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The risk of tuberculosis related to tumour necrosis factor antagonist therapies: a TBNET consensus statement

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ABSTRACT: Anti-tumour necrosis factor (TNF) monoclonal antibodies or soluble TNF receptors have become an invaluable treatment against chronic inflammatory diseases, such as rheumatoid arthritis, inflammatory bowel disease and psoriasis. Individuals who are treated with TNF antagonists are at an increased risk of reactivating latent infections, especially tuberculosis (TB).

Following TNF antagonist therapy, the relative risk for TB is increased up to 25 times, depending on the clinical setting and the TNF antagonist used. Interferon-γ release assays or, as an alternative in individuals without a history of bacille Calmette–Guérin vaccination, tuberculin skin testing is recommended to screen all adult candidates for TNF antagonist treatment for the presence of latent infection with *Mycobacterium tuberculosis*.

Moreover, paediatric practice suggests concomitant use of both the tuberculin skin test and an interferon-γ release assay, as there are insufficient data in children to recommend one test over the other. Consequently, targeted preventive chemotherapy is highly recommended for all individuals with persistent *M. tuberculosis*-specific immune responses undergoing TNF antagonist therapy as it significantly reduces the risk of progression to TB.

This TBNET consensus statement summarises current knowledge and expert opinions and provides evidence-based recommendations to reduce the TB risk among candidates for TNF antagonist therapy.

KEYWORDS: Interferon-γ release assay, tuberculin skin test, tuberculosis, tumour necrosis factor

Tumour necrosis factor (TNF) and TNF receptors play a key role in mediating immune responses in acute and chronic inflammation [1–3]. Over the past decade, TNF antagonists in the form of anti-TNF monoclonal antibodies or TNF fusion protein have become an invaluable treatment against chronic inflammatory diseases, such as rheumatoid arthritis, psoriasis and psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis and inflammatory bowel disease [4–7].

Tuberculosis (TB) is a granulomatous disease caused by infection with *Mycobacterium tuberculosis*. Most of the individuals who are thought to have become infected with *M. tuberculosis* will never develop TB due to the control exercised by the host immune system [8, 9]. One of the key cytokines in the immune response against infection with *M. tuberculosis* is TNF, which is also critical for the integrity of the granuloma [10]. Individuals who are being treated with anti-TNF therapies are at increased risk of developing TB. Following TNF antagonist therapy, the relative risk for TB is increased 1.6–25.1 times, depending on the clinical setting and the TNF antagonist used [4, 7, 11, 12]. The majority of cases of TB related to TNF antagonist therapies occur in close temporal proximity to

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treatment initiation with TNF antagonists [7, 13] and reactivation of latent infection with *M. tuberculosis* shows characteristically rapid progression.

Preventive chemotherapy can substantially reduce the incidence of TB in individuals with latent infection, who are being identified by positive *M. tuberculosis* specific immune responses either by the tuberculin skin test or an *in vitro* interferon-γ release assay (IGRA).

In the only prospective cohort study to date that evaluated the effect of prevention of TB in individuals undergoing TNF antagonist therapies, the risk in individuals who exhibited positive immune responses in a two-step tuberculin skin test prior to TNF antagonist therapies could be dramatically reduced by 9 months isoniazid preventive therapy [14]. However, this effect was only apparent in those who were compliant with preventive therapy.

Recently, IGRAs have been introduced for the diagnosis of latent infection with *M. tuberculosis*. The sensitivity of IGRA for the detection of latent infection is generally superior to the tuberculin skin test [15, 16] and is most apparent in immunocompromised individuals [17]. With a few exceptions, immune responses that are assayed through the IGRAs are not affected by infections of non-tuberculous mycobacteria. Importantly, antigens that elicit immune responses in IGRAs are absent in *Mycobacterium bovis* bacille Calmette–Guérin (BCG) and consequently IGRAs have superior specificity for *M. tuberculosis* infection compared to the tuberculin skin test in individuals with a history of BCG vaccination [15, 16]. The positive predictive value of an IGRA result for the development of TB is accordingly superior compared to that of a tuberculin skin test [18].

Because of the superior performance of IGRAs for the diagnosis of latent infection with *M. tuberculosis* in general, national guidelines for screening prior to TNF antagonist therapies in Germany [19] and Switzerland [20] advocate the use of IGRAs in this situation. However, IGRAs are not universally available and it is currently unclear whether they are superior to the tuberculin skin test in identifying individuals at risk of TB following TNF antagonist therapy who should be offered preventive therapy.

There is substantial uncertainty among clinicians about the management of patients undergoing TNF antagonist therapies and the best strategies for the prevention of TB. As international guidelines do not currently exist on this topic and clinical decisions have to rely on expert opinions, this document by a TBNET consensus group summarises the current knowledge of the risk of TB following TNF antagonist therapies and provides evidence graded recommendations (evidence categories A–D) (table 1) for the screening for latent infection with *M. tuberculosis* and for preventive chemotherapies in individuals undergoing TNF antagonist therapies.

TNF AND TNF ANTAGONIST THERAPIES: MODE OF ACTION AND SIDE-EFFECTS

TNF biology

TNF and TNF receptors are important regulators of immune cell activation, proliferation, differentiation, survival and apoptosis [1–3]. TNF is produced as a transmembrane protein (tmTNF) which is cleaved by a metalloproteinase (TACE) to a soluble form (sTNF). TNF associates to a homotrimer which binds to cell surface TNFR1 and TNFR2. TNFR2 is fully activated by tmTNF but not by sTNF. TNFR1 signals *via* death domain caspase-dependent pathways and induces apoptosis. Both TNFR1 and TNFR2 also signal pro-inflammatory pathways [21].

TNF increases the phagocytic capacity of macrophages and enhances the killing of intracellularly viable bacteria *via* the generation of reactive nitrogen and oxygen intermediates, effectively synergising with interferon (IFN)-γ [22]. Neutralisation of TNF activity leads to resumption of mycobacterial growth within granulomas during chronic latent infection [23, 24]. Mice deficient in TNF or TNFR p55 have dramatically increased microbial loads and succumb prematurely to disease

TABLE 1 Description of levels of evidence

Evidence category	Sources of evidence	Definition
A	Randomised controlled trials Rich body of data	Evidence is from end-points of well-designed randomised controlled trials that provide a consistent pattern of findings in the population for which the recommendation is made. Category A requires substantial numbers of studies involving substantial numbers of participants.
B	Randomised controlled trials Limited body of data	Evidence is from end-points of intervention studies that include only a limited number of patients, *post hoc* or subgroup analysis of randomised controlled trials, or meta-analysis of randomised controlled trials. In general, category B pertains when few randomised trials exist, they are small in size, they were undertaken in a population that differs from the target population of the recommendation, or the results are somewhat inconsistent.
C	Nonrandomised trials Observational studies	Evidence is from outcomes of uncontrolled or nonrandomised trials or from observational studies.
D	Panel consensus judgement	This category is used only in cases where the provision of some guidance was deemed valuable but the clinical literature addressing the subject was deemed insufficient to justify placement in one of the other categories. The panel consensus is based on clinical experience or knowledge that does not meet the above-listed criteria.

caused by *Listeria monocytogenes*, *M. tuberculosis* or *Histoplasmosis capsulatum* [25–27].

