

The risk of tuberculosis in patients treated with TNF antagonists

Expert Rev. Clin. Immunol. 7(3), 329–340 (2011)

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Over the last 12 years, TNF antagonists have been successfully used for the treatment of numerous patients afflicted by chronic inflammatory disorders. However, data from clinical trials and registries have shown that patients treated with these biologics have an increased risk of reactivating latent TB. The fact that TNF plays a role in the immune cell response and, more specifically, in maintenance of granuloma integrity is the accepted grounds for reactivation of TB following inhibition of TNF. Appropriate screening of latent TB and proper management of cases substantially reduces the incidence of active TB. Nevertheless, debate still remains regarding the value of the tuberculin skin test and IFN- γ -release assays as diagnostic tools, and treatment across guidelines and recommendations. This largely reflects differences in background population.

KEYWORDS: adalimumab • ankylosing spondylitis • certolizumab • etanercept • golimumab • granuloma • IGRA • infliximab • isoniazid • latent TB • *Mycobacterium tuberculosis* • rheumatoid arthritis • rifampicin • TB • tuberculin skin test • tumor necrosis factor

TNF is a ubiquitous cytokine involved in mechanisms that form part of the host response to infection and cancer [1]. It also has a critical role in the pathogenesis of chronic inflammatory diseases such as rheumatoid arthritis (RA), psoriasis, psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis and inflammatory bowel disease.

Over the last 12 years, TNF antagonists have been successfully used for the treatment of chronic inflammatory diseases. Noticeably, data from clinical trials and clinical observation show an increased risk of non-opportunistic intracellular infections and opportunistic infections associated with TNF antagonist use, with TB being one of the most difficult to manage [2]. *Mycobacterium tuberculosis* infection is commonplace; the bacteria causes a granulomatous disease, however, most individuals infected with *M. tuberculosis* will never develop TB owing to elimination or containment of the bacteria by host immune mechanisms. The role of TNF in this immune response, particularly against intracellular bacteria and maintenance of the granuloma integrity, explains the mechanism of reactivation of latent granulomatous diseases following the inhibition of TNF [3]. Thus, appropriate screening and management

of latent TB is crucial for patients undergoing TNF antagonists treatment [4]. At present, there is a shortage of evidence to support either the best screening method for latent infection or the best regimen for latent TB. Therefore, clinical decisions are merely supported by expert recommendations such as the recently published Tuberculosis Network European Trials Group (TbNET) consensus statement [5]. The current knowledge of TB disease in patients treated with TNF antagonist will be reviewed in this article.

TNF biology

TNF molecule

TNF has an important role in the immune cell response and inflammatory network. TNF is produced by different cell types including macrophages, T cells, fibroblasts and keratinocytes. TNF production is regulated by different stimuli, and it is released from cells in a soluble form (sTNF) following cleavage from its transmembrane precursor (tmTNF) by the metalloproteinase TNF- α -converting enzyme. Both sTNF and tmTNF are biologically active and ligands of the TNF receptor (TNFR)1 and 2. sTNF preferentially binds TNFR1, and tmTNF to TNFR2. In addition,

tmTNF can function as both ligand and receptor. Different signaling pathways activated by TNFR1, TNFR2 and tmTNF have been described [6].

TNF in inflammatory diseases

The majority of the inflammatory effects of TNF are due to its local effect on the vascular endothelium and endothelial leukocyte interactions [1]. RA is a chronic autoimmune disease, characterized by synovial tissue inflammation. Inflammatory cells including T cells and macrophages are recruited into the synovium, and a number of proinflammatory cytokines such as IL-1, IL-6, TNF and GM-CSF are locally produced. In this scenario, TNF plays a relevant role. Culture cells from patients with RA treated with TNF antibodies downregulate a range of proinflammatory cytokines [7,8]. In murine models of arthritis, inhibition of TNF ameliorates joint disease [9,10]. In another murine model, overexpression of TNF results in the development of arthritis and inflammatory bowel disease [11]. In patients with RA, treatment with TNF antagonists reduces joint inflammation and slows the progression of joint damage [12–14]. Ankylosing spondylitis is an inflammatory arthritis characterized by enthesitis and synovitis. TNF is expressed in the sacroiliac joints of patients with ankylosing spondylitis and elevated serum levels of TNF correlate with disease activity [15,16]. Three TNF antagonists have demonstrated their ability to improve the signs and symptoms of ankylosing spondylitis. Immune-reactive TNF is found in both Crohn's disease and ulcerative colitis bowel mucosa [17]. TNF, TNFR1 and TNFR2 are all upregulated in dermal blood vessels involved in psoriatic skin [18]. Treatment with TNF antagonists is effective for the therapy of psoriasis and psoriatic arthritis, as well as for inflammatory bowel diseases [19–21]. A role for TNF has also been suggested in lung, cardiovascular and CNS inflammatory diseases. Low levels of TNF enhance host defense mechanisms against infection whereas high levels are proinflammatory and promote tissue injury, as occurs in sepsis [6,22].

TNF in intracellular bacterial infection

Alveolar macrophages (AMs) constitute the initial defense against mycobacteria inhaled into the lung (FIGURE 1). Resident AMs phagocytose and kill mycobacteria, which may survive and multiply intracellularly [23]. Persistent infection is contained by recruitment and activation of circulating leukocytes to the site of infection, providing new phagocytes and T cells to lyse infected cells and secrete Th1 cytokines [24,25]. Infection of AM with *M. tuberculosis* induces the release of multiple factors, including the early inflammatory cytokines TNF and IL-1 β , which have autocrine-activating effects and promote recruitment of circulating leukocytes [26–28]. The structure of the granuloma protects against dissemination of mycobacteria. Phagocytosis of infected cells including infected macrophages by new arriving macrophages has recently been proposed as a relevant mechanism of granuloma expansion in TB infection [29]. Matrix metalloproteinases (MMPs) are endopeptidases implicated in tissue remodeling and play a significant role in immune response and granuloma formation [30]. The mycobacterial-secreted protein, 6-kD early secreted antigenic target (ESAT-6), has been proposed as an inducer of MMP-9 in a zebrafish model resulting

in macrophage recruitment for granuloma maturation [29,31]. In this scenario, TNF is a macrophage survival factor that enhances its phagocytic capacity and the killing of intracellular bacteria by reactive oxygen and nitric oxide derivatives [32]. TNF also induces the expression of chemokines that are critical for cell recruitment and vascular adhesion cytokines, thereby allowing the recruitment of immune-competent cells [33,34]. β -chemokines contribute to the innate immune response to *M. tuberculosis* infection, and their diminution could lead to mycobacteria survival [35]. An excess of TNF appears to damage the host in advanced TB disease. In a recent pilot study, etanercept improved the health of HIV-infected patients with TB, presumably by interfering with the negative effect of TNF [36]. This is consistent with the notion that TNF plays a crucial positive role in host defense during primary infection and in maintaining latency, whereas excessive TNF during TB disease is detrimental to the host. This apparent benefit seen with TNF antagonists in TB disease highlights the difference between TB and the sepsis syndrome, where TNF inhibition did not improve outcomes [37]. In humans, therapy with TNF antagonists results in reduction of granulysin-expressing CD8⁺CCR7⁺CD45RA⁺ effector memory T cells, disrupting a component of protective immunity against intracellular bacteria [38]. The modulation of the excessive inflammatory response is also regulated by IFN- γ via apoptosis of effector T cells [39]. TNF is essential for the maintenance of granuloma structure. Neutralization of TNF in a murine model of TB infected with *M. tuberculosis* results in the disintegration of previously formed granulomas [40]. In another murine model infected with *M. tuberculosis* with a disruption in the gene encoding for the 55-kDa TNF receptor, a delay in granuloma formation, as well as lack of epithelioid cells and loose organization of granuloma was found [41]. The TNF-related molecule lymphotoxin- α also contributes to granuloma formation by promoting T-cell migration to the site of infection [42,43]. Therapy with TNF antagonists provides a unique model to study TNF function in humans. Recent work in a nonhuman primate model shows that TNF neutralization prior to *M. tuberculosis* infection induces an aggressive and disseminated disease. In contrast to murine models, no differences in granuloma formation were observed in macaques with TB treated with neutralizing TNF agents compared to TB-infected macaques not treated with neutralizing TNF agents [44]. This independence of granuloma structure from TNF has also been described in the zebrafish model of *Mycobacterium marinum* infection [45].

