted to sulfasalazine which is mainly active in patients with peripheral arthritis.

With a better understanding of the pathophysiology of these inflammatory diseases, specific therapeutic targets have emerged. In this sense, it is now well-demonstrated that certain cytokines play a central role in the inflammatory process, namely the pro-inflammatory cytokines TNF, IL-1 and IL-6 [1]. Recently, *N*-Aryl 4-(optionally fused heteroaryl)-2-thiazolamines are reported as TNF and cytokine inhibitors which are helpful for inflammatory disorders, e.g.

arthritis [2-4]. Therefore, therapeutic targets have been introduced in order to neutralize the biological effects of these cytokines [5]. TNF is a pro-inflammatory cytokine that many cells, monocytes and T lymphocytes, produce in response to various stimuli, notably microorganisms. It is also involved in a wide range of physiologic processes, such as apoptosis, cell activation, induction of other inflammatory cytokines, and recruitment of inflammatory cells to sites of infection. TNF also plays a role in cancer immune surveillance [6].

Beside these physiologic roles, TNF have deleterious effects in inflammatory conditions such as RA, SpA, JIA, and also in psoriasis, Crohn's disease and a wide range of systemic diseases (including sarcoidosis and polymyositis) [7]. The knowledge of this important role led to the development of TNF antagonists [8,9]. However, because of the central role of TNF in inflammation and particularly in the normal immune response to pathogens, the question of an infectious risk in TNF antagonist recipients is a relevant issue. Thus, infectious complications have been observed during the clinical trials of these agents and post marketing reports gave also additional data [10]. The spectrum of pathogens that have been associated to anti TNF therapies ranges from common bacteria to more opportunistic organisms such as *Mycobacterium tuberculosis* [11]. The infection may have a benign course or may be a serious, life threatening disease, and the extent of infection may be localized or disseminated. Moreover, it appears that the pattern of infections under TNF blockade therapy involved certain pathogens and that the different TNF blockers are not associated with the same risk of infection.

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The purpose of this review is to provide an overview of the infectious complications observed with the different anti-TNF antagonists. A literature review covering the 2000-2006 period was thus performed including published papers, recent meeting abstracts and recent patents on anti-TNF agents, discussing TNF-associated microbial infections [12].

1- ROLE OF TNF IN HOST DEFENCE

TNF is a cytokine of the TNF superfamily. It is expressed as a transmembrane protein which is cleaved by specific metalloprotease and released as soluble homotrimer. TNF binds to membrane receptor p55 or TNF-RI and p75 or TNF-RII. TNF has a wide range of biologic effects such as cellular activation of cells playing a role in host defence: monocytes/ macrophages, B and T lymphocytes and neutrophils. It activates monocytes/macrophages, autoinduces the production of TNF and other proinflammatory cytokines, induces the chemotaxis and migration of these cells, increases the activities of polymorphonuclear cells (phagocytosis, production of superoxide), induces T and B cell functions, apoptosis of mature T cells and activates cytotoxic T cell invasiveness. It facilitates cell-to-cell communications in the control of invasive infection [5,6,13]. In parallel, TNF has also a major role in granuloma formation, thus explaining the influence of anti-TNF agents in the development of granulomatous diseases such as tuberculosis (TB). Finally, TNF must be considered as a strong macrophage activator and consequently, blocking TNF inhibits macrophage function, leading to impaired defence mechanisms against infections, notably those caused by intracellular organisms.

2- INFECTIONS IN RHEUMATIC DISEASES

Infections are common in subjects with rheumatic diseases [14]. The risk of infection in rheumatic diseases is explained by the use of immunosuppressive drugs, perturbations of immune functions, impairment of general health, disability, comorbidities, denutrition and reduced albumin. Infections such as joint sepsis, skin/soft tissue or pulmonary infections are commonly observed. According to the published studies, results were given as Odd Ratio for the risk of infection or the number of infections per patient-year. Certain studies evaluated the infectious risk in RA, giving variable results. For instance, the occurrence of infections has been evaluated in Mexican RA patients, giving an incidence of new infection of 17/100 patient-years [15]. In another study, the development of infections in RA requiring hospitalisation was evaluated to 3.1/100 patient-years [16]. The rate of infections in a RA cohort was compared with controls and the risk of developing infection was increased in RA with an Odd Ratio of 1.7 [CI: 1.42-2.03], while the Odd Ratio for an infection requiring hospitalisation was 1.59 [CI: 1.28-1.97] [17].