TNF stimulates the production of chemokines such as CCL2, CCL3, CCL4, CCL5 and CCL8 in macrophages and T-cells and induces the expression of vascular adhesion molecules such as CD54, promoting a focused accumulation of immune cells at the site of infection [27, 28]. In this way, TNF is responsible for granuloma initiation and maintenance of granuloma integrity. In TNF-deficient mice infected with *M. tuberculosis*, granuloma formation is delayed and malorganised, leading to inefficient containment of infectious foci [29]. Similarly, neutralisation of TNF activity following the establishment of granulomas results in their structural disintegration [23, 24]. tmTNF alone is sufficient for mounting early resistance against mycobacterial infections by regulating T-helper (Th)1-type cytokine and chemokine expression but, in the absence of sTNF, is insufficient to provide lasting anti-mycobacterial protection (fig. 1) [30, 31].

TNF has long been postulated to be directly involved in caseation necrosis, because infection of cells with *M. tuberculosis* renders them highly sensitive to killing by TNF *in vitro* [32]. Moreover, treatment of *M. tuberculosis*-infected mice with recombinant TNF resulted in increased inflammation in the lungs and accelerated mortality [33]. However, TNF also plays a regulatory role during mycobacteria-induced inflammation. For example, TNF can induce apoptosis in TNF receptor p55 bearing cells thereby eliminating excessive cellular responses [24]. TNF can also act as a survival factor and may be involved in the maintenance of macrophage viability at the site of infection. In TNFR p55-knockout mice infected with *Mycobacterium avium*, the granuloma structure cannot be maintained, and the dysregulated, hyperinflammatory response causes premature death of infected mice [34]. TNF (and also IFN-γ), possibly *via* the induction of inducible nitric oxide synthase, therefore also serves to downregulate an exacerbated inflammatory response, in part by inducing apoptosis of effector T-cells [35].

Thus TNF plays a critical role in the host response to infection. The closely related cytokines, lymphotoxins (LT) α and β, which occur as homo- or heterotrimers, also contribute to anti-mycobacterial and granulomagenic activities, but are insufficient alone to support granuloma formation in the absence of TNF [36–38]. On the other hand, $LT\alpha_3$ is necessary for establishing the proper architecture of the granuloma, since, in the absence of $LT\alpha_3$, T-cells do not migrate into the granulomatous lesion but only accumulate in perivascular cuffs (fig. 1) [24].

TNF antagonists

Four monoclonal anti-TNF antibodies are currently in clinical use: infliximab, adalimumab, golimumab and certolizumab pegol (fig. 2) [21, 39]. Infliximab is comprised of human immunoglobulin (Ig)G1 constant regions and murine variable regions, whereas adalimumab and golimumab both have human IgG1 constant and variable regions. Certolizumab pegol is a pegylated, humanised Fab' fragment. Infliximab, adalimumab and golimumab are approved for treatment of rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. Infliximab, adalimumab and certolizumab are approved for treatment of Crohn's disease. Infliximab is also approved for ulcerative colitis, and may be effective in sarcoidosis. Certolizumab also appears to be effective for rheumatoid arthritis. Infliximab is administered by intravenous infusion, producing peak blood concentrations of 80 $\mu g \cdot mL^{-1}$. Adalimumab, certolizumab and golimumab are administered by subcutaneous injection. Peak blood concentrations of 10 $\mu g \cdot mL^{-1}$ have been reported for adalimumab, 90 $\mu g \cdot mL^{-1}$ for certolizumab and 2.5 $\mu g \cdot mL^{-1}$ for golimumab.

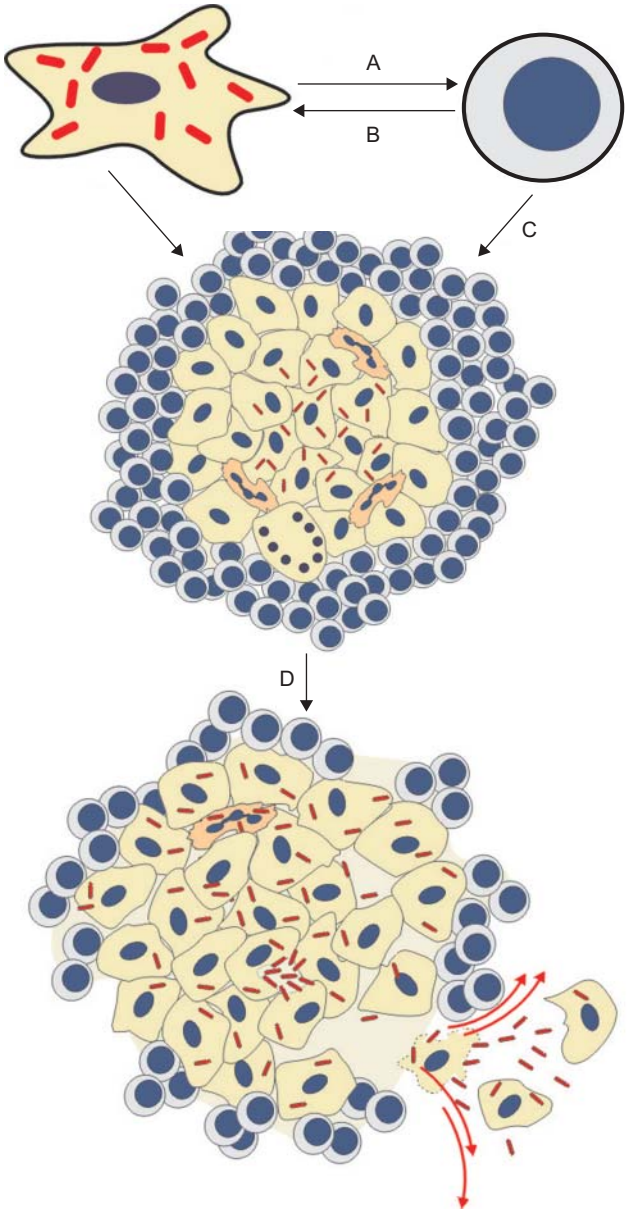

FIGURE 1. Tumour necrosis factor (TNF) acts at multiple steps in antibacterial and inflammatory responses to *Mycobacterium tuberculosis* infection. A: macrophage-derived TNF acts as a co-stimulus for T-cells. B: T-cell-derived TNF primes macrophages for mycobactericidal activity. C: macrophage- and T-cell-derived TNF (together with interferon (IFN)-γ and chemokines) induce recruitment and organised accumulation of mononuclear cells into highly structured granulomas. TNF and IFN-γ also regulate excessive inflammation by inducing apoptosis of T-cells. D: TNF antagonist therapy results in granuloma breakdown and dissemination of mycobacteria. Reproduced from [10] with permission from the publisher.

