Netherlands
The Journal of Medicine

REVIEW

# TNF-α blockade and tuberculosis: better look before you leap

**S.M. Arend[1*], F.C. Breedveld[2], J.T. van Dissel[1]**

Departments of [1]Infectious Diseases (C5P) and [2]Rheumatology, Leiden University Medical Centre, PO Box 9600, 2300 RC Leiden, the Netherlands, tel.: +31 (0)71-526 26 20, fax: +31 (0)71-526 67 58, e-mail: s.m.arend@lumc.nl, * corresponding author

## ABSTRACT

**According to several reports, the risk of active tuberculosis in patients who are latently infected with *Mycobacterium tuberculosis* is increased after treatment with tumour necrosis factor α (TNF)-blocking agents. These drugs have demonstrated effectiveness and are increasingly being used for treatment of several inflammatory diseases, including rheumatoid arthritis and Crohn's disease. Specialists prescribing TNF-blocking agents should be aware of the risk of tuberculosis and other infections, the unusual and severe clinical presentations and the available preventive measures. In this review, we will weigh currently available data on the risk of infection with intracellular pathogens and in particular tuberculosis in patients treated with TNF-blocking agents, discuss the role of TNF in the pathogenesis of tuberculosis and describe the risk profile of this complication. Awaiting further consensus protocols, a provisional flow chart is presented that is based on clinical parameters to provide a logical framework to reduce and minimise the risk of tuberculosis during TNF blockade.**

## INTRODUCTION

An impairment of the cellular immune system due to treatment with immunosuppressive drugs increases the risk of infections with intracellular pathogens, which were either already latently present within the host and reactivated or are newly acquired and cannot be controlled. That novel and highly effective immunosuppressive or immunomodulating drugs may bring along new patterns of reactivation of latent infections is illustrated by recent reports of an increased risk of reactivation tuberculosis (TB) during treatment with the novel tumour necrosis factor (TNF) α-blocking agents. An unusually high proportion of these patients presented with extrapulmonary or disseminated TB resulting in delayed diagnosis and treatment. During the past decades, the development of novel immunosuppressive drugs and regimens has led to a considerable improvement in the management of rheumatic diseases, vasculitis, malignancies and solid organ or haematopoietic cell transplantations. An arsenal of immunosuppressive drugs are currently available, including prednisone and related glucocorticosteroids, methotrexate, cyclosporine, azathioprine, and antirejection drugs such as mycophenolate mofetil axetil, sirolimus, tacrolimus and antithymocyte globulin. The mechanism of action of these drugs has recently been summarised,[1] their main collective effect being either to decrease T-cell numbers or their function, or interfere with the production or effect of interleukin (IL)-2. Thus, these drugs cause unequivocal suppression of the cellular immune system. The occurrence of opportunistic infections with micro-organisms that do not normally cause illness in immunocompetent persons, such as *Pneumocystis carinii*, is a well-known phenomenon during use of the above-mentioned agents. Other pathogens that can remain latently present for prolonged periods and may reactivate under failing cellular immune defences include *Mycobacterium tuberculosis, Strongyloides stercoralis* and *Histoplasma capsulatum*.

In this review, we will weigh currently available data as to whether, and if so by how much, the risk of infection with intracellular pathogens and in particular TB is increased in patients treated with TNF-blocking agents. Furthermore we will discuss the role of TNF in the pathogenesis of TB and describe the risk profile of this

complication. Awaiting further consensus protocols, a provisional flow chart is presented that is based on clinical parameters to provide a logical framework to reduce and minimise the risk of TB during TNF blockade.

## TNF-BLOCKING AGENTS: INFLIXIMAB AND ETANERCEPT

Two TNF-blocking agents have thus far been approved for clinical use and others are currently being evaluated. The precise time line of the history of TNF-blocking agents has recently been reviewed in detail.[2] Infliximab (Remicade®, Centocor Inc) is a chimeric anti-TNF antibody, consisting of two murine antigen-binding fragments (Fab) with a high affinity for soluble as well as membrane-bound TNF, coupled to three-quarters of the human constant part of immunoglobulin G (Fc-IgG1). Etanercept (Enbrel®, Wyeth/Immunex) is a hybrid molecule composed of two TNF-receptor 2 molecules linked to human Fc-IgG in a similar way as in infliximab. Infliximab has been approved for the treatment of patients with severe rheumatoid arthritis (RA) not responding to optimal treatment with at least two disease-modifying antirheumatic drugs (DMARDs) including methotrexate, and patients with Crohn's disease that is refractory to optimal standard immunosuppressive treatment. Etanercept is approved for the treatment of similar RA patients as well as patients with juvenile idiopathic arthritis (formally known as juvenile chronic arthritis) and psoriatic arthritis.