The risk of infection in RA raised the problem of the causative role of DMARDs. Indeed, immunosuppressive agents represent a dominant factor for infection in RA and the specific likelihood of serious infections associated with the different DMARDs used in RA has been previously examined. Methotrexate is one of the most popular and effective agent in RA and is used at low dose, ranging from

7.5 to 20 mg/ week. This low dose is associated with impaired immune function such as cytokine secretion (including TNF), immunoglobulin function, T and B cell immunity as well as neutrophil function. The overall rate of infection has been examined and some authors considered that MTX is associated with an increased frequency of infection, but the results were not significant compared to a population of RA patients without MTX. The Odd Ratio for objective infection in a large cohort of RA patients was 0.96 [CI 0.65-1.45] and thus, the risk of infection in MTX-treated RA patients was considered to be small [18]. However, some opportunistic infections including *Pneumocystis jirovecii (carinii)* Pneumonia, Herpes zoster, Histoplasmosis or Aspergillosis, Tuberculosis have been reported in a limited number of patients under MTX [14].

Infectious complications have also been reported with the use of cyclophosphamide, azathioprine or cyclosporine A, but these infections occurred in patients with severe disease who usually required a combination of immunosuppressive agents [14].

Finally, when considering infections in RA, one must consider the potential risk with the use of corticosteroids. There are evidences suggesting that corticosteroids augment the risk of infection, particularly at high dose. In a meta-analysis, the relative risk of infection in patients under corticosteroids was 1.6 [CI: 1.3-1.9] [19]. However, the overall risk of infection associated with corticosteroids depends on the dose and the duration of treatment.

Taken together, these data suggest that the risk of infection in patients with RA is increased independently of the use of TNF blockers, with an influence of corticosteroids and certain immunosuppressive agents while MTX has been rarely associated with infections.

3- THE AVAILABLE TNF BLOCKERS

They are currently 3 TNF antagonists which are available for the treatment of RA, AS and PsA, JIA, and also psoriasis and Crohn's disease: 2 monoclonal antibodies and a soluble receptor (Table 1) [20]:

- infliximab is a chimeric monoclonal antibody that is 75% human and 25% mouse and consists of the constant region of human IgG1 coupled to the Fv region of high affinity neutralizing murine anti-human TNF antibody. It is given intravenously at week 0, 2, 6 and every 8 weeks. The half-life of the molecule is between 8 and 12 days. It binds to soluble monomers and trimers and membrane-bound forms of TNF with high affinity, specificity, but not to TNF or lymphotoxin. In addition, it is given with concomitant MTX in order to reduce the frequency of auto-antibodies directed against the murine portion of infliximab. Infliximab has been approved in North America and Europe for the treatment of RA, AS and PsA. It is also given in the treatment of Crohn's disease and psoriasis. The delivered dose depends on the underlying disease, 3 or 5 mg/kg (3 mg for RA, 5 mg for AS, Crohn's disease and PsA) [21]

- adalimumab is a fully human IgG1 antibody which has no non human or artificially fused human sequences. It has a half-life of 12- 15 days and is administered subcutaneously at a dosage of 40 mg every 2 weeks. In RA, it may be given

Table 1: Approved TNF Inhibitors in Rheumatic Diseases

Name	Structure	Half-life	Dose and mode of administration	Diseases for which the drug is licensed
Infliximab (REMICADE®)	Chimeric mouse Fv (75%) / Fc IgG1 kappa human (25%) anti-TNF α antibody	8-12 days	3 mg/kg or 5 mg/kg intravenously week 0, 2, 6 and every 8 weeks	- Rheumatoid arthritis - Ankylosing spondylitis - Psoriatic arthritis
Etanercept (ENBREL®)	Fusion protein of 2 p75 TNF receptors (TNF-RII) and Fc fragment of human IgG1	70 hours	25 mg sub-cutaneously twice weekly or 50 mg once weekly	- Rheumatoid arthritis - Ankylosing spondylitis - Psoriatic arthritis - Juvenile chronic arthritis
Adalimumab (HUMIRA®)	Recombinant fully humanized IgG1 antibody	11-14 days	40 mg sub-cutaneously every other week	- Rheumatoid arthritis - Psoriatic arthritis - Ankylosing spondylitis

alone, without concomitant DMARDs or in association with MTX or other DMARDs (leflunomide, sulfasalazine). In the clinical trials, the development of autoantibodies directed against adalimumab was very rare. Adalimumab is licensed for the treatment of RA, PsA and AS [22].