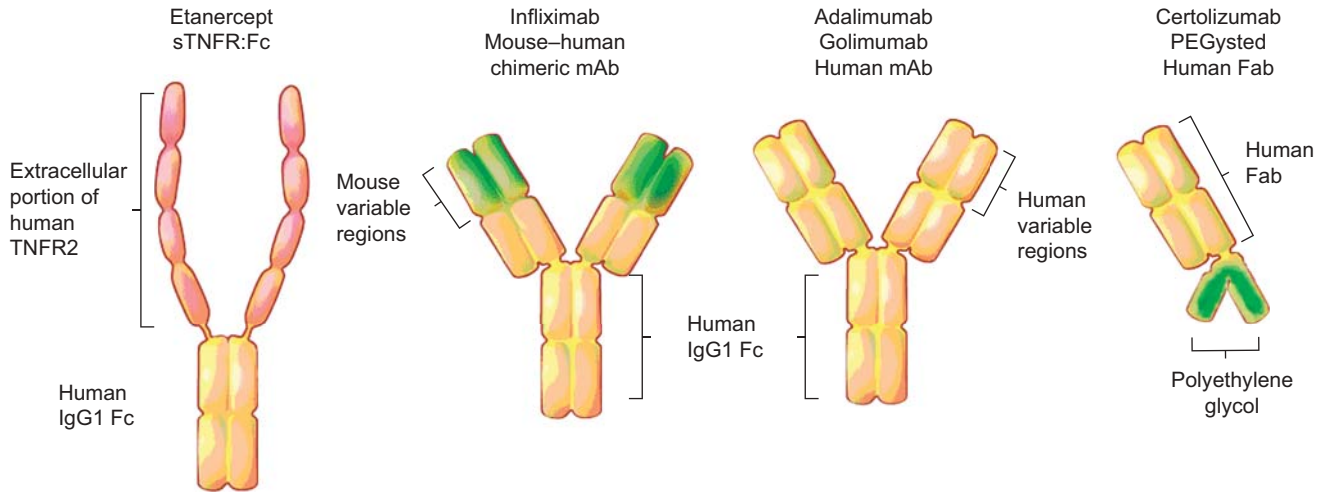

FIGURE 2. Structures of the tumour necrosis factor (TNF) antagonists. TNFR: TNF receptor; sTNFR: soluble TNFR; Ig; immunoglobulin; mAb: monoclonal antibody. Adapted from [39] with permission from the publisher.

Etanercept is the only soluble TNF receptor currently in clinical use. It is comprised of two extracellular domains of human TNF-R2 fused to the Fc fragment of human IgG1. It binds trimeric TNF and lymphotoxin. Etanercept is approved for the treatment of rheumatoid arthritis, psoriatic arthritis, psoriasis, juvenile rheumatoid arthritis and ankylosing spondylitis. Etanercept is not effective against granulomatous inflammatory conditions such as Crohn's disease or sarcoidosis. It is administered by subcutaneous injection, usually once or twice weekly, producing blood concentrations of 1–2.4 $\mu g \cdot mL^{-1}$.

Structure–function relationship: clues for better TNF antagonist therapies

It is biologically plausible that efficacy against chronic granulomatous inflammation and efficiency in reactivating latent *M. tuberculosis* infection are linked. Structural and functional differences among the TNF antagonists may account for their differences in these properties [39]. Peak blood levels of infliximab are several times those of other TNF antagonists; however, this does not appear to confer any unique clinical characteristics. TNF readily dissociates from etanercept which releases >90% of bound cytokine within 2–3 h; dissociation of TNF from infliximab was undetectable in the same study [40]. However, in a study using plasmon resonance to examine binding affinities of TNF antagonists for sTNF, adalimumab and infliximab were found to be less potent than etanercept and certolizumab. Etanercept binds less strongly to tmTNF than infliximab, so that neutralisation of tmTNF signalling is two-fold greater for certolizumab, infliximab and adalimumab compared with etanercept [40]. Anti-TNF monoclonal antibodies were reported to inhibit T-cell activation and cytokine (including IFN-γ) expression, while etanercept showed reduced or no effects in this regard [41–43].

Several studies have examined the ability of anti-TNF antibodies to cross-link transmembrane TNF and thereby induce apoptosis in TNF-expressing T-cells. This activity can be demonstrated *in vitro* using reporter cell constructs, and *in vivo* in cells infiltrating the gut of Crohn's disease patients [44–48]. Etanercept lacks this activity. Defective apoptosis in gut lymphocytes is thought to be central to the pathogenesis of Crohn's disease. Other studies have examined complement-mediated lysis of TNF-expressing T-cells. For example, BRUNS *et al.* [49] found that numbers of circulating effector memory CD8 T-cells were reduced by infliximab treatment.

However, experience with the Fab' TNF antibody fragment certolizumab pegol calls into question the significance of many of these observations. With only one TNF binding region and without Fc, certolizumab can neither crosslink tmTNF nor activate complement and, therefore, can induce neither apoptosis nor necrosis in TNF-expressing cells. Nonetheless, certolizumab is highly effective as therapy for Crohn's disease [50], and appears to efficiently reactivate TB (see below). These findings suggest that other properties, such as binding avidity and inhibition of cell activation must, therefore, be more important than induction of cell death. This is consistent with computer simulations indicating that even low levels of sTNF were sufficient for control of latent infection with *M. tuberculosis* [51].

These arguments notwithstanding, there are convincing experimental data that selective inhibition of sTNF only, while sparing tmTNF activity, may be beneficial. For example, a selective inhibitor of sTNF efficiently protected mice from acute liver inflammation yet maintained immunity to mycobacterial infections. In contrast, nonselective inhibition of both sTNF and tmTNF suppressed immunity to *M. bovis* BCG and *M. tuberculosis* [52, 53].