TNF antagonists

Four antibodies to TNF are currently licensed for clinical use: infliximab, adalimumab, golimumab and certolizumab (TABLE 1) [46]. Infliximab is a chimeric monoclonal antibody composed of a human IgG1 constant region and a murine variable region. It is approved for RA, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, ulcerative colitis and psoriasis. It is administered by intravenous infusion, usually every 4 or 6 weeks. Adalimumab and golimumab are monoclonal humanized antibodies composed of a human IgG1 constant and variable regions. Adalimumab and golimumab are approved for RA, ankylosing spondylitis and psoriatic arthritis. Further indications for adalimumab

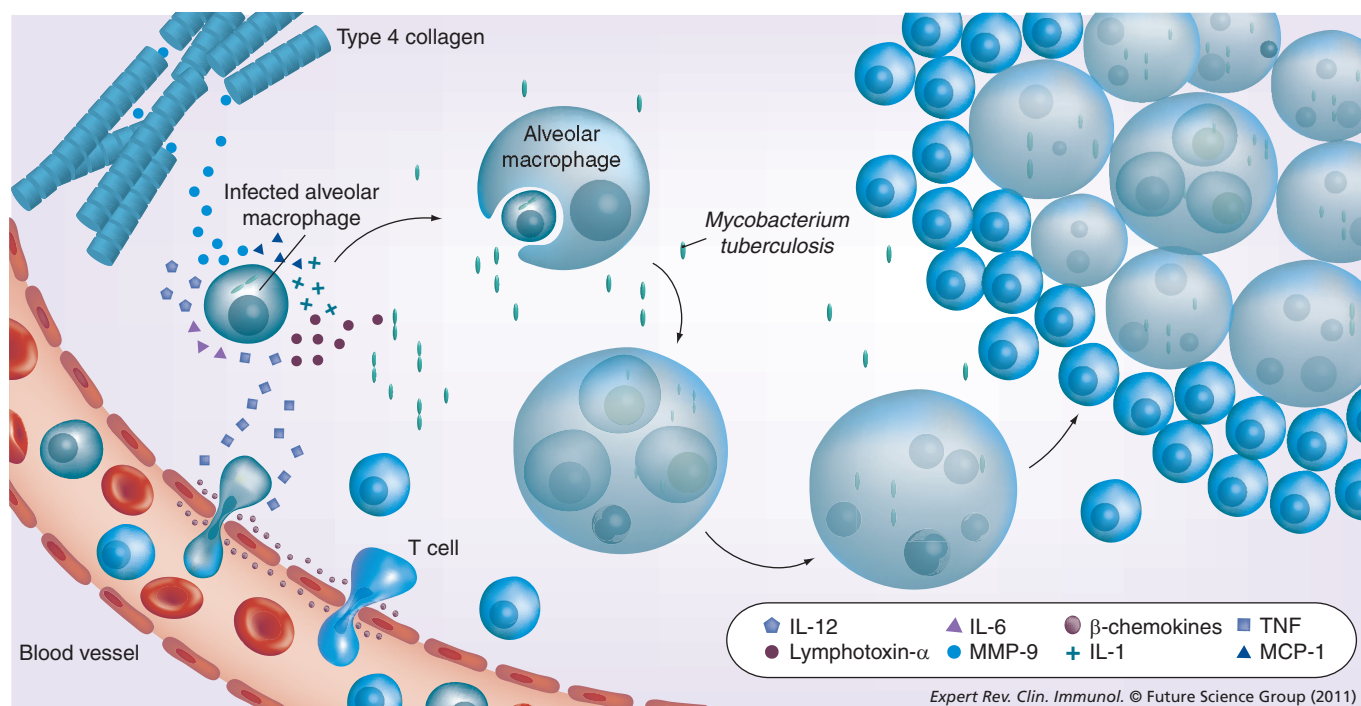


Figure 1. *Mycobacterium tuberculosis*-infected alveolar macrophages secrete IL-1, IL-6, IL-12, TNF and MCP-1. TNF regulates the expression of β-chemokines and recruits cells. Lymphotoxin-α promotes T-cell migration. Phagocytosis of infected macrophages and MMPs promotes granuloma expansion. MCP: Macrophage chemoattractant protein; MMP: Matrix metalloproteinase.

include juvenile idiopathic arthritis, Crohn's disease and psoriasis. Adalimumab and golimumab are administered by subcutaneous injection, every two weeks for adalimumab and monthly for golimumab. Certolizumab is a humanized pegylated Fab fragment. It is approved for the treatment of Crohn's disease and RA. Its administration is also monthly by subcutaneous injection.

Etanercept is the only soluble TNF receptor currently in clinical use. It is comprised of two extracellular domains of the human TNFR2 fused to the Fc fragment of human IgG1. Etanercept can bind TNF and lymphotoxin. It is licensed for the treatment of RA, ankylosing spondylitis, psoriasis, juvenile RA and psoriatic arthritis. Etanercept is ineffective for treatment of granulomatous diseases as Crohn's disease and sarcoidosis. The degree of effectiveness of TNF antagonists in the treatment of granulomatous diseases appears to be consistent with their different capacities to reactivate latent TB. Differences in peak blood levels, sTNF and tmTNF binding affinity and complement-mediated or antibody-dependent cytotoxicity of TNF antagonists have been proposed as main reasons for the disputed dissimilar risk for active TB in patients treated with TNF antagonists [46]. Complement-dependent cytotoxicity triggered by binding of tmTNF by anti-TNF antibodies has been proposed as an explanation for the lack of efficacy of etanercept in granulomatous diseases. Etanercept lacks the CH1 domain where C3 attaches. In addition, it lacks the hinge region in the Fc portion, hindering the access of complement factors because of an excess of stiffness [47]. However, the recent experience with certolizumab questions the relevance of tmTNF binding in granulomatous diseases. Certolizumab has a monovalent structure with

no Fc region, hence it can neither activate complement or cross-link tmTNF, yet this anti-TNF antibody is effective in the treatment of Crohn's disease, and cases of reactivation of TB are reported in clinical trials with certolizumab [48].

Risk of TB in chronic inflammatory conditions treated & not treated with TNF antagonists

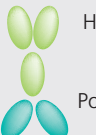
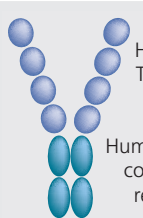
Risk of TB in inflammatory conditions

With the generalized use of TNF antagonists in RA, an increased risk of reactivation of latent TB in RA cohorts was soon reported [49–51]. To quantify the risk attributable to TNF antagonists, studies on the incidence of TB in RA cohorts were performed in different countries. In these studies the incidence rate of TB in RA cohorts was compared with the incidence rate in the general population (TABLE 2). On the whole, a higher susceptibility to development of TB was reported in the RA patients than in the general population. Conversely, in one study in the USA using nonstandardized rates for comparison, TB risk in RA did not differ from background, however, the incidence of TB in the USA is uneven and particularly low in the ethnic group of the study in question, in which 90.9% of enrolled patients were non-Hispanic white [52].

Risk of TB in patients treated with different TNF antagonists

Most of the active TB cases in patients treated with TNF antagonists are due to reactivation of latent TB. Reactivation of latent TB usually occurs concomitantly with initiation of TNF antagonist therapy and has a rapidly progressive course. Extrapulmonary TB

Table 1. Tumor necrosis factor antagonists.

Molecule	Structure	Administration	Approved indications
Infliximab	 Mouse variable region Human IgG1 constant region	Intravenous every 4 or 6 weeks	Rheumatoid arthritis Ankylosing spondylitis Psoriatic arthritis Crohn's disease Ulcerating colitis Psoriasis
Adalimumab	 Human variable region Human IgG1 constant region	Subcutaneous every 2 weeks	Rheumatoid arthritis Ankylosing spondylitis Psoriatic arthritis Juvenile idiopathic arthritis Crohn's disease Psoriasis
Golimumab	 Human variable region Human IgG1 constant region	Subcutaneous every 4 weeks	Rheumatoid arthritis Ankylosing spondylitis Psoriatic arthritis
Certolizumab	 Humanized Fab Polyethylene glycol	Subcutaneous every 2 or 4 weeks	Rheumatoid arthritis Crohn's disease
Etanercept	 Human TNF R2 Human IgG1 constant region	Subcutaneous weekly	Rheumatoid arthritis Ankylosing spondylitis Psoriatic arthritis Juvenile idiopathic arthritis Psoriasis

Data from [201].

is common in these patients. The risk of TB pertaining to the different TNF antagonists has been the subject of several reports (TABLE 3). Interpretation of the results is difficult, not only because of the influence of the ethnic group on the patients and the background TB rate of the study but also the different methods of data gathering. In one study in the US population that used a voluntary notification system of TB cases to the US FDA, the risk of developing TB caused by the first three available TNF antagonists was analyzed. They discovered that the risk attributed to infliximab was more than twofold that of etanercept. TB cases in the infliximab-treated group developed earlier than the etanercept-treated group [53]. Another study in Canadian RA patients based on a pharmacologic prescription database for data recruitment found that the adjusted relative risk of TB was 1.6 for infliximab and 1.2 for etanercept, but only infliximab carried a significantly increased risk for TB compared with background. However, in this analysis, diagnosis of TB was not validated because isoniazid prescription was

patients. However, the rate of latent TB treatment was lower in the infliximab-treated patients [50].