- Etanercept is a fusion protein of 2 p75 soluble receptors linked to the Fc domain of human IgG1. It is administered as subcutaneous injections with a recommended dosage of 25 mg twice weekly or 50 mg once weekly. Etanercept acts as a natural inhibitor of TNF and does not contain animal amino acids, and thus the risk for developing neutralizing antibodies is low. It binds to soluble and membrane bound TNF and TNF. The half life of the molecule is 72 hours. Etanercept has been approved for the treatment of RA, AS, PsA, JIA and psoriasis [23].

4- INFECTIONS ASSOCIATED WITH ANTI-TNF THERAPY IN PATIENTS WITH RHEUMATIC DISEASES

Anti-TNF agents are selectively used for treating autoimmune or inflammatory diseases [24-28]. Indeed, in RA, they gave substantial improvement in signs and symptoms, disability, quality of life and significantly inhibited the progression of joint damage in early and long-standing disease [20]. Similarly in AS and other SpA, TNF dramatically improved spinal symptoms and peripheral arthritis, enthesitis, physical function, quality of life and preliminary data also suggested that radiological progression was slowed down. In the same way, clinical symptoms of PsA were also ameliorated with in parallel, an inhibition of structural damage. It was also demonstrated that etanercept significantly improved JIA [9]. With the development and the use of this new class of drug, an important concern is the safety profile of these agents which determines in concert with their efficacy a risk / benefic ratio [10,11,29,30].

Safety of anti-TNF agents has been well examined and data may be obtained from different sources: large placebo-controlled randomized clinical trials, post-marketing surveillance and long term registries involved in drug safety or national pharmacological-surveillance systems [29-32].

However, there are numerous factors influencing interpretation of these adverse event data. The patients enrolled in clinical trials were selected in order to constitute a homogeneous population and in general, patients did not have comorbid illnesses, high corticosteroid dosage or concomitant immunosuppressive drugs. These clinical trials included small sample size and time to detect unusual adverse events was not sufficient. All these factors introduced a bias and may lead to the constitution of a low risk group which did not reflect a real clinical practice situation [30]. Post-approval data are limited by underreporting. Thus, it has been estimated that less of 5% of serious adverse events were reported to the Food and Drug Administration (FDA) Medwatch program. And the propensity of reports is influenced by seriousness of the adverse event [29]. Finally, national pharmacological vigilance systems are not developed in each country where TNF inhibitors are used and reports of infections to these systems are influenced by epidemiological factors such as the specific background rate of infection. Despite these limitations, data concerning infections with TNF antagonists may be obtained from the FDA and its Medwatch program, from the National Data Bank from rheumatic diseases of the USA, from the BIOBADASER database of Spain, from the Swedish registries and from the French RATIO observatory [33-38].

4-1: Infections Reported during Randomized Clinical Trials

The different TNF antagonists have been evaluated in well and adequately conducted randomized placebo-controlled trials. In each study, adverse events were recorded and rate of common infections was available as well as frequency of serious infections including opportunistic infections. With the 3 TNF blockers were commonly observed infections of the upper respiratory tract, but they were considered to be mild [20].

The ATTRACT trial reported that 44% of patients who received infliximab were treated with antibiotics compared to 35% in the placebo group [39]. Infections were located to the upper respiratory tract, sinus and pharynx. Serious infections (requiring hospitalization) occurred in a similar frequency (without significant difference) between the

infliximab cohort (8%) and the placebo group (6%) and included septicaemia, pneumonia, bronchitis, peritonitis, pyelonephritis, fungal infection, herpes zoster, urinary tract infection, cellulitis and tuberculosis [40].

For etanercept, there was no significant difference in infection rates between patients receiving etanercept and those given placebo. Upper respiratory tract infections were most commonly observed, similarly to infliximab [41,42].

In the ARMADA trial which evaluated the efficacy and safety of adalimumab in a 24 week placebo-controlled trial, comparable numbers of adalimumab-treated patients and placebo-treated patients reported infections: 1.55 vs 1.38 patient-years. The most common infections were rhinitis, upper respiratory tract infection and flu-syndrome. Two pneumonias (among 209 adalimumab-treated patients) were observed [43].