Summary

In summary, TNF is critical for macrophage activation and immune cell recruitment to the granuloma. In its absence, granulomas disintegrate and facilitate mycobacterial re-growth and dissemination. The efficacy of different TNF antagonists against granulomatous disorders correlates with their activity in reactivating TB. This is probably due to both different pharmacokinetics and different modes of action. Differential induction of apoptosis (particularly in T-cells) and differential inhibition of soluble *versus* transmembrane TNF may account for some of the observed differences in reactivating TB

following treatment with anti-TNF antibodies *versus* soluble TNF receptor constructs.

TNF ANTAGONIST THERAPY IN RHEUMATOID ARTHRITIS: HISTORY, CLINICAL EFFECT AND DOSING

TNF was found to be one of the key cytokines in the pathogenesis of rheumatoid arthritis and other inflammatory rheumatic diseases. This finding has led to the development of drug-targeted therapies for the first time in inflammatory rheumatic conditions [54]. Today, all the available TNF antagonists are licensed for the treatment of rheumatoid arthritis while their approval status for other rheumatic diseases differs (table 2).

Rheumatoid arthritis

Rheumatoid arthritis is the most common inflammatory rheumatic disease characterised by chronic synovial inflammation and progressive erosive polyarticular joint damage. Data from the first randomised controlled clinical trial on a TNF antagonist were reported in 1994 and showed significant improvement of signs and symptoms after treatment with infliximab compared with placebo [55]. Thereafter, numerous clinical trials demonstrated that infliximab, etanercept, adalimumab, golimumab and certolizumab improved not only signs and symptoms, and health-related quality of life but also delay the progression of joint damage [56]. TNF antagonists administered as single agents are not significantly superior to methotrexate in controlling signs and symptoms, but exhibit significant improvement compared with traditional disease modifying antirheumatic drugs (DMARD) when given together with methotrexate in DMARD-incomplete responder patients. Therefore, treatment with TNF-α antagonists in established rheumatoid arthritis is recommended in most guidelines for patients who partially respond to at least one conventional DMARD including methotrexate (table 2) [56, 57]. Infliximab is licensed only in combination with methotrexate. A clinically significant improvement with TNF antagonists in combination with methotrexate is seen in around two-thirds of the patients. Furthermore, clinical disease remission (*i.e.* DAS28 score <2.6) can be achieved in up to 30% of DMARD-incomplete responder patients and close to 50% of DMARD-naïve early rheumatoid arthritis patients [58].

Based on published evidence [59], the American College of Rheumatology recently recommended the use of a TNF antagonist in combination with methotrexate in DMARD-naïve early rheumatoid arthritis (disease duration <3 months) patients with high disease activity and markers of poor prognosis, in the absence of treatment cost-related limitations [57]. In contrast, the European League against Rheumatism recommends initial therapy with methotrexate in early rheumatoid arthritis because of a favourable benefit/to risk ratio and its cost-effectiveness [60].

Randomised clinical trials comparing the efficacy of the different TNF blocking agents have not yet been reported. However, none of the meta-analyses, including reported clinical trials, have provided evidence that one TNF antagonist is significantly superior over the other in terms of clinically relevant outcomes [56].

Ankylosing spondylitis

Efficacy of infliximab for treatment of ankylosing spondylitis was confirmed in a randomised clinical trial for the first time in 2002 [61]. Thereafter, several clinical trials have demonstrated that infliximab, adalimumab and etanercept provide significant and sustained improvement in clinical scores, such as the Bath Ankylosing Spondylitis Disease Activity Index and the Bath Ankylosing Spondylitis Functional Index, and in uveitis [62, 63]. In contrast to rheumatoid arthritis and psoriatic arthritis, the impact on joint damage is debated [64, 65]. Indirect comparisons of clinical trials did not demonstrate superiority of one TNF antagonist over the other in the improvement of signs and symptoms (table 2) [63].

Psoriatic arthritis

In psoriatic arthritis, infliximab, etanercept, adalimumab and golimumab are all efficacious in the treatment of both joint and skin disease [66]. Radiographic data show that etanercept and infliximab can also delay progression of joint damage (table 2) [66].

Juvenile idiopathic arthritis

At present, etanercept and adalimumab are approved for treatment of juvenile idiopathic arthritis incomplete DMARD responder patients (table 2). A significant and sustained reduction in disease activity is seen in ~60% of patients in articular manifestations and uveitis [67, 68]. However, only 25% of patients attain remission, and disease flares occur in ~50% once in remission [69].

Summary

In summary, in rheumatoid arthritis TNF antagonists not only improve signs and symptoms and health-related quality of life, but also delay the progression of joint damage. In ankylosing spondylitis, TNF antagonists are efficacious for treatment of axial involvement and extraarticular manifestations. In rheumatic diseases, there is as yet no evidence that one TNF antagonist is significantly superior over the other.

TNF ANTAGONIST THERAPY IN INFLAMMATORY BOWEL DISEASE: HISTORY, CLINICAL EFFECT AND DOSING

Presently, three different TNF antagonists are approved for the therapy of inflammatory bowel disease. These are infliximab (for both Crohn's disease and ulcerative colitis) [70–72], adalimumab (Crohn's disease) [73], and certolizumab pegol (Crohn's disease, not approved in the European Union) (table 2) [74, 75]. Apart from infliximab, adalimumab and certolizumab several further TNF antagonists are in development with golimumab being the one that is most advanced in development and presently undergoing phase III clinical trials in ulcerative colitis.

Clinical efficacy is similar between the different TNF antagonists that induce response in ~60% of patients with complicated Crohn's disease (table 2). This has first been established for infliximab through a landmark trial in which efficacy could be demonstrated in patients with Crohn's disease [70]. Of the responders ~40–50% could be maintained over a long time; several years of maintenance efficacy during open label follow-up have been documented for some of the agents. Interestingly, use of TNF antagonists early in the course of

TABLE 2 Tumour necrosis factor antagonists: licensed indications, conditions for prescription and dosing