TNF is a non-specific effector molecule that is excreted predominantly by macrophages in response to various stimuli and that can exert immunostimulatory or immunosuppressive effects depending on the precise setting in which it is produced. TNF was found to be abundantly present in active lesions of RA and Crohn's disease and thus was thought to play a central role in the pathogenesis of these disorders, through the induction of the production of many other cytokines such as IL-1. This hypothesis was affirmed by the impressive favourable effect of TNF blockade on the course of RA and Crohn's disease in the majority of treated patients in clinical studies.[3-5]

## TNF BLOCKADE AND TUBERCULOSIS

The first case of active TB during treatment with infliximab was observed during a phase III study, in which 340 patients were treated with infliximab in one of four different regimens.[3] In 2001, based on postmarketing surveillance data, a report of 70 cases of TB among approximately 147,000 patients treated with TNF-blocking agents worldwide was published.[6] In the ensuing correspondence in response to this publication, additional cases were described[7,8] and another report described a patient with presumed atypical Crohn's disease who was treated with TNF blockade, which was followed by rapidly progressive tuberculous enteritis.[9] By the end of 2001, the authors mentioned that the number of reported cases had increased to 117. From the data in the study by Maini *et al.*[3] the following absolute risk or incidence of TB (by TNF-blocking agent, indication, origin) can be deducted: 24.4/100,000 (infliximab, RA, USA); 203.8/100,000 (infliximab, all indications, non-USA); 8.8/100,000 (etanercept, all indications, all countries). As these risks were calculated from figures obtained by voluntary reporting, they probably underestimate the true risks. The authors calculated the relative risk in the 'infliximab, RA, USA' subgroup by comparing with the risk in the whole population of RA patients, which differed by a factor of four. It may be argued, however, that TNF blockade had at least until then been restricted to the most seriously ill patients who already had a prolonged history of use of corticosteroids, methotrexate or similar agents. Patients thus treated may therefore not be comparable with the general RA population with regard to their immune status, who on average will have received less immunosuppressive treatment. The precise incidence of TB in a comparable group of similarly immunosuppressed RA patients, but without TNF blockade, is not known. In a previous study of patients with systemic lupus erythematosus, polymyositis or similar non-RA inflammatory disorders in a high-endemic area, the cumulative corticosteroid dose, the mean daily dose and pulse therapy were found to be significantly associated with the occurrence of TB.[10] This indicates that previous immunosuppression cannot be ignored in this regard. In the last-mentioned study, the risk of TB was about five times greater than that found in the general population. It is therefore striking that patients who went through a prolonged period of treatment with corticosteroids or other immunosuppressive drugs without the development of active TB, first developed TB after TNF blockade was given. This raises the question whether this episode of TB resulted from reactivation of latent TB infection, primary infection or exogenous reinfection. The relatively short interval between start of TNF blockade and TB in most patients, with a median of 12 weeks, in combination with low background incidence rates in the reporting countries suggests reactivation rather than *de novo* infection.[6] But it can also be asked why if these persons already harboured latent TB infection, progression to active TB did not occur during previous immunosuppression. Reactivation of TB after TNF blockade but not during earlier immunosuppressive treatment would indicate either a much stronger or a qualitatively different effect of TNF blockade compared with the previously used drugs on the risk of reactivation TB. By comparison, corticosteroids have a widespread effect

on the immune system by regulation of the expression of many genes resulting in, among other things, decreased production of a number of cytokines including TNF, decreased production of prostaglandins and induction of apoptosis of lymphocytes, with a net anti-inflammatory effect. Cyclosporin A and tacrolimus inhibit T-cell activation by interference with intracellular signal transduction, resulting in decreased IL-2 production and T-cell proliferation. Serious opportunistic infections can occur when using these agents but the effect may be less specific than that of TNF-blocking agents. Indeed, the occurrence of TB first after TNF blockade but not during a previous period of immunosuppression strongly suggests a specific effect of TNF blockade and a crucial role of TNF in the maintenance of latency.

It cannot be excluded that at least some of the TB cases resulted from *de novo* infection, because despite low population average TB rates, the risk of infection is not homogenous within a population but instead concentrated in specific settings and population subgroups, such as in large cities or among recent immigrants or the homeless. More clarity about reactivation versus *de novo* infection could be provided by genotyping the causative *M. tuberculosis* isolates in a setting where all isolates are typed, such as has been done in the Netherlands since 1993: a unique fingerprint indicates reactivation TB whereas clustering of identical isolates points towards recent transmission. As long as such data are lacking, both reactivation TB and *de novo* infection must be considered as possible ways leading to active TB after TNF blockade.
The considerably lower risk of TB after TNF blockade in the USA compared with other countries was not explained. This could result from differences in reporting or in background rates of latent TB infection among patients who are eligible for treatment with TNF blockade, or more effective screening procedures before starting immunosuppression. Thus far, TNF-blocking agents are expensive (more than € 2000 per dose)[11] and have not yet been widely used in poorer areas where the rates of latent TB infection are much higher than in the USA and Western Europe. In high-incidence areas the risk of primary infection or reinfection with *M. tuberculosis* contributes significantly to the overall risk of TB.[12,13] Except for animal studies, there are no data on the course of primary infection or exogenous reinfection with *M. tuberculosis* during TNF blockade, but an increased susceptibility is likely, given the key role of TNF in the innate immune response to *M. tuberculosis*.

It might be questioned whether TNF blockade alone, without previous immunosuppressive treatment, is actually sufficient to cause reactivation TB. The answer may be found in the results of a study of patients with ankylosing spondylitis, a disease for which standard immunosuppressive therapy is ineffective, who were treated with infliximab.[14] One out of 34 patients treated with infliximab developed TB, suggesting that TNF blockade can in itself cause reactivation TB. Also, at least one case of TB was observed in several relatively small studies aimed at the evaluation of TNF blockade for various indications.[3,14-16] This suggests an extraordinarily large increase in risk of reactivation TB during TNF blockade and this would point to an essential role for TNF in the maintenance of latency.