These data concerned the use of TNF antagonists in RA. In AS and SpA, similar results were obtained with no increased rate of infections in TNF blocker recipients compared to placebo-treated patients. The initial placebo-controlled trial evaluating the efficacy of infliximab in AS reported infections at a frequency of 35% in the infliximab group compared to 51 % in the placebo group. Upper respiratory infections were the most common infections. Among 34 patients under infliximab, one developed tuberculosis [44]. Etanercept in AS was also well tolerated with minor infections involving the upper respiratory tract, without difference between placebo and etanercept treated patients [45,46]. In PsA, similar results were observed during the clinical trials with etanercept or infliximab. The first published study corresponded to etanercept treatment and during this randomized trial, no PsA patients developed infections that required hospitalisations or intravenous antibiotics [47]. In the IMPACT study which evaluated the efficacy of infliximab in PsA, similar data were obtained without increased rate of infection in the infliximab group [48]. In JIA, etanercept was in general well tolerated by pediatric patients and clinical trials did not evidenced a higher rate of infections in etanercept treated patients compared to those receiving placebo [49].

Taken together, these clinical trials did not evidence a higher rate of infections in patients treated by TNF antagonist, whatever the drug or the underlying disease was. Of note, patients with RA received concomitant corticosteroid therapy (at a low dose 10 mg daily) and MTX weekly.

4-2: Post Marketing Reported Infections

Numerous post licensure cases or small series of serious bacterial or opportunistic infections associated with TNF antagonists were reported [31,32]. Bacterial infections involved *Salmonella typhimurium*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Moxarella catarrhalis* and *Legionella pneumophila*. Fatal sepsis and pneumococcal necrotizing fasciitis in patients receiving etanercept have been described [31]. One study in Switzerland compared the rate of serious bacterial infections in RA patients treated with TNF antagonists to the same patients treated with conventional DMARDs before introducing biologics and calculated an incidence of 0.181 per year for TNF

inhibitors and 0.008 per year for DMARDs [50]. In this series, CRP levels appeared to be a sensitive marker of infections, since this marker rose before the infection was apparent. In Belgium, the systematic follow-up of a cohort of 107 patients with SpA treated with infliximab showed 8 (7%) severe infections including 3 retropharyngeal abscesses, indicative of an infection incidence of 4.2/100 patient years [51]. In a regional cohort study from France, severe pyogenic infections occurred in 6% of patients taking infliximab. The identifying factors for these infections were older age and high dose glucocorticosteroid therapy [52].

The French observatory for bacterial and opportunistic infections (RATIO) recorded 57 bacterial infections during a 3 year-period, including 30 septic arthritis, 24 septicaemia and 3 fasciitis [37,38]. In addition, an increased frequency of *Legionella pneumophila* infections was observed in France, independently of the underlying disease and the concomitant treatments [53]. Listeriosis has also been reported [54].

Beside these bacterial infections, opportunistic infections were reported with the use of TNF antagonists, caused by various viruses, fungi, parasites and mycobacterial agents [31,32,55,56]. Tuberculosis infection under anti TNF therapy is developed below. Cases described included infections associated with *Histoplasmosis*, *Coccidioidomycosis*, *Pneumocystis jiroveci (carinii)*, *Cryptococcus neoformans*, *Toxoplasma sp*, *Aspergillus sp*, *Candida sp*, *Nocardia sp*, *Sporothrix sp*, Herpes zoster, Varicella and Cytomegalovirus [31,57-60]. Data collected through the adverse event reporting system of the FDA for 1998 to 2002 included 716 granulomatous infections associated with infliximab and etanercept [61]. Tuberculosis was the main infection, but a wide range of other granulomatous infections were reported including 42 Histoplasmosis, 38 Listeriosis, 39 Aspergillosis, 19 Cryptococcosis, 11 Nocardiosis, and other cases caused by *Candida sp* [N= 46], *Toxoplasma sp* [N= 5], *Brucella sp* [N=2], *Bartonella sp* [N= 1], *Leishmania sp* [N=1]. In this report, Candidiasis, Coccidioidomycosis, Histoplasmosis, Listeriosis, Nocardiosis and Infections due to non tuberculous mycobacteria were reported with significantly greater frequency (3.25 fold) among infliximab treated patients.