Licensed indications	Infliximab	Etanercept	Adalimumab	Golimumab	Certolizumab
Rheumatoid arthritis	+[§]	+[§,ƒ]	+[§,ƒ]	+[§]	+[§,ƒ]
Active disease and inadequate response to DMARD including MTX[#]	+[§] Dosing: 3 mg·kg^{-1} *i.v.* week 0, 2, 6 then 8-weekly Inadequate response: increase to 7.5 mg·kg^{-1} 8-weekly or 3 mg·kg^{-1} 4-weekly	+[§,ƒ] Dosing: 25 mg sc twice a week or 50 mg sc once a week	+[§,ƒ] Dosing 40 mg sc 2-weekly	+[§] Dosing 50 mg sc 4-weekly	+[§,ƒ] Dosing 400 mg sc week 0 and 2, then once a month
Patients with severe and progressive/erosive disease without prior DMARD therapy[#]					
Patients with moderately to severely active disease[¶]					
Ankylosing spondylitis	+	+	+	+	
Inadequate response to conventional therapy (*i.e.* NSAID)[#]	Dosing: 3 mg·kg^{-1} *i.v.* week 0, 2, 6 then 6–8-weekly	Dosing: 25 mg sc twice a week or 50 mg sc once a week	Dosing 40 mg sc 2-weekly	Dosing 50 mg sc 4-weekly	
Active disease[¶]					
Psoriatic arthritis	+[§,ƒ]	+	+	+[§,ƒ]	
Active disease and inadequate response to DMARD including MTX[#]	Dosing: 3 mg·kg^{-1} *i.v.* week 0, 2, 6 then 8-weekly	Dosing: 25 mg sc twice a week or 50 mg sc once a week	Dosing 40 mg sc 2-weekly	Dosing 50 mg sc 4-weekly	
Active arthritis[¶]					
Juvenile idiopathic arthritis		+	+		
Age >4 and <18 yrs and active disease and inadequate response to or intolerance of DMARD including MTX[#]		Dosing: 0.4 mg·kg^{-1} sc twice a week	Dosing 40 mg sc 2-weekly		
Patients with moderately to severely active disease[¶]					
Crohn's disease	Dosing 5 mg·kg^{-1} *i.v.* week 0, 2, 6 then 8-weekly If ineffective increase to 10 mg·kg^{-1} every 8 weeks	Not used	Dosing 160 mg sc, followed by 80 mg sc then 40 mg every second week	Not approved	Dosing 400 mg sc at weeks 0, 2 and 4 followed by 400 mg every 4 weeks (not yet approved in Europe)
Ulcerative colitis	Dosing 5 mg·kg^{-1} *i.v.* week 0, 2, 6 then 8-weekly If ineffective increase to 10 mg·kg^{-1} every 8 weeks	Not used	Not yet approved	Not yet approved	Not yet approved
Psoriasis	Dosing	Dosing	Dosing	No current data	No current data
Very severe plaque psoriasis PASI >20, DLQI >18 and failure or contraindication to 2nd line drugs (MTX, cyclosporine, PUVA)	5 mg·kg^{-1} *i.v.* at weeks 0, 2, 6 and then every 8 weeks	25 mg sc twice weekly or 50 mg weekly up to 24 weeks or 50 mg twice weekly up to 12 weeks and weekly thereafter	80 mg sc week 0, 40 mg week 1 and alternate weeks thereafter		
Severe plaque psoriasis PASI >10, DLQI >10 and failure or contraindication to 2nd line drugs (MTX, cyclosporine, PUVA)					

DMARD: disease-modifying anti-rheumatic drug; MTX: methotrexate; NSAID: nonsteroidal anti-rheumatic drug; PASI: Psoriasis Area Severity Index; DLQI: Dermatology Life Quality Index; PUVA: psoralen ultraviolet A-range; sc: subcutaneously. [#]: plus MTX; [¶]: without MTX if contraindicated or not tolerated; [§]: European Medicines Agency approved indication; [ƒ]: Federal Drug Administration approved indication.

disease (*i.e.* before patients have received oral immunosuppressants such as azathioprine which corresponds to a median disease duration of ~2.4 yrs) leads to a much higher level of efficacy [76], with almost 70% of Crohn's disease patients achieving corticosteroid-free remission as an end-point after 1 yr of therapy. This end-point ''corticosteroid-free remission'' historically was first defined for TNF antagonist therapy, as former therapeutic options (standard therapy) were not capable of inducing corticosteroid-free remission in a larger percentage of patients. Treatment with TNF antagonists is the first therapy that leads to ulcer healing and closes other overt lesions in the inflamed mucosa as evidenced by endoscopy. This is seen as early as 10 weeks after the start of therapy. For the first time a correlation between Crohn's disease activity

index and Crohn's disease endoscopic index of severity has been observed under TNF antagonist therapies.

All TNF antagonising drugs close perianal and other fistulae. Again, this is a new therapeutic quality that was not achieved with the standard therapies available in the pre-TNF antagonist era. Maintenance of closure (which is successful in ~50% of cases over a 1-yr duration) requires continued TNF antagonist therapy.

Long-term problems in inflammatory bowel disease comprise structural damage (*e.g.* stenoses or fistulae) that lead to long-term morbidity and frequent hospitalisation and surgery. TNF antagonist therapy reduces the rate of disease-related hospitalisation and surgery. Infliximab is also approved for use in paediatric Crohn's disease.

Adverse drug-events due to TNF antagonist therapies are similar between the agents. Some differentiation in such events seen in inflammatory bowel disease from other disorders occurs as a result of the young age of patients with inflammatory bowel disease in comparison with other indications. Therefore, some problems are less frequently seen in inflammatory bowel disease (*e.g.* reactivation of TB) whereas others are unique (*e.g.* hepatosplenic lymphoma, a rare complication that occurs when infliximab is given in combination with azathioprine in young males). Crohn's disease appears to be a condition in which immunogenicity of foreign proteins may play a particular role. Overlooked abscesses, in particular in patients with fistula systems, are an important source of infectious complications. In past years it has become apparent that many of the adverse drug events associated with TNF antagonist therapy can be attributed to the co-medication (azathioprine and glucocorticoids) or to poorly managed chronic active disease.

Summary

In summary, three different TNF antagonists with clinical efficacy (infliximab, adalimumab and certolizumab pegol) for remission induction and maintenance of remission are available and a fourth agent (golimumab) is in advanced clinical development. Efficacy end-points include mucosal healing, glucocorticoid free remission and fistula closure. Doses needed for inflammatory bowel disease are, in general, higher than for rheumatoid arthritis. Infliximab is the only agent approved for ulcerative colitis and for paediatric Crohn's disease.

TNF ANTAGONIST THERAPY IN PSORIASIS: HISTORY, CLINICAL EFFECT AND DOSING

TNF is a product of various skin cell types and has been shown to be pro-inflammatory when released into the skin [77]. Its central importance in inflammatory skin disease has been demonstrated by the high level of effectiveness of TNF antagonists in psoriasis [78]. Although psoriasis is the most important dermatological indication for TNF antagonists (table 2), these drugs are now developing indications in other inflammatory dermatological conditions.

Psoriasis

Infliximab was first reported to be of utility in psoriasis in 2000 [79]. This was a serendipitous observation of clearing of psoriasis in a patient with co-existing Crohn's disease undergoing TNF antagonist treatment. Since then there have been numerous reports confirming the effectiveness of all TNF antagonists (infliximab, etanercept and adalimumab) in various forms of the disease.