## DIFFERENCES BETWEEN INFLIXIMAB AND ETANERCEPT

From the available data, it appears that the risk of TB after etanercept is lower than after infliximab, and in fact not above the population background rate,[6,17] which could be related to differences in the mechanism of action of these drugs. Both agents probably work by binding and inactivating TNF at the site of inflammation. Infliximab not only neutralises soluble TNF, but also binds to membrane-bound and receptor-bound TNF,[18,19] while etanercept has no such additional effects. Infliximab has been shown to induce apoptosis and cell-associated TNF infliximab complexes could initiate antibody-dependent cellular cytotoxicity resulting in cell lysis of the cells that contribute to the defence against mycobacteria.[18,20-22] However, it is unclear whether the proapoptotic effect of infliximab has clinical relevance for the risk of TB after TNF antibodies. An increased number of apoptotic cells were found in the lungs of mice who developed TB after treatment with TNF antibodies,[23] which is discordant with the minimal apoptosis found in the lungs of similarly treated humans with TB.[6] Downregulation of IFN-γ production of T cells by infliximab could add to the loss of resistance against infection with *M. tuberculosis*.[24] Different kinetics, dosages and intervals could affect the level and continuity of TNF blockade. Etanercept binds lymphotoxin (TNF-β) in addition to TNF-α. Yet another factor that could contribute to the different effects could be that both infliximab and etanercept have a high affinity for TNF but only the binding of monoclonal TNF antibodies is irreversible. The naturally occurring soluble TNF receptor 2, which constitutes the TNF binding part of etanercept, is thought to be a ligand-passing receptor. TNF bound to this receptor may thus form a TNF reservoir from which TNF can be released in the presence of a low concentration of soluble TNF. Together, these differences between TNF antibodies and the soluble TNF receptor-based hybrid may translate into differences in efficacy and toxicity. In accordance with the above, an increased risk of TB was also observed during the clinical development of adalimumab (D2E7, Abbott Laboratories), a 'human' monoclonal antibody directed

against TNF made by phage display from human components.[2] A safety update on TNF antagonists by the Arthritis Drugs Advisory Committee of the USA Food and Drug Administration can be found at: http://www.fda.gov/ohrms/dockets/ac/01/briefing/3779b2.htm.

## ROLE OF TNF DURING INFECTION WITH *M. TUBERCULOSIS*

During active TB disease, TNF appears to be involved with tissue necrosis and systemic symptoms[25] but the study of its role during latent infection has been hampered because the immune responses responsible for maintaining the latent state of TB in humans are poorly understood. This is related to the fact that latent TB does not occur after infection with *M. tuberculosis* in animals and thus far no experimental model of latency is available that is truly comparable with latent TB infection in humans. Notwithstanding the limitations of animal models, both in TNF and TNF receptor knock-out mice and in mice treated with TNF antibodies, the course of TB was rapidly progressive.[26,27] In an artificial murine latency model, using low-dose intravenous infection, TNF antibodies led to rapidly fatal 'reactivation' TB.[23] In these mice, the infection was spread throughout the body, which reminds one of the frequent presentation with extrapulmonary or disseminated TB in patients after TNF blockade. These findings are in accordance with an important role of TNF in granuloma formation and local containment of infection.

The factors that underlie reactivation TB in persons without recognised immune disorders are not known, although previous studies suggest that the risk is influenced by general health and deficiencies in specific nutrients such as vitamin D.[28] It is generally thought that Th1 responses, especially IFN-γ production, confer protection to *M. tuberculosis*, but precise cell populations, the characteristics and kinetics of a protective immune response have not yet been defined, although they are of great interest in the light of the development of an improved vaccine against TB.[29] If genetic determinants of the risk of active TB exist, no convincing factors have thus far been identified.

Other cytokines besides TNF play a role in the pathogenesis of inflammatory disorders and it is to be expected that novel drugs targeting different cytokines will become available. The question is then whether such new drugs will have a similar effect on the risk of TB. While TNF is central to the triggering of inflammation in RA, interleukin 1 appears to be particularly involved in tissue destruction.[30] Treatment with recombinant IL-1 receptor antagonist (anakinra) was effective in a proportion of RA patients and appeared to increase the risk of serious infections, although so far it has not been associated with an increased risk of TB.[31,32] Nevertheless, IL-1β and natural IL-1 receptor antagonists probably play a role in the defence against TB,[25] and polymorphisms in the genes coding for these proteins were associated with clinical manifestations and the occurrence of false-negative tuberculin skin tests (TSTs) in TB patients.[33] This both justifies an increased awareness of the possibility of reactivation TB during use of novel anticytokine drugs in general and suggests that interference with cytokines might decrease the reliability of the TST.

## PREVENTION OF TB DURING TNF BLOCKADE

### Identification of patients at risk

How can we identify patients eligible for TNF blockade who are at an increased risk of reactivation TB? Some of the patients who had developed active TB during TNF blockade were positive to the tuberculin skin test (TST) before the start of treatment or had a history of insufficiently treated TB.[6,9,34] This highlights the importance of not missing the opportunity for prevention when it is still possible, i.e. before starting treatment with TNF blockade, or even better, before any immunosuppression is given. For an individual patient, the risk of TB during and after TNF blockade is the resultant of host factors, those determining the risk of latent TB infection and the status of the cellular immune system, and environmental factors determining the risk of *de novo* infection. The *a priori* risk of latent TB infection depends on factors such as age, country of origin, age at migration or immigration, travel and occupational history, recognised exposure to a patient with pulmonary TB or regular exposure to persons belonging to a risk group for TB (prison inmates, inhabitants of mental institutions, immigrants and asylum seekers from high-endemic countries, the homeless, drug abusers). The underlying disease and the type and intensity of the cellular immune defect induced by previous treatment can contribute to the risk of TB, although this effect may be overshadowed by the effect of TNF blockade, as was discussed above.