However, these infections are related to the specific epidemiology and geographic localization of the causative agents and thus, for instance, Histoplasmosis or Coccidioidomycosis were mainly observed in North America. In France, only 3 pneumocystosis, 2 nocardiosis, 4 systemic fungal infections were declared to the RATIO registry [37].

Of note, all these infections were mainly described in patients with RA (or Crohn's disease), but patients with SpA or JIA are also susceptible to develop bacterial or opportunistic infections. In fact, the frequency of declared infections in patients with SpA or JIA appears lower than in patients with RA, but it must be reminded that TNF antagonists were first approved for the treatment of RA (and Crohn's disease for infliximab) and their use was then extended to the other diseases. In addition, patients with SpA (and certain subsets of JIA) do not required corticosteroids and/or immunosuppressive agents, treatments which can favour infections (see above).

4-3: Information from National Databases or Special Registries: Tuberculosis and Anti-TNF Antagonists.

The most important concern with anti-TNF therapy is the risk of TB [55]. In a randomized phase III trial comparing infliximab with placebo treatment in RA, only 1 case of TB was reported [39]. However, in 2001 after drug approval, the alert was given by the report of 70 cases of TB with infliximab treatment [62]. Therefore, after this report, evaluation of the risk of developing TB with infliximab and other TNF antagonists was required, and specific recommendations emerged with a careful screening for latent TB.

Indeed, TNF plays a central role in host response to *Mycobacterium tuberculosis* [63]. It stimulates macrophage/monocyte functions. TNF is involved in the recruitment of inflammatory cells at the site of infection by stimulating the production of chemokines (CCL-2, 3, 4, 5 and 8) by macrophages and T cells and inducing the expression of vascular adhesion molecules. TNF is a cytokine which strongly activates macrophages, thereby stimulating phagocytosis activity and the killing of viable mycobacteria. However, one main role for TNF during mycobacterial infection is granuloma formation which allows the containment of the mycobacteria and thereby, the prevention of its dissemination [64]. Experimental data highlighted the importance of TNF for the granuloma: in TNF deficient mice infected with *Mycobacterium tuberculosis*, granuloma formation is delayed and poorly organized, which leads to insufficient bacterial containment. The p55 TNF receptor or TNF-RI is important for granuloma formation and for the susceptibility to intracellular infection as suggested by animal models while TNF-RII seems to have a lesser role [64].

Clinical use of TNF antagonists has been associated with the description of reactivation of recent or acquired TB (Table 2).

- Still, in October 2001, Keane *et al.* reported 70 cases of TB in patients who had received infliximab for RA, Crohn's disease or other conditions [62]. These cases were declared through the MedWatch program of the FDA. The main features of these TB were a high frequency of extra-pulmonary diseases (40/70)(with lymph node, peritoneal, pleural, enteric, bone, genital or bladder disease), a significant proportion of disseminated diseases (17/70) and a short interval from the beginning of treatment until the development and diagnosis of TB (median: 12 weeks). Twelve patients died. The unusual presentation of these TB cases may explain why the diagnosis was difficult. Of note, most of the reports were from countries with a low incidence of TB. On the basis of this report, the estimated rate of TB among patients with RA who received infliximab was 24.4 cases/100,000 patient per year compared to 6.2 cases /100,000 per year as the background rate of TB in RA patients in the USA. This report was the first medical alert about the risk of TB with the use of TNF inhibitors and therefore, the manufacturers of infliximab modified its package insert and add a warning black box (high-level risk of TB and other opportunistic infections). In addition, specific recommendations for screening patients prior to TNF antagonist treatment were developed.

Since this first series of TB observed during infliximab therapy, there were 4 other TB reports associated with the different TNF blockers coming from distinct geographic area, North America or Europe:

- Granulomatous infectious diseases associated with TNF antagonists were largely collected through the same Adverse Event Reporting System of the US FDA between 1998 and 2002 [61]. This is the largest report of TB and other granulomatous infections (see above) observed with TNF antagonists. Tuberculosis was the most frequently reported disease, with the description of 335 TB in the infliximab group, 39 TB in the etanercept group, giving an incidence rate of 144 and 35 per 100,000 infliximab- treated and etanercept- treated patients, respectively.
- The Spanish Society of Rheumatology collected all the cases of adverse events under TNF inhibitors in a special data base (BIOBADASER) [35]. All the events were collected during the period ranging from January 2000 to February 2002. Seventeen cases of TB were declared in patients treated with infliximab among 1,540 patients receiving infliximab or etanercept (the 2 agents which were available at the beginning of the registry). Most of these TB were diagnosed within 3 months of treatment initiation. Extra-pulmonary disease was found in 65% cases. The calculated risk ratio of TB associated with infliximab in RA patients compared to the background rate in the Spanish population was 90.1 (95% CI: 58.8-146.0) in the year 2000 and 53.0 (95% CI: 34.5-89.0) in the year 2001. By contrast, the estimated risk ratio of TB in patients who did not receive TNF inhibitors was 4.13 (95% CI: 2.59-6.83) in Spain. The relative risk of TB in infliximab treated RA patients was 19.9 (95% CI: 16.2- 24.8) in 2000 and 11.7 (95%CI: 9.5-14.6) in 2001.
- Another source of information for TB risk with infliximab in the USA is the National Data Bank for rheumatic diseases of Dr Frederick Wolfe [34]. The baseline rate of TB in RA prior to the introduction of infliximab and the rate of TB in patients receiving infliximab was determined using this important data base. The study was conducted between 1998 and 1999, prior to infliximab use (10,782 RA patients were evaluated) and between 2000 and 2002, after the introduction of infliximab (evaluating 6,460 patients). The rate of TB did not appear to be increased in RA patients who were not receiving infliximab while there were an increase rate of TB under infliximab which was evaluated to 52.5 cases per 100,000 patient-years of exposure (95% CI: 14.3-134.4) (4 cases of TB were reported during the observational period).
- Swedish registries gave also relevant information about TB risk associated with TNF antagonists in RA [36]. Indeed, using data from nationwide and population based registers and surveillance program of TNF antagonists, the relative risk of TB in RA patients and in RA patients under TNF antagonists were calculated. Risks were evaluated between 1999 and 2004. There was an increased risk of TB in patients with RA compared to the general population with a relative risk of 2.0 (95% CI:

Table 2. Series of Tuberculosis Cases Occurring with TNF Inhibitors (Infliximab and Etanercept)

Author (reference)	Date of report (period of surveillance)	Source and country of declaration	Drug associated with tuberculosis	Number of cases	Estimated frequency	Background rate of tuberculosis in rheumatoid arthritis without anti TNF agents
Keane (61)	2001 (1998-2001)	FDA (AERS) USA and Europe	Infliximab	70	24.4 cases / 100,000 patient-years (USA)	6.2 cases / 100,000 patient-years
Gomez-Reino (34)	2003 (2000-2002)	BIOBADASER Spain	Infliximab	17	RR 19.9-11.7	RR 4.3
Wallis (60)	2004 (1998-2002)	FDA (AERS) USA	Infliximab Etanercept	374 (335 with infliximab 39 with etanercept)	Infliximab: 144 / 100,000 patient-years Etanercept: 35 / 100,000 patient-years	5.6 / 100,000 patient-years
Wolfe (33)	2004 (2000-2002)	National Data bank for rheumatic diseases USA	Infliximab	4	52.5 / 100,000 patient-years	6.2 / 100,000 patient-years
Askling (35)	2005 (1999-2004)	Swedish registries Sweden	Infliximab Etanercept	15 (9 with infliximab, 4 with etanercept, 2 with both)	RR: 4.0	RR: 2.0
Tubach (36)	2005 (2001- today)	RATIO France	Not detailed	24	ND	ND

FDA: Food and Drug Administration

BIOBADASER: data base of biological products from the Spanish Society for Rheumatology.

AERS: adverse event reporting system

RR: relative risk

RATIO: registry of opportunistic infections, severe bacterial infections and lymphomas complicating anti TNF therapy.

1.2-3.4), while RA patients treated with TNF antagonists had a 4 fold increased risk of TB (relative risk 4.0; 95% CI: 1.3-12), compared to RA not treated with TNF antagonists. Between 1999 and 2004, 15 cases of TB were reported, 11 with infliximab, 6 with etanercept (2 patients had had both treatment), with a median duration of treatment of 8 months and most patients (67%) had pulmonary disease.

- In France, the RATIO group collected 24 TB between February 2004 and January 2006 in patients treated with TNF antagonists (including a majority of RA patients) which corresponded to an estimated incidence ranging from 53.3 to 67.7 /100,000 [65].