Infliximab has been used in the treatment of psoriasis at doses of 3–10 $mg \cdot kg^{-1}$ and is now generally used at a dose of 5 $mg \cdot kg^{-1}$ with an induction regimen consisting of dosing at 0, 2 and 6 weeks followed by regular 8-weekly infusions. Secondary treatment failure appears to be minimised by regular rather than intermittent dosing [80]. There is also an increasing trend towards concomitant use of low dose methotrexate in patients on infliximab [81] in order to reduce the risk of secondary failure, although firm evidence of this is lacking [78]. Secondary failure with infliximab is unpredictable, although it seems to be associated with the development of antinuclear antibodies [82]. Infliximab is highly effective, resulting in 75% clearance of psoriasis (Psoriasis Area and Severity Index (PASI) 75) in >70% patients at 12 weeks [83]. In addition to improving the chronic plaque form of the disease, infliximab has been shown to be of utility in generalised pustular psoriasis in small case series [84], although palmar plantar pustular psoriasis does not appear to respond and may even be precipitated by TNF antagonist therapy [85]. Improvement of nail disease has been demonstrated [86].

Etanercept appears less effective than infliximab, although it is more convenient for patients as it can be administered at home. Doses of 25–50 mg twice weekly are employed with typical PASI75 responses of 34–48% at 12 weeks [87]. Longer dosing periods result in increases in PASI75 response to 43–57%. Etanercept has been shown to be effective in the treatment of psoriasis in children [88] and is licensed for use in children in the UK at a dose of up to 0.8 $mg \cdot kg^{-1}$ to a maximum of 50 mg weekly.

Adalimumab appears to combine advantages of infliximab and etanercept in that it seems to have a similar efficacy to infliximab, yet can be administered at home by the patient [89, 90]. It is generally used with an induction regimen of 80 mg at week 0, followed by 40 mg and 12-week PASI75 responses of 69–80% have been reported.

There are currently few data to guide sequencing of TNF antagonist therapies in patients who either fail to respond to treatment at all (primary failure) or who respond initially and then lose efficacy (secondary failure), although failure of response to one drug does not appear to predict failure of response to another [91, 92].

Adverse effects of TNF antagonists in the treatment of dermatological disease are much the same as those experienced in other indications reviewed elsewhere in this article. Mention should however be made of the rare paradoxical appearance of psoriasis-like skin lesions in patients with rheumatological and gastrointestinal disease treated with TNF antagonists [93, 94]. The mechanisms underlying these reactions, which tend to resolve following withdrawal of treatment, are unclear. They do however suggest that psoriasis is not one disease but potentially the result of several different pathogenetic pathways.

Dermatological indications other than psoriasis

Whilst TNF antagonists have been used successfully off-label in a number of other dermatological conditions including

hidradenitis suppurativa [95], sarcoidosis [96] and pyoderma gangrenosum [97], robust data on their effectiveness is awaited and will depend on properly controlled clinical studies. It seems clear, however, that with time, the indications for these drugs in dermatology will expand.

Summary

In summary, infliximab, adalimumab and etanercept are licensed for the treatment of moderate to severe psoriasis. Infliximab and adalimumab are highly effective, resulting in positive treatment responses in >70% of patients with psoriasis. Secondary treatment failure appears to be minimised by regular rather than intermittent dosing.

THE RISK OF TB FOLLOWING TNF ANTAGONIST THERAPIES

In Canada, Europe and Asia, the relative risk of TB in rheumatoid arthritis ranges between 2 and 16 owing to the disease itself and the use of non-biological medications [4, 98–101]. In contrast, in one study from the US using non-standardised rates for comparison, no increased risk was found [11]. In rheumatic diseases other than rheumatoid arthritis this information is missing.

TNF is crucial in host immunity to *M. tuberculosis* and other intracellular bacteria [102]. In murine models, TNF deficiency increases susceptibility to primary infection with M. tuberculosis [29] and experimental depletion of TNF causes active TB in mice that previously controlled *M. tuberculosis* infection [36, 103, 104]. 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 [49]. Clinical studies of the impact of TNF antagonists on TB face several challenges, as TB rates vary substantially by country and ethnicity, and may be influenced by underlying medical conditions (table 3). Three strategies for data collection have been used. A study published in 2004 identified 138 TB cases in patients treated with TNF antagonists that had been voluntarily reported to the US Food and Drug Administration through its adverse event reporting system [12]. The TB risk posed by infliximab appeared to be twice that of etanercept. Risks of histoplasmosis and coccidioidomycosis were also increased six to seven-fold. A study published in 2006 identified 51 TB cases in Canadian rheumatoid arthritis patients treated with TNF antagonists through a search of a large pharmacy prescription database [105]. The risk posed by infliximab was 1.3 times that of etanercept. However, the authors used prescriptions for isoniazid as an indicator for TB and, therefore, probably misclassified latent infection with *M. tuberculosis* as TB [108, 109]. Another study from the BIOBADASER (Spanish Registry of Adverse Events of Biological Therapies in Rheumatic Diseases) registry reported a not significantly different risk of active TB posed by all three TNF antagonits; a trend toward a two-fold increased rate was noted for infliximab, but the study was limited in its statistical power [14]. A recent study identified 69 TB cases prospectively through the French RATIO registry [106]. The sex and age-adjusted TB incidence rate was 1.17 per 1,000 patient-yrs, 12.2 times that of the general population. Nearly all of the excess risk was due to infliximab (standardised incidence ratio (SIR) 18.6, 95% CI 13.4–25.8) and adalimumab (SIR 29.3, 95% CI 20.2–42.4) rather than etanercept (SIR 1.8, 95% CI 0.7–4.3). A similar conclusion was reached by a Portuguese biologics registry study of 13 TB cases that found the TB risk with anti-TNF antibodies to be 12-fold greater than with etanercept [110]. In the most recent study by the British Society for Rheumatology Biologics Register, the rate of TB in patients with rheumatoid arthritis treated with TNF antagonist therapies was three to four-fold higher in patients receiving infliximab and adalimumab than in those receiving etanercept [110]. These studies indicate that the antibodies adalimumab and infliximab share a higher risk of progression to TB than soluble TNF receptor, correlating with therapeutic efficacy against chronic granulomatous inflammation in Crohn's disease. It does not correlate with the risk of other mycobacterioses, which appears to be similar for both drug classes [12, 112].