In conclusion, TNF antibodies appear to share a higher risk to TB reactivation than soluble receptors. The greater association of active TB with TNF antibody-treated patients caused by disruption of the granuloma is consistent with the lack of effectiveness of soluble receptors in granulomatous diseases such as sarcoidosis or Crohn's disease [59,60] and the lack of efficacy of soluble receptor TNF etanercept. Differences in the mechanism of action appear to be related to the aforementioned risk of TB development as discussed earlier [46].

Diagnosis of latent TB

Treatment of latent TB is the best option to avoid active TB, but requires a correct diagnosis [16]. *M. tuberculosis* bacilli are difficult to identify in patients with latent TB. Detection of an adaptive type I cellular immune response strongly induced by *M. tuberculosis* is the current diagnostic method to detect latent TB. There

considered the indicator of active TB [54,55]. A Spanish study where TB rates were estimated only after the establishment of recommendations to prevent reactivation of latent TB did not find a significantly different risk posed by three antagonists [49]. The values of incidence rate are shown in TABLE 3. In the French registry (Registry of Infections and Lymphoma in Patients Treated With TNF- α Antagonists [RATIO]), the rate of TB in patients treated with TNF antagonists for different diseases was 12.2 times more than in the general population [56]. Exposure to TNF antibodies proved to be an independent risk factor for TB compared with soluble TNF receptor (odds ratio: 13.3; 95% CI: 2.6–69.0 and odds ratio: 17.1; 95% CI: 3.6–80.6, respectively). None of the 69 TB patients had received appropriate chemoprophylaxis treatment according to the French recommendations. The analysis of 13 cases from the Portuguese registry concurs with the increased risk of TNF antibodies compared with soluble TNF receptor. However, the history of latent TB was unknown. In four patients starting TNF antagonists before 2002, screening of latent TB was not performed [57]. In a recent study from the British register, 40 TB cases were identified. The rate of TB was higher in the antibody TNF-treated than in the etanercept-treated patients. No stratified analysis of the presence of latent TB in infliximab-treated patients was carried out [58]. The risk of TB in RA patients was studied in Korea, where a higher incidence was seen in the infliximab-treated patients than in the general population but not etanercept-treated

Table 2. Risk of TB in rheumatoid arthritis patients compared with the general population.

Study (year)	Country	Incidence rate per 100,000 people		Relative risk in rheumatoid arthritis (95% CI)	Comments	Ref.
		General population	Rheumatoid arthritis patients			
Wolfe <i>et al.</i> (2004)	USA	6.4 [†]	6.2 (1.6–34.4)		This study measured the incidence of TB in rheumatoid arthritis patients from July 1998–December 1999	[52]
Seong <i>et al.</i> (2007)	Korea	67.2	257		This study measured the incidence of TB in rheumatoid arthritis patients over the period 2001–2004	[50]
Askling <i>et al.</i> (2005)	Sweden			2.0 (1.2–3.4)	This study measured the incidence of hospitalization from TB in rheumatoid arthritis patients over the period 1999–2001	[111]
Carmona <i>et al.</i> (2003)	Spain	23	134	3.68 (2.36–5.92)	This study measured TB incidence in rheumatoid arthritis patients over the period 1990–2000	[112]
Yamada <i>et al.</i> (2006)	Japan	All: 25.8 Men: 34.2 Women: 17.7	42.4 173.4 13.1	3.21 (1.21–8.55) 10.6 (3.42–32.78) 1.48 (0.20–10.00)	This study measured the incidence of TB in rheumatoid arthritis patients over the period October 2000–October 2002. The relative risk for women is not significant	[113]
Brassard <i>et al.</i> (2009)	Canada	4.2	45.8		The population in this study consisted of the Quebec population and Quebec rheumatoid arthritis cohort over the period 1992–2003	[114]
Tam <i>et al.</i> (2010)	Hong Kong		2.35 [†] (1.17–4.67)		The population of this study consisted of rheumatoid arthritis patients followed at five hospitals in Hong Kong over the period 2004–2008	[115]

[†]Data from [116].

[‡]Shows the standardized incidence rate.

Adapted with permission from [113].

are two techniques to detect this response: the *in vivo* tuberculin skin test (TST) and the *ex vivo* IFN- γ -release assays (IGRAs). Adaptive immune responses can persist in the absence of viable mycobacteria. Therefore, the proportion of patients who are actively infected with *M. tuberculosis* after a positive TST or IGRA result is unknown [61].

TST consists of an intradermic injection in the forearm dermis with a mixture of antigens from the supernatant of an *M. tuberculosis* culture that elicits a skin induration in individuals previously exposed to the bacteria. The skin reaction is caused by a delayed-type hypersensitivity response against *M. tuberculosis* in the site of injection by CD4⁺ lymphocytes. The measure of the largest axis of the consequential dermal reaction is taken 48–72 h later. Limitations of TST include the false-positive results caused by Bacille Calmette–Guérin (BCG) vaccination or other environmental mycobacteria, and the failure to discriminate true negative responses from anergy. In addition, sensitivity of TST depends on the cutoff positivity point, which differs in different recommendations. Some national guidelines for the screening of latent TB in patients who are undergoing TNF antagonists treatment propose a two-step TST to increase sensitivity particularly in immunosuppressed patients [4,57]. If a two-step test is performed in these patients, a positive conversion by boosting can result. In order to distinguish new infection from boosting

phenomenon, the second TST has to be repeated 1–4 weeks after the initial negative test, and induration in the second test must be considered as the baseline.

IGRA tests are based on the release of IFN- γ in patients' blood samples after stimulation *in vitro* with *M. tuberculosis*-specific antigens such as ESAT-6, culture filtrate protein 10 or TB7.7 antigen. These antigens are absent in all strains of BCG vaccines and in most other nontuberculous mycobacteria such as the *Mycobacterium avium* complex. After stimulation, effector T cells are activated and release several cytokines, including IFN- γ . The amount of IFN- γ released could be estimated by the percentage of blood cells releasing IFN- γ using enzyme-linked immunospot assay (ELISPOT) or by quantifying the IFN- γ released into the supernatant using an ELISA. There are other assays to detect intracellular accumulated IFN- γ , for example, flow cytometry [62]. The ELISA method is marketed as QuantiFERON-TB Gold In-Tube (Cellestis, Australia) and the ELISPOT as T-SPOT.TB (Oxford Immunotec, UK). These commercially available kits carry a mitogen used as a positive control to assess T-cell responsiveness, a reduced mitogen response being suggestive of immunosuppression. Unlike TST, a negative IGRA test can differentiate anergy from a true negative result. The higher sensitivity of T-SPOT.TB compared with QuantiFERON-TB in immunosuppressed patients has been described [63].

Table 3. Risk of active TB in patients suffering from rheumatic diseases treated with TNF antagonists.

Study (year)	Country	Type of study	TNF antagonist (95% CI)			Comments	Ref.
			<i>Adalimumab</i>	<i>Etanercept</i>	<i>Infliximab</i>		
Wallis <i>et al.</i> (2004)	USA	Cases of TB voluntarily reported to the US FDA		IR: 28 [†]	IR: 54 [†]	Etanercept versus infliximab $p < 0.0001$	[53]
Brassard <i>et al.</i> (2006)	Canada	Search of a large pharmacy prescription database		RR: 1.2 (0.9–1.8)	RR: 1.6 (1.0–2.6)	TB diagnosis was not validated. Results showed that only infliximab has a significant risk	[54]
Gomez-Reino <i>et al.</i> (2007)	Spain	Data from registry	IR: 176 [†] (24–1254)	IR: 114 [†] (28–459)	IR: 383 [†] (159–921)	The p-value was not significant and there were wide confidence intervals	[49]
Tubach <i>et al.</i> (2009)	France	Data from registry	IR: 215.0 [†] (0.0–521.7)	IR: 9.3 [†] (0.0–9.4)	IR: 187.5 [†] (0.1–374.8)	SIRs were as follows: adalimumab: 29.3; etanercept: 1.8; infliximab: 18.6 ($p < 0.0001$)	[56]
Fonseca <i>et al.</i> (2006)	Portugal	Data from registry	Four cases out of 171 patients	One case out of 333 patients	Eight cases out of 456 patients	Exposures were not provided	[57]
Dixon <i>et al.</i> (2010)	England	Data from registry	IR: 144 [†] (72–258)	IR: 39 [†] (13–92)	IR: 136 [†] (68–244)	Includes patients collected prior to TB screening recommendations and patients following these recommendations	[58]

[†]All IR values are given per 100,000 people.