The first and most important part of the evaluation (*figure 1*) should consist of an in-depth interview to establish the risk of prior exposure to *M. tuberculosis*. Such an interview could include questions regarding the place of birth of the patient, the present residence, a travel history including means of transport and the housing, whether TB has ever been diagnosed and how this was treated, if there has been any contact with a patient diagnosed with pulmonary TB or with persons belonging to a risk group for TB, and whether a TST has ever been performed at school, during military service or in a contact investigation. If a positive TST is reported, it is essential to find out if this was followed by drug treatment, which drug was prescribed, for how long and whether the patient adhered to the treatment.

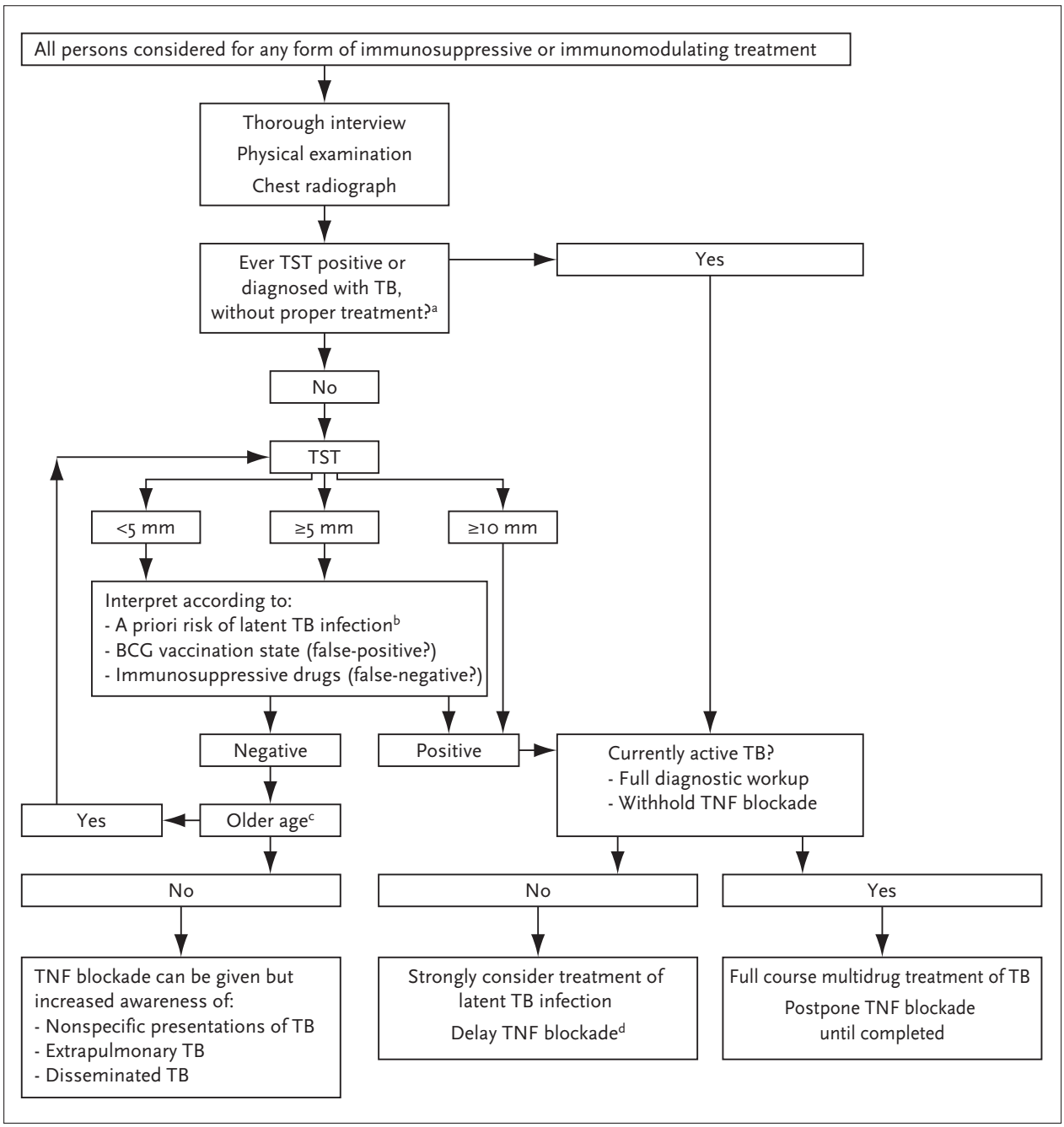


**Figure 1**

*Provisional flow chart for the evaluation of tuberculosis infection in patients eligible for treatment with TNF-blocking agents*