Most of the active TB cases in patients treated with TNF antagonists are due to reactivation of latent infection with *M. tuberculosis*. TB in patients who have been treated with TNF antagonist therapies usually progresses rapidly and is frequently disseminated. The most effective way to avoid reactivation is the treatment of the latent infection. A number of countries have generated national guidelines to deal with

TABLE 3 Risk of active tuberculosis in different studies in patients suffering from rheumatic diseases treated with TNF antagonists

First author [ref.]	Country	Type of study	Adalimumab	Etanercept	Infliximab	Comments
Wallis [12]	USA	Cases voluntarily reported to US FDA		IR 28/100000	IR 54/100000	Etanercept *versus* infliximab p<0.0001
Brassard [105]	Canada	Search of a large pharmacy prescription database		RR 1.2 (0.9–1.8)	RR 1.6 (1.0–2.6)	
Gomez-Reino [14]	Spain	Data from registry	IR 176/100000	IR 114/100000	IR 383/100000	p=NS, wide confidence interval
Tubach [106]	France	Data from registry	IR 215/100000	IR 9.3/100000	IR 187.5/100000	SIR 29.3 for adalimumab SIR 1.8 for etanercept SIR 18.6 for infliximab. p<0.0001
Fonseca [107]	Portugal	Data from registry	4 cases/171 patients	1 case/333 patients	8 cases/456 patients	Exposure is not provided

US FDA: US Food and Drug Administration; IR: incidence rate; RR: adjusted rate ratio; NS: nonsignificant; SIR: standardised incidence ratio.

latent infection with *M. tuberculosis* before treatment with TNF antagonists [20, 113–118], with significant differences regarding the use and interpretation of the tuberculin skin test, IGRA and the indications for preventive treatment. The diagnosis of latent infection with *M. tuberculosis* is traditionally based on tuberculin skin test positivity in the absence of manifest TB. The skin test has a low sensitivity in patients with rheumatoid arthritis [119], and may be falsely positive in patients with prior BCG vaccination or prior sensitisation resulting from infection with environmental mycobacteria. Therefore, skin test results must be interpreted taking the pre-test risk of infection attributable to *M. tuberculosis* and the risk of reactivation into consideration. A positive tuberculin skin test in populations in whom TB is or has been highly incident should be considered as positive, regardless of a history of prior BCG vaccination. Conversely, it may be difficult to exclude latent infection with *M. tuberculosis* in regions where TB has a low incidence but the prevalence of prior BCG vaccination is high. IGRAs are proposed as an alternative for the tuberculin skin test [120]. The positive predictive value of an IGRA for the development of TB is most probably better than that for a positive skin test, but the negative predictive value is unclear.

Definitive recommendations to use IGRAs as the only diagnostic method to test for latent TB infection cannot be made before more clinical data on their role in predicting TB become available.

Some patients have developed TB after receiving infliximab despite a negative initial skin test result [121]. Despite negative results of immunodiagnostic tests, physicians should carefully question candidates for TNF antagonists therapies about prior exposure to TB. Chest radiographs may be helpful to identify radiographic evidence of prior TB or signs of current TB among such patients. Thus, when indicated, appropriate bacteriological examinations, and if *M. tuberculosis* is isolated, drug susceptibility testing by rapid methods (either liquid culture or molecular testing) are essential diagnostic procedures to prevent disease progression and dissemination. Standard four-drug therapy for TB should be started soon in all cases of suspected or documented active TB.

Summary

In summary, the risk of active TB is increased in rheumatoid arthritis. Treatment with TNF antagonists further increases the risk over the background in this and other chronic inflammatory arthropathies. Reactivation of latent infection with *M. tuberculosis* is the pathogenetic pathway in the majority of active TB cases in chronic inflammatory arthropathies. Tuberculin skin testing and preventive therapy is successful in programmes to prevent reactivation of TB in patients with chronic inflammatory rheumatic conditions (evidence level C). Similar evidence concerning IGRA is lacking.

IMMUNODIAGNOSTICS TO IDENTIFY INDIVIDUALS AT RISK OF DEVELOPING TB ON IMMUNOBIOLOGICALS

Infection with *M. tuberculosis* induces a strong Th1-type cellular immune response [8, 122, 123]. As it is currently impossible to directly identify tubercle bacilli from persons latently infected with *M. tuberculosis*, the presence of a cellular immune response serves as the only diagnostic measure to assess prior contact and future risk of developing TB [122, 124]. Two test principles are currently available to detect specific immunity. The tuberculin skin test has been in use for more than a century [125] and elicits a delayed-type hypersensitivity response after local intradermal application of purified protein derivative (PPD), an extract of the sterile supernatant of *M. tuberculosis* culture filtrate. The largest diameter in millimetres of the tuberculin skin test induration transverse to the long axis of the arm is measured 48–72 h after antigen injection. Reliability of the measurement might be improved by using the ''ballpoint technique'' [126]. More recently, *in vitro* tests to detect specific cell-mediated immune responses towards *M. tuberculosis* have been developed and implemented for clinical routine that share many basic principles of skin testing, yet have a number of operational advantages and a superior diagnostic accuracy. When performing *in vitro* tests, peripheral blood cells are stimulated with specific antigens. Effector T-cells recognising these antigens are rapidly activated and secrete a variety of cytokines within hours after stimulation. As the cytokine IFN-γ is a good marker for specific activation of T-cells, and has been widely used to detect *M. tuberculosis*-specific responses, these assays have been termed IGRAs [127]. The percentage of blood cells releasing IFN-γ may be determined using an enzyme-linked immunospot (ELISPOT) assay [128, 129] or the amount of IFN-γ released into the supernatant may be quantified using an ELISA [130]. Commercial tests are available for both formats (ELISPOT as T-SPOT.*TB*; Oxford Immunotec, Oxford, UK, and ELISA as QuantiFERON TB Gold in-tube; Cellestis Ltd, Carnegie, Australia). Alternatively, IFN-γ may be accumulated intracellularly and detected using flow-cytometry [131–134]. An increase in specificity of IGRA over tuberculin skin testing has resulted from the identification of genomic segments (regions of difference (RD) 1 or 11) within *M. tuberculosis* that are absent in all strains of BCG and most environmental mycobacteria including the *M. avium* complex [127, 135, 136]. Among those, early secretory antigenic target-6, culture filtrate protein-10, both RD1-derived, or TB7.7 (RD11-derived) are used in the commercially available assays and most in-house assays, as they elicit strong Th1 type immune responses. Hence, when used as stimuli, a specific T-cell response towards those antigens is a more specific marker for *M. tuberculosis* infection than a positive tuberculin skin test [129, 137], thereby reducing the frequency of false-positive skin test results in BCG-vaccinated individuals. *In vitro* assays have also been studied as an approach to increase sensitivity as compared to skin testing. This is of particular relevance in immunocompromised patients on immunosuppressive drug therapy, where skin testing has the inherent problem of potentially being falsely negative [134, 138]. Interestingly, the gain in sensitivity varies between studies and is dependent on the overall level of immunosuppression and on the *in vitro* assay that is applied, in that ELISPOT-based assays seem to be of higher sensitivity in immunocompromised patients compared to studies that used ELISA [16, 139]. As an operational advantage of *in vitro* assays that is of particular relevance in immunocompromised patients, specific stimulation reactions are not only accompanied by a negative control that allows assessment of nonspecific background reactivity, but also by a mitogen stimulus that is used as a positive control to assess general T-cell responsiveness. Although formally scored as