IR: Incidence rate; RR: Adjusted rate ratio; SIR: Standardized incidence ratio.

Adapted with permission from [5].

Owing to the use of specific antigens, IGRA tests have higher specificity than TST, particularly in populations with a high prevalence of BCG vaccination. Positive and negative predictive values of TST and IGRA are unknown in patients scheduled to be treated with TNF antagonists because there is no gold standard for the diagnosis of latent TB, and no comparison between two methods is possible. However, two studies in HIV-infected individuals estimate a positive predictive value for IGRA test of approximately 9% [64–66]. Agreement between TST and IGRA, and association of positive results with different latent TB risk factors are indirect methods of approaching the difference between the two methods [62,67–77]. Low numbers of patients, different immunosuppression status, high rates of BCG vaccination and methodological differences in IGRA make comparing the results of different studies that compare TST and IGRA tests impossible. In one study, the authors report that steroid exposure increases the number of indeterminate results in IGRA [76]. Larger concordance of TST and IGRA has been seen in populations with low prevalence of TB and BCG vaccination. Risk of overtreatment with resulting risk of drug toxicity due to a false-positive screening [78–80], and undertreatment due to a false-negative screening [81] are the main concerns. In immunosuppressed patients, IGRA tests appear to be superior to TST in discriminating anergy from true negative results [82]. However,

there is insufficient evidence to recommend one method over the other for the screening of patients scheduled for treatment with TNF antagonist. In accordance, the TBNET consensus suggests using the QuantiFERON-TB Gold In-Tube or T-SPOT.TB test, or the TST in patients without a history of BCG vaccination [5].

Management of latent TB in patients undergoing treatment with TNF antagonists

Although terms such as ‘chemoprophylaxis’ and ‘preventive chemotherapy’ have been used, ‘treatment of latent TB’ is recommended by the American Thoracic Society. Investigation of latent TB is mandatory prior to the initiation of TNF antagonist therapy. Notwithstanding the fact that monoclonal antibodies seem to present a higher risk for reactivation of latent TB than soluble TNF receptors, screening and treatment of latent TB is warranted for all TNF antagonists regardless of their different molecular structure. This recommendation is supported by an observational study of the Spanish register BIOBADASER. The rate of TB was reduced by 80% after implementation of the official recommendations for isoniazid therapy for 9 months in patients with either positive TST (or two-step TST), past history of untreated TB or chest radiograph suggestive of past TB [4]. Recommendations for the general population by the American

Thoracic Society and the British Thoracic Society in 2000 underscore the relevance of performing targeted TST in patients at risk such as those with recent TB exposure or those receiving prolonged immunosuppressive therapies [83,84]. Special attention was paid to children because youth implies recent infection and an increased likelihood of developing disease. More recommendations and evidence-based guidelines for patients undergoing treatment with TNF antagonists are available in several countries [4,57,85–88]. These national guidelines establish recommendations on screening methods and test cutoffs, and interpretation for diagnosis of latent TB. The best therapy for latent TB and the time delay before starting TNF antagonist therapy are also included in these guidelines. However, recommendations have disagreements; the TBNET consensus is the only international document that provides evidence-based advice for the assessment of latent TB in these patients. Experts recommend treating latent TB in all patients with positive IGRA tests or TST. However, IGRA can give false-negative results in approximately 20% of TB patients [68,89], therefore different screening tools for diagnosis of latent TB must also be considered. Most guidelines recognize a history of significant past exposure or abnormal chest x-rays (suggestive of past TB) as indication for treatment of latent TB in the absence of an immune response to *M. tuberculosis* [4,85,87,90]. In patients treated adequately in the past, treatment of latent TB is not recommended despite persistent specific immune responses. On the other hand, guidelines emphasize that in patients with a negative TST or IGRA result, treatment is required if there has been past exposure or documented prior untreated TB. When IGRA and TST tests yield discordant results, the TBNET consensus recommends a consideration of history of prior BCG vaccination. If BCG vaccination was performed, IGRA test result should prevail over the TST result. If the patient has never been vaccinated with BCG, positive IGRA or TST result should be considered as such (FIGURE 2). Different delay periods between TNF antagonist therapy and initiation of latent TB treatment have been proposed. Recommendations range from starting both treatments concurrently to waiting until 1 month after finishing latent TB treatment. Therapy recommended for the treatment of latent TB includes 9–12 months of isoniazid in monotherapy [5], or combining 3 months of isoniazid and rifampicin [90]. UK and Swiss guidelines propose isoniazid for 6 months or rifampicin for 4 months to minimize hepatotoxicity [87,88]. Shorter regimens might avoid poor adherence to the treatment, and improve prevention of active diseases [49]. The case of active disease is different;

there is no evidence that length of anti-TB treatment needs to be prolonged in patients who develop active TB while undergoing treatment with TNF antagonists. Recommendations on delay before recommencing TNF antagonist therapy differs between countries. French guidelines advise waiting at for at least 2 months after the completion of active TB treatment. No data is available regarding TNF antagonist treatment while the patient is receiving active anti-TB chemotherapy [91], however Portuguese and English guidelines suggest commencing treatment after 2 months of TB treatment. The TBNET consensus recommends completing the active TB treatment before starting TNF antagonist. The effect of TNF antagonist therapy on response to treatment of TB is unknown, and paradoxical responses to treatment after discontinuing infliximab have been interpreted as a possible immune reconstitution reaction. Nevertheless, this observation does not support continuing TNF antagonist therapy in the presence of active TB [92,93].

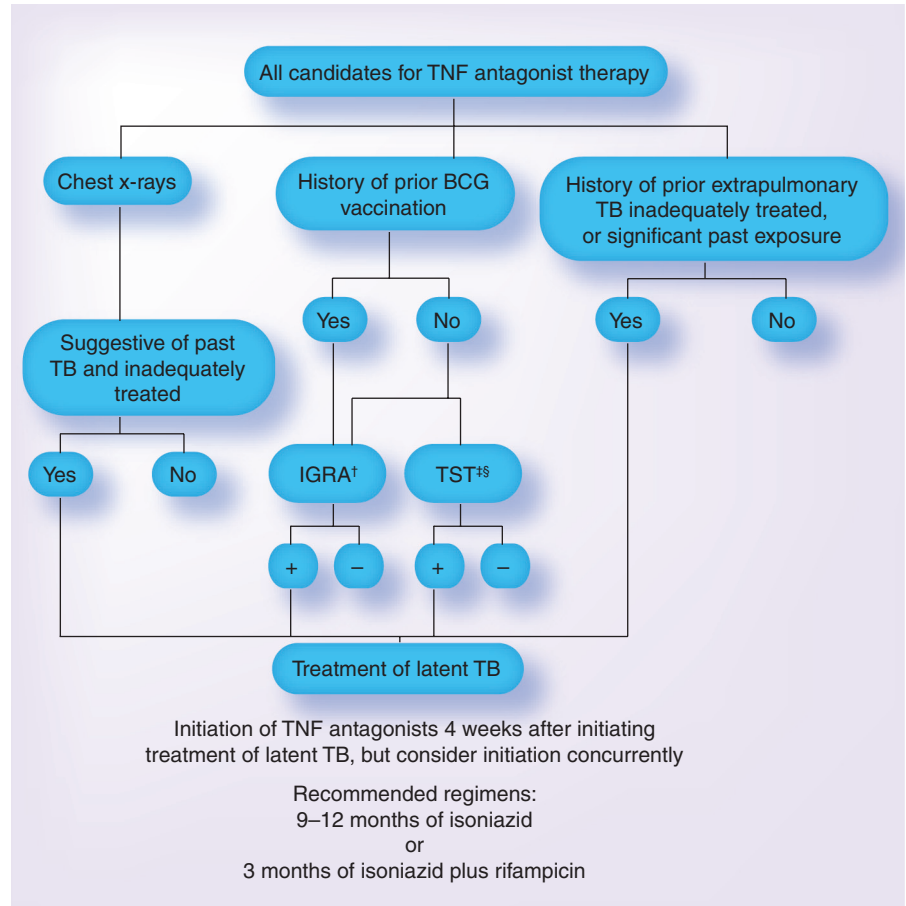


Figure 2. Screening and treatment of latent TB.

*IGRA, Both T-SPOT.TB and QuantiFERON-TB Gold In-Tube test are equally valid.

*Cutoff >10 mm is generally recommended.

§Two-step is recommended by the authors.