[a] **Adequate treatment of active TB is defined as ≥6 months treatment, including ≥2 months rifampin combined with pyrazinamide. Adequate treatment of latent TB infection consists of either ≥6 months of isoniazid, ≥2 months rifampin plus pyrazinamide or ≥4 months rifampin.**

[b] **The risk of latent TB infection, as deducted from the presence of risk factors for prior exposure, depends on age, country of origin, travel and occupational history, recognised exposure to a patient with pulmonary TB or regular exposure to persons belonging to a risk group for TB (prison inmates, inhabitants of mental institutions, immigrants and asylum seekers from high-endemic countries, homeless persons, drug abusers).**

[c] **In persons who may have been infected long ago, the response to a first TST may be negative, but positive after a second test as a result of a booster phenomenon. Two-step testing could be useful in the cohort in which the prevalence of TB infection exceeds 5%, i.e. in persons born before 1945. Two-step testing may also be valuable in immunosuppressed persons, irrespective of age.**

[d] **There are no evidence-based data to determine a safe interval between the start of treatment of latent TB infection and TNF blockade (also, see text).**

The history of the introduction of the anti-TB drugs, streptomycin in the mid-1940s, isoniazide in 1952 and rifampin in 1964, may act as a guideline to assess whether treatment has been effective according to current standards. A physical examination and chest radiograph are part of the workup and additional diagnostic tests should be performed if so indicated by the history or clinical findings.

**Detection of latent TB infection: tuberculin skin testing and its limitations**

Prevention of TB during TNF blockade requires the detection of latent TB infection, but this is problematic as the definition requires that *M. tuberculosis* can not be identified and that there are no signs or symptoms of active infection. A positive response to tuberculin (purified protein derivative, PPD) is currently the only and by its nature indirect method to detect latent infection with *M. tuberculosis*. In a statement by the American Thoracic Society and the Centres for Disease Control and Prevention (ATS/CDC), guidelines for targeted testing and treatment of latent TB infection are provided,[35] including criteria to define a positive TST response. According to the ATS/CDC guidelines, the criterion to define a positive TST response depends on an individual's clinical and epidemiological characteristics, resulting in three different cut-off levels.[35] In patients with a HIV infection and in those immunosuppressed by treatment or exposed to a patient with contagious pulmonary TB, an induration of ≥5 mm is defined to indicate a positive response, ≥10 mm is advocated in the presence of less severe risk factors and ≥15 mm in the absence of specific risk factors. In the Netherlands, a single cut-off value of ≥10 mm has thus far been applied to indicate a positive TST response, although the criterion of ≥5 mm has been adopted for HIV-infected persons. Along the same line, it may be argued that a cut-off level of ≥5 mm would be more appropriate for patients on immunosuppressive drugs or those with serious illness. However, following Dick Menzies' dictum 'once positive, no longer useful',[36] a TST should only be performed in the absence of a history of a positive TST or previously diagnosed TB.

The technical or biological reasons for false-positive and false-negative TST results have been reviewed.[37-39] In the Netherlands, vaccination with *Mycobacterium bovis* Bacille Calmette-Guérin (BCG) has never been part of the routine vaccination policy but has been restricted to persons working in high-risk professions and long-term travellers to high-endemic countries. In contrast to the native Dutch population, most immigrants have been vaccinated with BCG and false-positive TST results due to cross-reactive immune responses can be expected in this population. Recent studies have shown that false-positive responses are avoided through the use of *M. tuberculosis*-specific antigens (named ESAT-6 and CFP-10) in an *in vitro* T-cell assay.[40] Results from an enzyme-linked immunospot (ELISPOT) assay based on ESAT-6 in immunocompetent persons gave a stronger positive relation with exposure to *M. tuberculosis* than the TST.[41] In a study of HIV-infected persons, an ESAT-6/CFP-10-based ELISPOT assay was found to be highly sensitive for detection of active TB as well as more specific and possibly more sensitive than the TST for detection of latent TB infection.[42] Thus, such alternative diagnostic tests may provide important information in patients eligible for TNF-blocking agents and who had previously received immunosuppressive treatment. However, an assay based on such specific antigens is not yet available for daily practice.

In the context of TNF blockade, TST results can be false-negative in persons using immunosuppressive agents such as corticosteroids or methotrexate. The demonstration of skin test anergy could help to earmark a negative TST result as unreliable, but unfortunately there are no defined control antigens and results do not help to predict the risk of TB in either HIV-negative or HIV-positive patients. Anergy skin testing is therefore not advocated.[43] It is highly preferable that a TST is performed before any immunosuppressive drug is given and not just before the first dose of a TNF-blocking agent, but a TST is nevertheless indicated in a person who is already being treated with immunosuppressive drugs, because a positive result still provides relevant information although a negative result does not rule out latent TB infection. As a result of waning immune responses, a first TST may be negative or false-negative in older persons who were infected with *M. tuberculosis* in the remote past, while a repeat TST may be positive due to the boosting effect of the first test.[36] This method of two-step testing could be advocated in all persons above a certain age, e.g. those born before 1945, the cohort in which the prevalence of TB infection exceeds 5%. Two-step testing may also be valuable in immunosuppressed persons, although this has not been studied.