Taken together, these data clearly indicated that TB risk is increased in RA patients receiving TNF antagonists. Most cases were reported with infliximab while only a few cases occurred with etanercept. Tuberculosis has some characteristics in the series reported by Keane *et al.* in 2001, such as extrapulmonary or disseminated diseases, a short interval between beginning of the treatment and TB diagnosis and a severe life-threatening course in some cases [62]. However, these characteristics were not all confirmed by subsequent reports, particularly the time of TNF exposure to develop TB [36]. These discrepancies may be

related to the epidemiology of TB in these different countries. In addition, after the report by Keane *et al.*, recommendations for screening patients on the risk of TB appeared but differed among the countries [66,67]. The short interval between infliximab therapy and the occurrence of TB argue for a mechanism of recent infection or a reactivation of latent TB. However, in most cases, patients did not have a recent history of contact with patients having TB. In contrast to infliximab, the development of TB in etanercept treated patients occurred later after the start of therapy (median 11.5 months), suggesting that patients were being newly infected. It is currently believed that both infliximab and etanercept increase the risk of active TB, although the true risk with infliximab is likely to be higher. The differential mode of action of these 2 agents might explain this difference [68].

- infliximab and etanercept have different pharmacokinetics and pharmacologic properties
- TNF blockade is more complete with infliximab which neutralizes both soluble and membrane bound TNF than etanercept which binds only soluble TNF. Thus, infliximab can activate complement and causes antibody dependent cellular cytotoxicity, which could lyse granuloma macrophages.

- infliximab may induce apoptosis of monocytes.
- infliximab and etanercept target TNF receptors differently: infliximab inhibits both p75 and p55 whereas etanercept leaves at least p75 partially intact. And it has been suggested that TNFR p75 provides protective immunity in TNF deficient mice transgenic for the transmembrane form of TNF .

In the initial reports, all the TB cases were described with the use of infliximab (and a few cases with etanercept). However, there is also a limited number of TB cases associated with adalimumab. In the initial clinical development trials, 8 cases of TB were reported among 477 RA treated patients (1.7%). However, these cases occurred in Europe and before screening measures were implemented [54]. Consequently, a boxed warning about the risk of TB was added to the package insert for adalimumab, similar to that of infliximab. Analysis of post marketing safety of adalimumab after 2 years of approval showed 11 cases of TB in the USA, giving a reporting rate of 0.02 / 100 patient-years [69]. In Europe, this risk has been evaluated to 0.27 patient-years [70]. It must also be reminded that adalimumab came to market after the association between TNF antagonists and TB was established and thus, screening measures for TB were applied since its approval, probably explaining this low rate of TB.

The risk of reactivation of TB from anti-TNF therapy depends on the immunomodulation induced by the treatment but also on the underlying rate of latent TB or risk of previous infection of the population. On the other hand, the rate of latent TB depends on many variables such as age, country of origin, socioeconomic status, ethnicity, travel history to high prevalence-countries [54]. It is thus essential to screen a patient before initiating anti-TNF therapy in order to determine if he belongs to a high risk population. In France, patients with a high risk of TB reactivation were defined by the French agency for health care products (AFSSAPS) and included those with a past history of TB treated before the seventies, those with a skin test giving a wheel of 5 mm (or a blister) or residual chest X ray TB lesion larger than 1 cm³ in size with no proof of eradication treatment [66].

Specific recommendations were given by specific health care agencies in the different countries using TNF antagonists, but these recommendations differed according to the prevalence and epidemiology of TB in each country. The procedure includes a tuberculin skin test (tuberculin 5 UI, 0.1 ml) and published guidelines recommended an induration size equal or more than 5 mm as a threshold for initiating treatment in patients who are considered at risk of developing active TB [66,67]. Persons at high risk include those who had a recent contact with a person with active TB, subjects who travelled in endemic countries, subjects with fibrotic changes seen on chest X ray and those who have significant immunosuppression (for instance corticosteroid treatment > 15 mg prednisone /day). A chest X-ray should also be obtained. Some other points should be examined: detailed interview on the date of *Bacille Calmette-Guérin* (BCG) vaccination (if performed), results of previous tuberculin skin testing, history of contact with patients with active TB, history of staying in countries where TB is

endemic, past history of latent or active TB, whether antituberculous treatment was given, which drugs were used and duration of treatment. If the tuberculin skin test produces a blister, the mycobacteria should be looked for in gastric aspirates and/or sputum collected on 3 consecutive days. One problem with tuberculin skin test is a negative result. In fact, there is a high frequency of anergy in patients with a state of immunodepression including RA, and anergy cannot exclude latent TB infection [31,55,64].