BCG: Bacille Calmette–Guérin; IGRA: IFN- γ -release assay; TST: Tuberculin skin test.

Expert commentary

In animal models of *M. tuberculosis*, there is comprehensive information on the mechanisms of defense that protects from the

disease. However, mechanisms of protective immunity to *M. tuberculosis* infection in humans remain undetermined. The information regarding TB provided by the therapy of patients with TNF antagonists has been decisive in the understanding of this mechanism. In mice, depletion of TNF using neutralizing antibodies prevents granuloma formation and the ability to contain infection with BCG [94]. Furthermore, TNF-deficient mice failed to form granuloma in response to mycobacterial infection [33]. TNF has also been shown to be critical in controlling long-term and persistent infections, with depletion resulting in failure to maintain the granuloma [95]. Correspondingly, the risk of active TB is increased in patients treated with a TNF antagonist over the background due to reactivation of latent TB. The soluble TNF receptor may have a lower risk compared with TNF antibodies to reactivate TB, suggesting a different role for the membrane bound and soluble TNF in containing TB infection. Available information is helping to design preventive strategies, and to evaluate the value of diagnostic tools based on the response of the immune system to the microbial exposure. A critical re-evaluation of the ability of tests to evaluate the immune response to mycobacterial antigens (TST and IGRA) as diagnostic tools has followed the need to detect and treat latent TB in patients undergoing TNF inhibition. Also, reappraisal of the treatment of latent TB has been undertaken. In conclusion, different risk management plans have led to a better outcome in these patients, and a better understanding of the role of TNF in the response to *M. tuberculosis* infection.

Five-year view

It is believed that cellular immunity plays the predominant role in the defense against *M. tuberculosis* infection [96]. The role of specific cytokine pathways on the induction, expansion and control of the response is being actively investigated [97]. The contribution of cellular immunity triggered by B cells is under debate. In recent years, numerous biologics that target cytokines, deplete B cells or modulate T cells have become available for treatment of immune-mediated chronic inflammatory condition in humans. This may be an unexpected opportunity to recognize the role of specific cells and cytokine pathways on the induction, expansion, and control of the immune response to *M. tuberculosis*. In the near future, we will learn more about biologics other than TNF antagonists. Studies on the role of IL-6 in the control of mycobacterial diseases have yielded conflicting results, in particular regarding the role of IL-6 in the protective granuloma formation [98]. Few cases of reactivation of latent TB in RA patients treated with an antibody against the IL-6 receptor have been reported in clinical trials in an exposure of over 10,000 patient-years. A definitive demonstration of the increased risk over background is required. IFN- γ plays an essential role in host defense against infection by *M. tuberculosis*, and its synthesis is critically regulated by the interleukins IL-12, IL-18 and IL-23. A monoclonal antibody against IL-12/IL-23 p40 (ustekinumab) has been administered to patients with psoriasis, multiple sclerosis and Crohn's disease in clinical trials [99–102]. Thus far, no cases of active TB have been reported. Whether this is due to the exclusion of patients at risk from the clinical trial or otherwise will be recognized in the future when patients at risk (i.e.,

positive TST or high background exposure) are treated in clinical practice. Meanwhile, close follow-up of treated patients would define the role of this cytokine in human TB. In animal models, neither IL-23 or IL-17 is required for control of *M. tuberculosis* in the lung. Preliminary data regarding treatment of chronic inflammatory conditions with an anti-IL-17 antibody was not accompanied by cases of active TB in humans [103]. This information requires further refinement in the future. Results of studies of *M. tuberculosis* infection in B-cell-deficient mice have been variable with reports of either immunity being diminished, pathologic progression being delayed or no apparent effects [104,105]. In humans, depletion of B cells with a monoclonal antibody against CD-20 (rituximab) in RA patients is not associated with an increased risk of active TB, suggesting that this cell type may not be a critical cell for the containment of this infection [106]. CTLA-4 blockade does not alter the number or function of lymphocytes at the primary site of mycobacterial infection and therefore does not lead to enhanced clearance of the infection. In humans, treatment of RA patients with CTLA-4–IgG1 fusion protein does not increase the risk of reactivation of TB [107–110]. In conclusion, treatment of chronic inflammatory conditions with biologics that target specific cells and soluble factors is generating a large population of patients with readily identified incomplete immune system deficiencies. An excellent scenario to study the participation of immune system components in the defense against infection by *M. tuberculosis* is beginning to arise.

Financial & competing interests disclosure

Juan J Gómez-Reino is on the Advisory Boards of Schering-Plough, Wyeth, MSD, Bristol-Meyers Squibb and Roche, and has received lecture fees from Abbott Laboratories, Wyeth, MSD, Roche, Bristol-Meyers Squibb and Schering-Plough. This work is partially supported by RIER from the Instituto de Salud Carlos III, Spain. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Key issues

- Patients with chronic inflammatory diseases treated with TNF antagonists have an increased risk of reactivation of latent TB.
- In patients with rheumatoid arthritis, the risk of reactivation of latent TB is increased, and the treatment with TNF antagonists further increases the risk.
- The role of TNF in inflammation, especially in the maintenance of granuloma integrity, explains the reactivation of latent granulomatous diseases after the inhibition of this cytokine.
- Active TB in patients treated with TNF antagonist is often rapidly progressive.
- Screening of latent TB and proper treatment is the most effective way to prevent reactivation of latent TB.
- Treatment of latent TB is indicated for all patients treated with TNF antagonists irrespective of the molecule, whether it be in the form of a monoclonal antibody or soluble receptor.