**Who to treat and when can TNF blockade be given safely?**

In persons with (a history of) a positive TST response, strong epidemiological evidence for an increased risk of latent infection with *M. tuberculosis*, such as a family member being diagnosed with pulmonary TB in the past, or in case of untreated or insufficiently treated TB in the past it is mandatory to exclude active TB before a TNF-blocking agent is given. This implies that TNF blockade must be withheld until all results are available, including the results of cultures which may imply a period of six to eight weeks. When active TB is diagnosed or strongly suspected, a full course of antituberculosis treatment should be prescribed according to current guidelines[44] and TNF-blocking agents withheld, preferably until treatment of TB is completed. When latent TB infection is recorded or strongly suspected and active TB is ruled out, the decision to

start early or pre-emptive treatment should always be made on an individual basis, weighing such factors as the risk of side effects, which depends on age, alcohol consumption, pre-existing liver function disturbances and co-medication.[45] In general, the benefits of screening and preventive therapy were found to outweigh the risks for all risk groups, including immunocompromised persons.[46] There are no data on which to base a safe interval between the start of treatment of latent TB infection and TNF blockade. In France, the 'Groupe Tuberculose et infliximab' and the French agency for healthcare product safety (AFSSAPS) have provisionally advocated an interval of two months.[47]

**How to treat and for how long?**

The first choice of treatment for latent TB infection should consist of isoniazid for nine months, except when there is a high risk of infection with isoniazid-resistant *M. tuberculosis* or if a shorter duration of treatment is essential.[35,48] Treating for six months was found to be less effective, while 12 months of treatment did not decrease the risk of TB any further compared with nine months.[35] Especially in persons suspected to be infected by an isoniazid-resistant strain of *M. tuberculosis* and in those originating from countries with a high prevalence of isoniazid-resistant TB, alternative regimens such as rifampin plus pyrazinamide for two months or rifampin monotherapy for three to four months should be considered.[49-51] Besides the lack of proof of efficacy of these regimes in HIV-negative persons, there have been reports of serious hepatotoxicity and fatal liver failure with the rifampin-plus-pyrazinamide regimen[52,53] and rifampin can interact with various other drugs which makes the alternative regimes unattractive for wide-scale use.

**Recommendations during TNF blockade**

In general, patients treated with TNF-blocking agents should be advised to avoid contact with persons known to have or who are at increased risk of pulmonary TB, including the risk of travel, and to seek medical advice immediately if symptoms or signs compatible with TB, such as weight loss, fever, sweats or persistent cough, occur during or after treatment. A high index of suspicion of TB is justified in all patients with unexplained symptoms, and those who have been or are being treated with a TNF-blocking agent. However, miliary TB can be notoriously difficult to diagnose despite a thorough diagnostic workup,[54,55] arguing for empiric treatment of TB if the suspicion is high and no alternative diagnosis has been made.[56] Apart from the risk of TB, the occurrence of other opportunistic infections such as *Pneumocystis carinii* pneumonia, histoplasmosis and listeriosis has been reported during TNF blockade and the clinician should keep an open mind regarding the differential diagnosis.

## CONCLUSION

TNF-blocking agents are not a panacea for all diseases in which TNF is thought to play a role, as they were found to be ineffective and possibly even deleterious in multiple sclerosis and congestive heart failure. However, the number of disorders for which TNF-blocking agents appear to be effective is rapidly increasing, starting with RA and Crohn's disease, followed by ankylosing spondylitis, Still's disease, psoriatic arthritis, progressive systemic sclerosis, Wegener's granulomatosis, chronic uveitis and TRAPS (TNF receptor-associated periodic syndrome) and new indications might follow.[14,57,58] Until the time of this writing, the TNF-blocking agents are only fully reimbursed according to the reimbursement system for medications in the Netherlands for use in RA, Crohn's disease, juvenile idiopathic arthritis and psoriatic arthritis. If they prove to be highly effective for less severe cases of RA as well and if health insurance companies start reimbursing the costs the use of these drugs could increase considerably. It is therefore mandatory that protocols aimed at optimal prevention of reactivation TB and early detection of active TB are rapidly developed and evaluated prospectively. In conclusion, TNF-blocking agents are highly valuable drugs with a straightforward clinical effect in several inflammatory disorders, but can increase the risk of infection with intracellular pathogens, in particular TB. Thus, as holds true for cytokines in general, TNF is good for you as long as it does not harm you.

## REFERENCES

1. Pascual M, Theruvath T, Kawai T, Tolkoff-Rubin N, Cosimi AB. Strategies to improve long-term outcomes after renal transplantation. N Engl J Med 2002;346:580-90.
2. Feldmann M. Development of anti-TNF therapy for rheumatoid arthritis. Nat Rev Immunol 2002;2:364-71.
3. Maini R, St. Clair EW, Breedveld F, et al. Infliximab (chimeric anti-tumour necrosis factor α monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet 1999;354:1932-9.
4. D'haens G, Deventer S van, Hogezand R van, et al. Endoscopic and histological healing with infliximab anti-tumor necrosis factor antibodies in Crohn's disease: A European multicenter trial. Gastroenterology 1999;116:1029-34.
5. Present DH, Rutgeerts P, Targan S, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. N Engl J Med 1999;340:1398-405.
6. Keane J, Gershon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumor necrosis factor α-neutralizing agent. N Engl J Med 2001;345:1098-104.
7. Rosa FG de, Bonora S, Perri G di. Tuberculosis and treatment with infliximab. N Engl J Med 2002;346:624-5.