Management of latent TB depends on the different recommendations: isoniazid during 9 months or a combination of isoniazid and rifampicin during 3 months. It is recommended that treatment for latent TB should be started before TNF antagonist is begun, but there are currently no consensus. In France, the agency for health care products recommends to start TNF agent after a minimum of 3 weeks of anti-tuberculosis treatment [66].

Since the introduction of these recommendations and strategies to treat latent TB, the likelihood of active TB in patients treated with TNF antagonists has decreased.

However, active TB may be observed despite these recommendations and specific chemoprophylaxis. For instance, in a retrospective Greek study, 11 patients developed active TB (6 pulmonary and 5 extra-pulmonary TB) among 613 patients with rheumatic diseases who had received anti-TNF agents. All the patients had had specific procedure before initiating TNF inhibitor and when required, chemoprophylaxis with 6 months isoniazid or the combination of isoniazid and rifampicin during 3 months. These TB cases were observed with infliximab and adalimumab [71].

Tuberculosis was mainly reported in patients with RA. However, the other conditions which required TNF antagonists are not protected against mycobacterial and other opportunistic infections. Thus, a limited number of TB were reported in SpA or PsA treated with anti TNF agents, but for these diseases, anti TNF agents were used after approval for RA and therefore, patients were carefully screened for the risk of TB.

There are some particular clinical situations, leading to use TNF blockers with caution:

- a limited number of patients with concomitant hepatitis B or C virus infection has been treated with TNF antagonists. For hepatitis C infection, the administration of anti TNF agents appears to be safe [72], whereas TNF blocking agents increase viral load of hepatitis B virus [73]. Therefore, careful viral screening before starting TNF antagonists is recommended. Patients with human immunodeficiency virus infection should not receive TNF antagonists.
- Vaccination using live vaccine should be avoided for patients under anti-TNF agents. We reported in our centre the case of a patient with RA who had received accidentally BCG vaccine while she was treated by infliximab. This patient was treated with isoniazid during 3 months with a favorable course since she had neither local reaction nor systemic symptoms [74].
- Finally, there are currently no established recommendations about the management of patients under TNF antagonists and requiring a surgical procedure. Some authors

reported no increased risk in this situation [75] while there were data indicating that there was a high complication rate in this situation [76]. Considering the risk of post-operative infections, it is currently recommended to stop the treatment before the surgical procedure and to reintroduce it after a variable period depending on the half-life of the drug.

CURRENT & FUTURE DEVELOPMENTS

A preliminary conclusion about the safety of TNF inhibitors could be that these drugs are double-edged sword since they ameliorate clinical symptoms in inflammatory rheumatic diseases in one hand, but they increase the risk of infections in the other. However, the introduction of TNF antagonists constitutes a major advance for these diseases since they have revolutionized their therapeutic management. The overall safety of these agents appears good and comparable to certain DMARDs. However, with their common utilisation and the growing number of patients receiving these agents, specific adverse events were observed including infections. A wide spectrum of infections has been described in association with anti TNF agents, but opportunistic infections predominate, particularly those caused by intracellular organisms. Tuberculosis is the most frequent granulomatous disease which has been reported, and the highest risk appears to be associated with infliximab, and at a lesser extent with etanercept. Currently available data on the risk of TB with adalimumab are not sufficient to conclude, but TB cases were also reported with this agent. The post marketing surveillance recorded significant cases of TB infection, leading to the establishment of guidelines for screening patients at high risk of developing TB. Besides TB, other opportunistic infections have been linked to TNF antagonists, but also common bacterial or viral infections. Therefore, before initiating TNF antagonists, a complete interview of past medical conditions is required with a special attention for history of severe or opportunistic infections including TB. Physicians should also use their clinical judgement when initiating treatment in patients from region where opportunistic disease like TB is common.

Ongoing surveillance is crucial to accurately define the true incidence of infections under TNF antagonists with a special focus on TB. This is the challenge of pharmacological surveillance systems and special registries which recorded all the new cases of infections as completely as possible. The clinicians have a key role to play in actively contributing to these post marketing surveillance programs.

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