References

Papers of special note have been highlighted as:
• of interest

- 1 Bradley JR. TNF-mediated inflammatory disease. *J. Pathol.* 214(2), 149–160 (2008).
- **Brief review of the role of tumor necrosis factor (TNF) in the various inflammatory diseases.**
- 2 Gomez-Reino JJ, Carmona L, Valverde VR, Mola EM, Montero MD. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report. *Arthritis Rheum.* 48(8), 2122–2127 (2003).
- 3 Harris J, Keane J. How tumour necrosis factor blockers interfere with tuberculosis immunity. *Clin. Exp. Immunol.* 161(1), 1–9 (2010).
- **Brief review and update of the structural differences between TNF antagonists and their possible connection to the risk of developing TB.**
- 4 Carmona L, Gomez-Reino JJ, Rodriguez-Valverde V *et al.* Effectiveness of recommendations to prevent reactivation of latent tuberculosis infection in patients treated with tumor necrosis factor antagonists. *Arthritis Rheum.* 52(6), 1766–1772 (2005).
- 5 Solovic I, Sester M, Gomez-Reino JJ *et al.* The risk of tuberculosis related to TNF antagonist therapies: a TBNET consensus statement. *Eur. Respir. J.* DOI: 10.1183/09031936.00028510 (2010) (Epub ahead of print).
- **Comprehensive review of current scientific evidence on the risk of TB in patients treated with TNF antagonists, and valuable expert opinion on different clinical challenges.**
- 6 Tracey D, Klareskog L, Sasso EH, Salfeld JG, Tak PP. Tumor necrosis factor antagonist mechanisms of action: a comprehensive review. *Pharmacol. Ther.* 117(2), 244–279 (2008).
- 7 Brennan FM, Chantry D, Jackson A, Maini R, Feldmann M. Inhibitory effect of TNF α antibodies on synovial cell interleukin-1 production in rheumatoid arthritis. *Lancet* 2(8657), 244–247 (1989).
- 8 Butler DM, Maini RN, Feldmann M, Brennan FM. Modulation of proinflammatory cytokine release in rheumatoid synovial membrane cell cultures. Comparison of monoclonal anti TNF- α antibody with the interleukin-1 receptor antagonist. *Eur. Cytokine Netw.* 6(4), 225–230 (1995).
- 9 Williams RO, Feldmann M, Maini RN. Anti-tumor necrosis factor ameliorates joint disease in murine collagen-induced arthritis. *Proc. Natl Acad. Sci. USA* 89(20), 9784–9788 (1992).
- 10 Piguet PF, Grau GE, Vesin C, Loetscher H, Gentz R, Lesslauer W. Evolution of collagen arthritis in mice is arrested by treatment with anti-tumour necrosis factor (TNF) antibody or a recombinant soluble TNF receptor. *Immunology* 77(4), 510–514 (1992).
- 11 Kontoyiannis D, Pasparakis M, Pizarro TT, Cominelli F, Kollias G. Impaired on/off regulation of TNF biosynthesis in mice lacking TNF AU-rich elements: implications for joint and gut-associated immunopathologies. *Immunity* 10(3), 387–398 (1999).
- 12 Nam JL, Winthrop KL, van Vollenhoven RF *et al.* Current evidence for the management of rheumatoid arthritis with biological disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of RA. *Ann. Rheum. Dis.* 69(6), 976–986 (2010).
- 13 Chen YF, Jobanputra P, Barton P *et al.* A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost–effectiveness. *Health Technol. Assess.* 10(42), III–IV, XI–XIII, 1–229 (2006).
- 14 Keystone E, Genovese MC, Klareskog L *et al.* Golimumab in patients with active rheumatoid arthritis despite methotrexate therapy: 52-week results of the GO-FORWARD study. *Ann. Rheum. Dis.* 69(6), 1129–1135 (2010).
- 15 Braun J, Bollow M, Neure L *et al.* Use of immunohistologic and *in situ* hybridization techniques in the examination of sacroiliac joint biopsy specimens from patients with ankylosing spondylitis. *Arthritis Rheum.* 38(4), 499–505 (1995).
- 16 Lange U, Teichmann J, Stracke H. Correlation between plasma TNF- α , IGF-1, biochemical markers of bone metabolism, markers of inflammation/disease activity, and clinical manifestations in ankylosing spondylitis. *Eur. J. Med. Res.* 5(12), 507–511 (2000).
- 17 Murch SH, Braegger CP, Walker-Smith JA, MacDonald TT. Location of tumour necrosis factor α by immunohistochemistry in chronic inflammatory bowel disease. *Gut* 34(12), 1705–1709 (1993).
- 18 Ettehad P, Greaves MW, Wallach D, Aderka D, Camp RD. Elevated tumour necrosis factor- α (TNF- α) biological activity in psoriatic skin lesions. *Clin. Exp. Immunol.* 96(1), 146–151 (1994).
- 19 Woolacott NF, Khadjesari ZC, Bruce IN, Riemsma RP. Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review. *Clin. Exp. Rheumatol.* 24(5), 587–593 (2006).
- 20 Rutgeerts P, Sandborn WJ, Feagan BG *et al.* Infliximab for induction and maintenance therapy for ulcerative colitis. *N. Engl. J. Med.* 353(23), 2462–2476 (2005).
- 21 Colombel JF, Sandborn WJ, Rutgeerts P *et al.* Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology* 132(1), 52–65 (2007).
- 22 Hehlhans T, Pfeffer K. The intriguing biology of the tumour necrosis factor/ tumour necrosis factor receptor superfamily: players, rules and the games. *Immunology* 115(1), 1–20 (2005).
- 23 Fenton MJ, Vermeulen MW. Immunopathology of tuberculosis: roles of macrophages and monocytes. *Infect. Immun.* 64(3), 683–690 (1996).
- 24 Fenton MJ. Macrophages and tuberculosis. *Curr. Opin. Hematol.* 5(1), 72–78 (1998).
- 25 Fischl MA, Daikos GL, Uttamchandani RB *et al.* Clinical presentation and outcome of patients with HIV infection and tuberculosis caused by multiple-drug-resistant bacilli. *Ann. Intern. Med.* 117(3), 184–190 (1992).
- 26 Hirsch CS, Ellner JJ, Russell DG, Rich EA. Complement receptor-mediated uptake and tumor necrosis factor- α -mediated growth inhibition of *Mycobacterium tuberculosis* by human alveolar macrophages. *J. Immunol.* 152(2), 743–753 (1994).
- 27 Kurashima K, Mukaida N, Fujimura M *et al.* Elevated chemokine levels in bronchoalveolar lavage fluid of tuberculosis patients. *Am. J. Respir. Crit. Care Med.* 155(4), 1474–1477 (1997).
- 28 Jones BW, Heldwein KA, Means TK, Saukkonen JJ, Fenton MJ. Differential roles of Toll-like receptors in the elicitation of proinflammatory responses by macrophages. *Ann. Rheum. Dis.* 60(Suppl. 3), iii6–iii12 (2001).
- 29 Davis JM, Ramakrishnan L. The role of the granuloma in expansion and dissemination of early tuberculous infection. *Cell* 136(1), 37–49 (2009).

- 30 Taylor JL, Hatttle JM, Dreitz SA *et al.* Role for matrix metalloproteinase 9 in granuloma formation during pulmonary *Mycobacterium tuberculosis* infection. *Infect. Immun.* 74(11), 6135–6144 (2006).
- 31 Volkman HE, Pozos TC, Zheng J, Davis JM, Rawls JF, Ramakrishnan L. Tuberculous granuloma induction via interaction of a bacterial secreted protein with host epithelium. *Science* 327(5964), 466–469 (2010).
- 32 Bekker LG, Freeman S, Murray PJ, Ryffel B, Kaplan G. TNF- α controls intracellular mycobacterial growth by both inducible nitric oxide synthase-dependent and inducible nitric oxide synthase-independent pathways. *J. Immunol.* 166(11), 6728–6734 (2001).
- 33 Roach DR, Bean AG, Demangel C, France MP, Briscoe H, Britton WJ. TNF regulates chemokine induction essential for cell recruitment, granuloma formation, and clearance of mycobacterial infection. *J. Immunol.* 168(9), 4620–4627 (2002).
- 34 Mulligan MS, Vaporciyan AA, Miyasaka M, Tamatani T, Ward PA. Tumor necrosis factor α regulates *in vivo* intrapulmonary expression of ICAM-1. *Am. J. Pathol.* 142(6), 1739–1749 (1993).
- 35 Saukkonen JJ, Bazydlo B, Thomas M, Strieter RM, Keane J, Kornfeld H. β -chemokines are induced by *Mycobacterium tuberculosis* and inhibit its growth. *Infect. Immun.* 70(4), 1684–1693 (2002).
- 36 Wallis RS, Kyambadde P, Johnson JL *et al.* A study of the safety, immunology virology, and microbiology of adjunctive etanercept in HIV-1-associated tuberculosis. *AIDS* 18(2), 257–264 (2004).
- 37 Abraham E. Why immunomodulatory therapies have not worked in sepsis. *Intensive Care Med.* 25(6), 556–566 (1999).
- 38 Bruns H, Meinken C, Schauenberg P *et al.* Anti-TNF immunotherapy reduces CD8⁺ T cell-mediated antimicrobial activity against *Mycobacterium tuberculosis* in humans. *J. Clin. Invest.* 119(5), 1167–1177 (2009).
- Research article that provides an explanation of the specific effect of TNF antagonists in memory T cells.
- 39 Dalton DK, Haynes L, Chu CQ, Swain SL, Wittmer S. Interferon γ eliminates responding CD4 T cells during mycobacterial infection by inducing apoptosis of activated CD4 T cells. *J. Exp. Med.* 192(1), 117–122 (2000).
- 40 Mohan VP, Scanga CA, Yu K *et al.* Effects of tumor necrosis factor α on host immune response in chronic persistent tuberculosis: possible role for limiting pathology. *Infect. Immun.* 69(3), 1847–1855 (2001).
- 41 Flynn JL, Goldstein MM, Chan J *et al.* Tumor necrosis factor- α is required in the protective immune response against *Mycobacterium tuberculosis* in mice. *Immunity* 2(6), 561–572 (1995).
- 42 Roach DR, Briscoe H, Saunders B, France MP, Riminton S, Britton WJ. Secreted lymphotoxin- α is essential for the control of an intracellular bacterial infection. *J. Exp. Med.* 193(2), 239–246 (2001).
- 43 Ehlers S, Holscher C, Scheu S *et al.* The lymphotoxin β receptor is critically involved in controlling infections with the intracellular pathogens *Mycobacterium tuberculosis* and *Listeria monocytogenes*. *J. Immunol.* 170(10), 5210–5218 (2003).
- 44 Lin PL, Myers A, Smith L *et al.* Tumor necrosis factor neutralization results in disseminated disease in acute and latent *Mycobacterium tuberculosis* infection with normal granuloma structure in a cynomolgus macaque model. *Arthritis Rheum.* 62(2), 340–350 (2010).
- 45 Clay H, Volkman HE, Ramakrishnan L. Tumor necrosis factor signaling mediates resistance to mycobacteria by inhibiting bacterial growth and macrophage death. *Immunity* 29(2), 283–294 (2008).
- 46 Wallis RS. Tumour necrosis factor antagonists: structure, function, and tuberculosis risks. *Lancet Infect. Dis.* 8(10), 601–611 (2008).
- 47 Mitoma H, Horiuchi T, Tsukamoto H *et al.* Mechanisms for cytotoxic effects of anti-tumor necrosis factor agents on transmembrane tumor necrosis factor α -expressing cells: comparison among infliximab, etanercept, and adalimumab. *Arthritis Rheum.* 58(5), 1248–1257 (2008).
- 48 Nesbitt A, Fossati G, Bergin M *et al.* Mechanism of action of certolizumab pegol (CDP870): *in vitro* comparison with other anti-tumor necrosis factor α agents. *Inflamm. Bowel Dis.* 13(11), 1323–1332 (2007).
- 49 Gomez-Reino JJ, Carmona L, Angel Descalzo M. Risk of tuberculosis in patients treated with tumor necrosis factor antagonists due to incomplete prevention of reactivation of latent infection. *Arthritis Rheum.* 57(5), 756–761 (2007).
- The interest of this paper lies in the design of the analysis that allows the evaluation of the impact of following recommendations for prevention of reactivation of latent TB in comparison with not following recommendations.
- 50 Seong SS, Choi CB, Woo JH *et al.* Incidence of tuberculosis in Korean patients with rheumatoid arthritis (RA): effects of RA itself and of tumor necrosis factor blockers. *J. Rheumatol.* 34(4), 706–711 (2007).
- 51 Keane J, Gershon S, Wise RP *et al.* Tuberculosis associated with infliximab, a tumor necrosis factor α -neutralizing agent. *N. Engl. J. Med.* 345(15), 1098–1104 (2001).
- 52 Wolfe F, Michaud K, Anderson J, Urbansky K. Tuberculosis infection in patients with rheumatoid arthritis and the effect of infliximab therapy. *Arthritis Rheum.* 50(2), 372–379 (2004).
- 53 Wallis RS, Broder MS, Wong JY, Hanson ME, Beenhouwer DO. Granulomatous infectious diseases associated with tumor necrosis factor antagonists. *Clin. Infect. Dis.* 38(9), 1261–1265 (2004).
- 54 Brassard P, Kezouh A, Suissa S. Antirheumatic drugs and the risk of tuberculosis. *Clin. Infect. Dis.* 43(6), 717–722 (2006).
- 55 Mines D, Novelli L. Antirheumatic drugs and the risk of tuberculosis. *Clin. Infect. Dis.* 44(4), 619–620; author reply 620–611 (2007).
- 56 Tubach F, Salmon D, Ravaut P *et al.* Risk of tuberculosis is higher with anti-tumor necrosis factor monoclonal antibody therapy than with soluble tumor necrosis factor receptor therapy: the three-year prospective French Research Axed on Tolerance of Biotherapies registry. *Arthritis Rheum.* 60(7), 1884–1894 (2009).
- 57 Fonseca JE, Canhao H, Silva C *et al.* Tuberculosis in rheumatic patients treated with tumour necrosis factor α antagonists: the Portuguese experience. *Acta Reumatol. Port.* 31(3), 247–253 (2006).
- 58 Dixon WG, Hyrich KL, Watson KD *et al.* Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register (BSRBR). *Ann. Rheum. Dis.* 69(3), 522–528 (2010).
- 59 Utz JP, Limper AH, Kalra S *et al.* Etanercept for the treatment of stage II and III progressive pulmonary sarcoidosis. *Chest* 124(1), 177–185 (2003).
- 60 Sandborn WJ, Hanauer SB, Katz S *et al.* Etanercept for active Crohn's disease: a randomized, double-blind, placebo-controlled trial. *Gastroenterology* 121(5), 1088–1094 (2001).