8. Riminton S, Pearce N, Antony B. Tuberculosis and treatment with infliximab. N Engl J Med 2002;346:623-5.
9. Wagner TE, Huseby ES, Huseby JS. Exacerbation of Mycobacterium tuberculosis enteritis masquerading as Crohn's disease after treatment with a tumor necrosis factor-α inhibitor. Am J Med 2002;112:67-9.
10. Kim HA, Yoo CD, Baek HJ, et al. Mycobacterium tuberculosis infection in a corticosteroid-treated rheumatic disease patient population. Clin Exp Rheumatol 1998;16:9-13.
11. Hommes DW, Parlevliet W, Sterringa GJ, Hermans M, Bartelsman JFWM, Deventer SJH van. Infliximab therapy in patients with Crohn's disease; experience with 132 patients. [Toepassing van infliximab bij patiënten met de ziekte van Crohn; ervaringen bij 132 patiënten]. Ned Tijdschr Geneeskd 2002;146:1187-91.
12. Sonnenberg P, Murray J, Glynn JR, Shearer S, Kambashi B, Godfrey-Faussett P. HIV-1 and recurrence, relapse, and reinfection of tuberculosis after cure: a cohort study in South African mineworkers. Lancet 2001;358:1687-93.
13. Rie A van, Warren R, Richardson M, et al. Exogenous reinfection as a cause of recurrent tuberculosis after curative treatment. N Engl J Med 1999;341:1174-9.
14. Braun J, Brandt J, Listing J, et al. Treatment of active ankylosing spondylitis with infliximab: a randomised controlled multicentre trial. Lancet 2002;359:1187-93.
15. Temekonidis TI, Georgiadis AN, Alamanos Y, Bougias DV, Voulgari PV, Drosos AA. Infliximab treatment in combination with cyclosporin A in patients with severe refractory rheumatoid arthritis. Ann Rheum Dis 2002;61:822-5.
16. Den BF van, Kruithof E, Baeten D, et al. Randomized double-blind comparison of chimeric monoclonal antibody to tumor necrosis factor α (infliximab) versus placebo in active spondylarthropathy. Arthritis Rheum 2002;46:755-65.
17. Fleischmann R, Iqbal I, Nandeshwar P, Quiceno A. Safety and efficacy of disease-modifying anti-rheumatic agents: focus on the benefits and risks of etanercept. Drug Saf 2002;25:173-97.
18. Deventer SJ van. Transmembrane TNF-α, induction of apoptosis, and the efficacy of TNF-targeting therapies in Crohn's disease. Gastroenterology 2001;121:1242-6.
19. Arend WP. The mode of action of cytokine inhibitors. J Rheumatol 2002;29(suppl 65):16-21.
20. Lügering A, Schmidt M, Lügering N, Pauels HG, Domschke W, Kucharzik T. Infliximab induces apoptosis in monocytes from patients with chronic active Crohn's disease by using a caspase-dependent pathway. Gastroenterology 2001;121:1145-57.
21. Ohshima S, Mima T, Sasai M, et al. Tumour necrosis factor α (TNF-α) interferes with Fas-mediated apoptotic cell death on rheumatoid arthritis (RA) synovial cells: a possible mechanism of rheumatoid synovial hyperplasia and a clinical benefit of anti-TNF-alpha therapy for RA. Cytokine 2000;12:281-8.
22. Hove T ten, Montfrans C van, Peppelenbosch MP, Deventer SJ van. Infliximab treatment induces apoptosis of lamina propria T lymphocytes in Crohn's disease. Gut 2002;50:206-11.
23. Mohan VP, Scanga CA, Yu K, et al. Effects of tumor necrosis factor alpha on host immune response in chronic persistent tuberculosis: possible role for limiting pathology. Infect Immun 2001;69:1847-55.
24. Agnholt J, Kaltoft K. Infliximab downregulates interferon-γ production in activated gut T-lymphocytes from patients with Crohn's disease. Cytokine 2001;15:212-22.
25. Tsao TC, Hong J, Li LF, Hsieh MJ, Liao SK, Chang KS. Imbalances between tumor necrosis factor-α and its soluble receptor forms, and interleukin-1β and interleukin-1 receptor antagonist in BAL fluid of cavitary pulmonary tuberculosis. Chest 2000;117:103-9.
26. Bean AG, Roach DR, Briscoe H, et al. Structural deficiencies in granuloma formation in TNF gene-targeted mice underlie the heightened susceptibility to aerosol Mycobacterium tuberculosis infection, which is not compensated for by lymphotoxin. J Immunol 1999;162:3504-11.
27. Flynn JL, Goldstein MM, Chan J, et al. Tumor necrosis factor-alpha is required in the protective immune response against Mycobacterium tuberculosis in mice. Immunity 1995;2:561-72.
28. Wilkinson RJ, Llewelyn M, Toossi Z, et al. Influence of vitamin D deficiency and vitamin D receptor polymorphisms on tuberculosis among Gujarati Asians in west London: a case-control study. Lancet 2000;355:618-21.
29. Andersen P. TB vaccines: progress and problems. Trends Immunol 2001;22:160-8.
30. Dayer JM. Interleukin 1 or tumor necrosis factor-α: which is the real target in rheumatoid arthritis? J Rheumatol 2002;29(suppl 65):10-5.
31. Hallegua DS, Weisman MH. Potential therapeutic uses of interleukin 1 receptor antagonists in human diseases. Ann Rheum Dis 2002;61:960-7.
32. Weisman MH. What are the risks of biological therapy in rheumatoid arthritis? An update on safety. J Rheumatol 2002;29(suppl 65):33-8.
33. Wilkinson RJ, Patel P, Llewelyn M, et al. Influence of polymorphism in the genes for the interleukin (IL)-1 receptor antagonist and IL-1β on tuberculosis. J Exp Med 1999;189:1863-74.
34. Mayordomo L, Marenco JL, Gomez-Mateos J, Rejon E. Pulmonary miliary tuberculosis in a patient with anti-TNF-alpha treatment. Scand J Rheumatol 2002;31:44-5.
35. American Thoracic Society. Targeted tuberculin testing and treatment of latent tuberculosis infection. Am J Respir Crit Care Med 2000;161:S221-47.
36. Menzies D. Interpretation of repeated tuberculin tests. Boosting, conversion, and reversion. Am J Respir Crit Care Med 1999;159:15-21.
37. Huebner RE, Schein MF, Bass JB jr. The tuberculin skin test. Clin Infect Dis 1993;17:968-75.
38. Menzies RI. Tuberculin skin testing. In: Reichman LB, Hershfield ES (eds). Tuberculosis, a comprehensive international approach. 2nd ed. New York: Marcel Dekker Inc., 2000:279-322.
39. Arend SM, Soolingen D van, Ottenhoff TH, Dissel JT van. Repeatedly negative tuberculin skin tests followed by active tuberculosis in an immunocompetent individual. Neth J Med 2001;58:76-81.
40. Arend, SM. Cellular immune responses to mycobacteria: towards specific immunodiagnosis and protection. [Thesis]. Leiden: Leiden University Medical Centre, 2002.
41. Lalvani A, Pathan AA, Durkan H, et al. Enhanced contact tracing and spatial tracking of Mycobacterium tuberculosis infection by enumeration of antigen-specific T cells. Lancet 2001;357:2017-21.
42. Chapman AL, Munkanta M, Wilkinson KA, et al. Rapid detection of active and latent tuberculosis infection in HIV-positive individuals by enumeration of Mycobacterium tuberculosis-specific T cells. AIDS 2002;16:2285-93.
43. Slovis BS, Plitman JD, Haas DW. The case against anergy testing as a routine adjunct to tuberculin skin testing. JAMA 2000;283:2003-7.