- 61 Mack U, Migliori GB, Sester M *et al*. LTBI: latent tuberculosis infection or lasting immune responses to *M. tuberculosis*? A TBNET consensus statement. *Eur. Respir. J.* 33(5), 956–973 (2009).
- Another review from the Tuberculosis Network European Trials Group (TBNET) on the immune pathogenesis of *Mycobacterium tuberculosis*, and the current limitations of diagnostic methods for latent TB.
- 62 Dinser R, Fousse M, Sester U *et al*. Evaluation of latent tuberculosis infection in patients with inflammatory arthropathies before treatment with TNF- α blocking drugs using a novel flow-cytometric interferon- γ release assay. *Rheumatology (Oxford)* 47(2), 212–218 (2008).
- 63 Pai M, Zwerling A, Menzies D. Systematic review: T-cell-based assays for the diagnosis of latent tuberculosis infection: an update. *Ann. Intern. Med.* 149(3), 177–184 (2008).
- 64 Diel R, Goletti D, Ferrara G *et al*. Interferon- γ release assays for the diagnosis of latent *M. tuberculosis* infection: a systematic review and meta-analysis. *Eur. Respir. J.* DOI: 10.1183/09031936.00115110 (2010) (Epub ahead of print).
- 65 Aichelburg MC, Rieger A, Breitenacker F *et al*. Detection and prediction of active tuberculosis disease by a whole-blood interferon- γ release assay in HIV-1-infected individuals. *Clin. Infect. Dis.* 48(7), 954–962 (2009).
- 66 Clark SA, Martin SL, Pozniak A *et al*. Tuberculosis antigen-specific immune responses can be detected using enzyme-linked immunospot technology in human immunodeficiency virus (HIV)-1 patients with advanced disease. *Clin. Exp. Immunol.* 150(2), 238–244 (2007).
- 67 Mori T. Usefulness of interferon- γ release assays for diagnosing TB infection and problems with these assays. *J. Infect. Chemother.* 15(3), 143–155 (2009).
- 68 Cobanoglu N, Ozelik U, Kalyoncu U *et al*. Interferon- γ assays for the diagnosis of tuberculosis infection before using tumour necrosis factor- α blockers. *Int. J. Tuberc. Lung Dis.* 11(11), 1177–1182 (2007).
- 69 Matulis G, Juni P, Villiger PM, Gadola SD. Detection of latent tuberculosis in immunosuppressed patients with autoimmune diseases: performance of a *Mycobacterium tuberculosis* antigen-specific interferon γ assay. *Ann. Rheum. Dis.* 67(1), 84–90 (2008).
- 70 Vassilopoulos D, Stamoulis N, Hadziyannis E, Archimandritis AJ. Usefulness of enzyme-linked immunosorbent assay (ELISPOT) compared to tuberculin skin testing for latent tuberculosis screening in rheumatic patients scheduled for anti-tumour necrosis factor treatment. Addendum. *J. Rheumatol.* 35(7), 1464 (2008).
- 71 Bocchino M, Matarese A, Bellofiore B *et al*. Performance of two commercial blood IFN- γ release assays for the detection of *Mycobacterium tuberculosis* infection in patient candidates for anti-TNF- α treatment. *Eur. J. Clin. Microbiol. Infect. Dis.* 27(10), 907–913 (2008).
- 72 Bartalesi F, Vicidomini S, Goletti D *et al*. QuantiFERON-TB Gold and the TST are both useful for latent tuberculosis infection screening in autoimmune diseases. *Eur. Respir. J.* 33(3), 586–593 (2009).
- 73 Murakami S, Takeno M, Kirino Y *et al*. Screening of tuberculosis by interferon- γ assay before biologic therapy for rheumatoid arthritis. *Tuberculosis (Edinb.)* 89(2), 136–141 (2009).
- 74 Behar SM, Shin DS, Maier A, Coblyn J, Helfgott S, Weinblatt ME. Use of the T-SPOT.TB assay to detect latent tuberculosis infection among rheumatic disease patients on immunosuppressive therapy. *J. Rheumatol.* 36(3), 546–551 (2009).
- 75 Laffitte E, Janssens JP, Roux-Lombard P *et al*. Tuberculosis screening in patients with psoriasis before antitumour necrosis factor therapy: comparison of an interferon- γ release assay vs. tuberculin skin test. *Br. J. Dermatol.* 161(4), 797–800 (2009).
- 76 Soborg B, Ruhwald M, Hetland ML *et al*. Comparison of screening procedures for *Mycobacterium tuberculosis* infection among patients with inflammatory diseases. *J. Rheumatol.* 36(9), 1876–1884 (2009).
- 77 Inanc N, Aydin SZ, Karakurt S, Atagunduz P, Yavuz S, Direskeneli H. Agreement between Quantiferon-TB Gold test and tuberculin skin test in the identification of latent tuberculosis infection in patients with rheumatoid arthritis and ankylosing spondylitis. *J. Rheumatol.* 36(12), 2675–2681 (2009).
- 78 Forget EJ, Menzies D. Adverse reactions to first-line antituberculosis drugs. *Expert Opin. Drug Saf.* 5(2), 231–249 (2006).
- 79 Yew WW, Leung CC. Antituberculosis drugs and hepatotoxicity. *Am. J. Respir. Crit. Care Med.* 175(8), 858; author reply 858–859 (2007).
- 80 Haroon M, Martin U, Devlin J. High incidence of intolerance to tuberculosis chemoprophylaxis. *Rheumatol. Int.* DOI: 10.1007/s00296-010-1571-1576 (2010) (Epub ahead of print).
- 81 Ponce de Leon D, Acevedo-Vasquez E, Sanchez-Torres A *et al*. Attenuated response to purified protein derivative in patients with rheumatoid arthritis: study in a population with a high prevalence of tuberculosis. *Ann. Rheum. Dis.* 64(9), 1360–1361 (2005).
- 82 Sester U, Junker H, Hodapp T *et al*. Improved efficiency in detecting cellular immunity towards *M. tuberculosis* in patients receiving immunosuppressive drug therapy. *Nephrol. Dial. Transplant.* 21(11), 3258–3268 (2006).
- 83 Targeted tuberculin testing and treatment of latent tuberculosis infection. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. This is a joint statement of the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC). This statement was endorsed by the Council of the Infectious Diseases Society of America (IDSA), September 1999, and the sections of this statement. *Am. J. Respir. Crit. Care Med.* 161(4 Pt 2), S221–S247 (2000).
- 84 Control and prevention of tuberculosis in the United Kingdom: code of practice 2000. Joint Tuberculosis Committee of the British Thoracic Society. *Thorax* 55(11), 887–901 (2000).
- 85 Diel R, Hauer B, Loddenkemper R, Manger B, Kruger K. Recommendations for tuberculosis screening before initiation of TNF- α -inhibitor treatment in rheumatic diseases. *Pneumologie* 63(6), 329–334 (2009).
- 86 Kavanagh PM, Gilmartin JJ, O'Donnell J, O'Flanagan D. Tumour necrosis factor- α and tuberculosis: guidance from the National TB Advisory Committee. *Iran. Med. J.* 101(1), 6–7 (2008).
- 87 Beglinger C, Dudler J, Mottet C *et al*. Screening for tuberculosis infection before the initiation of an anti-TNF- α therapy. *Swiss Med. Wkly* 137(43–44), 620–622 (2007).
- 88 British Thoracic Society Standards of Care Committee. BTS recommendations for assessing risk and for managing *Mycobacterium tuberculosis* infection and disease in patients due to start anti-TNF- α treatment. *Thorax* 60(10), 800–805 (2005).

- 89 Ponce de Leon D, Acevedo-Vasquez E, Alvizuri S *et al.* Comparison of an interferon- γ assay with tuberculin skin testing for detection of tuberculosis (TB) infection in patients with rheumatoid arthritis in a TB-endemic population. *J. Rheumatol.* 35(5), 776–781 (2008).
- 90 Mariette X, Salmon D. French guidelines for diagnosis and treating latent and active tuberculosis in patients with RA treated with TNF blockers. *Ann. Rheum. Dis.* 62(8), 791 (2003).
- 91 Denis B, Lefort A, Flipo RM *et al.* Long-term follow-up of patients with tuberculosis as a complication of tumour necrosis factor (TNF)- α antagonist therapy: safe re-initiation of TNF- α blockers after appropriate anti-tuberculous treatment. *Clin. Microbiol. Infect.* 14(2), 183–186 (2008).
- 92 Garcia Vidal C, Garau J. Systemic steroid treatment of paradoxical upgrading reaction in patients with lymph node tuberculosis. *Clin. Infect. Dis.* 41(6), 915–916; author reply 916–917 (2005).
- 93 Belknap R, Reves R, Burman W. Immune reconstitution to *Mycobacterium tuberculosis* after discontinuing infliximab. *Int. J. Tuberc. Lung Dis.* 9(9), 1057–1058 (2005).
- 94 Kindler V, Sappino AP, Grau GE, Piguet PF, Vassalli P. The inducing role of tumor necrosis factor in the development of bactericidal granulomas during BCG infection. *Cell* 56(5), 731–740 (1989).
- 95 Botha T, Ryffel B. Reactivation of latent tuberculosis infection in TNF-deficient mice. *J. Immunol.* 171(6), 3110–3118 (2003).
- 96 Cooper AM. Cell-mediated immune responses in tuberculosis. *Annu. Rev. Immunol.* 27, 393–422 (2009).
- 97 Cooper AM, Khader SA. The role of cytokines in the initiation, expansion, and control of cellular immunity to tuberculosis. *Immunol. Rev.* 226, 191–204 (2008).
- 98 Ladel CH, Blum C, Dreher A, Reifenberg K, Kopf M, Kaufmann SH. Lethal tuberculosis in interleukin-6-deficient mutant mice. *Infect. Immun.* 65(11), 4843–4849 (1997).
- 99 Sandborn WJ, Feagan BG, Fedorak RN *et al.* A randomized trial of Ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with moderate-to-severe Crohn's disease. *Gastroenterology* 135(4), 1130–1141 (2008).
- 100 Segal BM, Constantinescu CS, Raychaudhuri A, Kim L, Fidelus-Gort R, Kasper LH. Repeated subcutaneous injections of IL12/23 p40 neutralising antibody, ustekinumab, in patients with relapsing–remitting multiple sclerosis: a Phase II, double-blind, placebo-controlled, randomised, dose-ranging study. *Lancet Neurol.* 7(9), 796–804 (2008).
- 101 Leonardi CL, Kimball AB, Papp KA *et al.* Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). *Lancet* 371(9625), 1665–1674 (2008).
- 102 Papp KA, Langley RG, Lebwohl M *et al.* Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). *Lancet* 371(9625), 1675–1684 (2008).
- 103 Hueber W, Patel DD, Dryja T *et al.* Effects of AIN457, a fully human antibody to interleukin-17A, on psoriasis, rheumatoid arthritis, and uveitis. *Sci. Transl. Med.* 2, 52–72 (2010).
- 104 Casadevall A, Pirofski LA. A reappraisal of humoral immunity based on mechanisms of antibody-mediated protection against intracellular pathogens. *Adv. Immunol.* 91, 1–44 (2006).
- 105 Maglione PJ, Xu J, Chan J. B cells moderate inflammatory progression and enhance bacterial containment upon pulmonary challenge with *Mycobacterium tuberculosis*. *J. Immunol.* 178(11), 7222–7234 (2007).
- 106 van Vollenhoven RF, Emery P, Bingham CO 3rd *et al.* Longterm safety of patients receiving rituximab in rheumatoid arthritis clinical trials. *J. Rheumatol.* 37(3), 558–567 (2010).
- 107 Schiff M, Pritchard C, Huffstutter JE *et al.* The 6-month safety and efficacy of abatacept in patients with rheumatoid arthritis who underwent a washout after anti-tumour necrosis factor therapy or were directly switched to abatacept: the ARRIVE trial. *Ann. Rheum. Dis.* 68(11), 1708–1714 (2009).
- 108 Genovese MC, Becker JC, Schiff M *et al.* Abatacept for rheumatoid arthritis refractory to tumor necrosis factor α inhibition. *N. Engl. J. Med.* 353(11), 1114–1123 (2005).
- 109 Kremer JM, Genant HK, Moreland LW *et al.* Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. *Ann. Intern. Med.* 144(12), 865–876 (2006).
- 110 Weinblatt M, Combe B, Covucci A, Aranda R, Becker JC, Keystone E. Safety of the selective costimulation modulator abatacept in rheumatoid arthritis patients receiving background biologic and nonbiologic disease-modifying antirheumatic drugs: a one-year randomized, placebo-controlled study. *Arthritis Rheum.* 54(9), 2807–2816 (2006).
- 111 Askling J, Forel CM, Brandt L *et al.* Risk and case characteristics of tuberculosis in rheumatoid arthritis associated with tumor necrosis factor antagonists in Sweden. *Arthritis Rheum.* 52(7), 1986–1992 (2005).
- 112 Carmona L, Hernandez-Garcia C, Vadillo C *et al.* Increased risk of tuberculosis in patients with rheumatoid arthritis. *J. Rheumatol.* 30(7), 1436–1439 (2003).
- 113 Yamada T, Nakajima A, Inoue E *et al.* Increased risk of tuberculosis in patients with rheumatoid arthritis in Japan. *Ann. Rheum. Dis.* 65(12), 1661–1663 (2006).
- 114 Brassard P, Lowe AM, Bernatsky S, Kezouh A, Suissa S. Rheumatoid arthritis, its treatments, and the risk of tuberculosis in Quebec, Canada. *Arthritis Rheum.* 61(3), 300–304 (2009).
- 115 Tam LS, Leung CC, Ying SK *et al.* Risk of tuberculosis in patients with rheumatoid arthritis in Hong Kong – the role of TNF blockers in an area of high tuberculosis burden. *Clin. Exp. Rheumatol.* 28(5), 679–685 (2010).
- 116 CDC. *Reported TB in the United States, 2000.* US Department of Health and Human Services, CDC, Atlanta, GA, USA (2001).

Website

- 201 Drug Information Portal
<http://druginfo.nlm.nih.gov/drugportal/drugportal.jsp>