44. Small PM, Fujiwara PI. Management of tuberculosis in the United States. N Engl J Med 2001;345:189-200.
45. Gilroy SA, Rogers MA, Blair DC. Treatment of latent tuberculosis infection in patients aged ≥ 35 years. Clin Infect Dis 2000;31:826-9.
46. Rose DN. Benefits of screening for latent Mycobacterium tuberculosis infection. Arch Intern Med 2000;160:1513-21.
47. Salmon D. Recommendations about the prevention and management of tuberculosis in patients taking infliximab. Joint Bone Spine 2002;69:170-2.
48. Jasmer RM, Nahid P, Hopewell PC. Latent tuberculosis infection. N Engl J Med 2002;347:1860-6.
49. Khan K, Muennig P, Behta M, Zivin JG. Global drug-resistance patterns and the management of latent tuberculosis infection in immigrants to the United States. N Engl J Med 2002;347:1850-9.
50. Pablos-Mendez A, Raviglione MC, Laszlo A, et al. Global surveillance for antituberculosis-drug resistance, 1994-1997. N Engl J Med 1998;338:1641-9.
51. Espinal MA, Laszlo A, Simonsen L, et al. Global trends in resistance to antituberculosis drugs. World Health Organization-International Union against Tuberculosis and Lung Disease Working Group on Anti-Tuberculosis Drug Resistance Surveillance. N Engl J Med 2001;344:1294-303.
52. Anonymous. Fatal and severe hepatitis associated with rifampin and pyrazinamide for the treatment of latent tuberculosis infection – New York and Georgia, 2000. MMWR Morb Mortal Wkly Rep 2001;50:289-91.
53. Jasmer RM, Saukkonen JJ, Blumberg HM, et al. Short-course rifampin and pyrazinamide compared with isoniazid for latent tuberculosis infection: a multicenter clinical trial. Ann Intern Med 2002;137:640-7.
54. Rovere Querini P, Vecellio M, Sabbadini MG, Ciboddo G. Miliary tuberculosis after biological therapy for rheumatoid arthritis. Rheumatology (Oxford) 2002;41:231.
55. Vonkeman HE, Valk PD van der, Mulder L, Laar MA van de. Fatal extra-pulmonary tuberculosis during treatment with the immunosuppressive infliximab [Fatale miliaire tuberculose tijdens behandeling met infliximab]. Ned Tijdschr Geneeskd 2002;146:1196-9.
56. Verhave JC, Sprenger HG, Essen LH van, Monteban WE, Mannes GP, Altena R van. Signs of miliary tuberculosis: which diagnostic tests and when to treat? [Aanwijzingen voor miliaire tuberculose: welke diagnostiek en wanneer behandelen?]. Ned Tijdschr Geneeskd 2002;146:1161-5.
57. Criscione LG, St. Clair EW. Tumor necrosis factor-α antagonists for the treatment of rheumatic diseases. Curr Opin Rheumatol 2002;14:204-11.
58. Drenth JP, Meer JW van der. Hereditary periodic fever. N Engl J Med 2001;345:1748-57.