''indeterminate result'', a reduced mitogen response in patients on immunosuppressive drug therapy may be interpreted as a meaningful measure to assess the overall extent of immunosuppression. Therefore, unlike skin testing, *in vitro* tests may be able to discriminate true negative responses from anergy. Given the clear advantages over tuberculin skin testing, *in vitro* assays have been evaluated for their ability to assess evidence of prior infection with *M. tuberculosis* in both immunocompetent individuals as well as patients with immunodeficiencies, and are now licensed for clinical use in many countries [137, 140–142]. To date, however, no blood-based test allows distinction of active TB from latent infection or successfully treated disease.

As patients with immune-mediated inflammatory diseases are candidates for immunosuppressive and immunomodulatory medication that increase the risk for TB reactivation, and tuberculin skin test results in these patients are prone to be falsely negative, a number of cross-sectional and cohort studies have been performed to evaluate the use of IGRA as a clinically valuable alternative to skin testing. A summary of the main outcome of seminal studies that analysed the concordance of IGRA and tuberculin skin testing for screening of latent infection with *M. tuberculosis* in patients with immune-mediated inflammatory diseases is given in table 4 [132, 143–149, 150–154]. In general, results of IGRAs and tuberculin skin tests correspond poorly, although agreement is stronger in countries with low TB prevalence and low BCG vaccination coverage [148]. In line with increased IGRA sensitivity and specificity in immunocompromised individuals, respectively, positive immune responses are more frequently observed with IGRAs than with the tuberculin skin test, especially in unvaccinated populations, and positive IGRA responses are more closely associated with risk factors for latent infection with *M. tuberculosis*. Moreover, the rate of indeterminate results was considerably low (0–10.3%) (table 4). One important finding is that up to 50% of the IGRA positive patients are actually missed by the skin test. In the clinical setting, immune-based diagnosis for latent infection with *M. tuberculosis* is performed to identify individuals at risk of developing TB. However, to date, the positive predictive value of IGRA responses for the development of TB in candidates undergoing therapy with TNF antagonists is not known. A study conducted among individuals with HIV-infection from a low endemic area for TB indicates a very high negative predictive value of IGRAs in immunocompromised patients [155]. Currently it is unknown, whether individuals with a negative IGRA result and a medical history of TB or with imaging study findings suggestive of past TB or individuals with reverting IGRA results run a lower risk of TB than those with persistently positive IGRA results. Moreover, it is a subject of debate whether IGRA testing may also be superior to tuberculin skin testing for screening of patients who have already received TNF antagonists, as results vary from one study to another [42, 144, 148]. Therefore, recommendations that favour the use of IGRA over tuberculin skin testing to evaluate the risk for progression to TB in candidates for treatment with TNF antagonists are based on potential superiority in identifying latently infected individuals. While this is plausible, it cannot be taken as firm evidence until the positive predictive value of different immunodiagnostic tests have been compared in these patients.

Summary

In summary, the tuberculin skin testing measures cell-mediated immunity towards PPD. Due to its poor specificity, the tuberculin skin test is inadequate to assess evidence of latent infection with *M. tuberculosis* in BCG-vaccinated patients and patients with low pre-test risk of TB infection. IGRAs are *in vitro* tests that rely on the rapid production of IFN-γ by circulating mononuclear cells in response to antigens which are more specific for the detection of *M. tuberculosis* infection than PPD. IGRA testing in patients with immune-mediated inflammatory diseases is feasible due to a strong correlation with risk factors for TB and a low percentage of indeterminate results. Further longitudinal studies are needed to estimate the risk for progression to TB after IGRA-based and/or tuberculin skin test-based diagnosis of latent infection with *M. tuberculosis* in patients undergoing therapy with TNF antagonists.

PREVENTIVE CHEMOTHERAPY

Although adalimumab and infliximab share a higher risk for progression from latent infection to TB than soluble TNF receptor [12, 14, 105–107], preventive therapy is warranted in any case. The available evidence from a carefully assembled register-based observational study from Spain using a course of 9-months preventive therapy with isoniazid in persons judged from a tuberculin skin test result as likely to be infected with *M. tuberculosis*, suggests that the risk reduction might be as large as 80% if adherence to the regimen can be assured.

The indication for preventive therapy in general is ideally based on quantified information of the risk of TB imparted by a risk factor relative to a population that is similar in every respect except for the presence of that factor. Because TB will only develop among persons who are latently infected with *M. tuberculosis*, the referent population must have latent infection with *M. tuberculosis*. As this cannot be measured with current tools, the proxy for its measurement is a positive tuberculin skin test or positive IGRA test [124]. However, for a decision to recommend antimicrobial therapy to prevent TB, knowledge about the timing of tuberculin skin test or IGRA conversion is very helpful as the risk for the development of TB is low (incidence of about one per 1,000 person-yrs) when infection with *M. tuberculosis* occurred >7 yrs before in an otherwise healthy individual [156].

Studies evaluating the relative risk of TNF antagonists compared to such a standard population are not currently available. TNF antagonists are commonly used among patients who differ from the general population by demographic characteristics and who have conditions that are frequently complicated by co-morbidities or additional medications that in themselves increase the risk of TB compared to the general population [4, 101]. This renders direct comparisons of incidence invalid if the purpose is to isolate the contribution of TNF antagonists to that incidence.

Given the critical role of TNF in the pathogenesis of TB, it should not be surprising that any TNF antagonist treatment might increase the risk of progression from a pre-existing latent infection with *M. tuberculosis* to clinically manifest TB. However, the relative risk of 4 among patients with rheumatoid arthritis receiving any of the compounds from the entire

TABLE 4 Summary of studies analysing the concordance of interferon-γ release assays (IGRA) and tuberculin skin testing (TST) for the screening of tuberculosis infection in patients with chronic immune-mediated inflammatory diseases (IMID)

First author [ref.]	Country	IGRA	TST cut-off mm[#]	Participants n	IMID condition	BCG %	Indeterminate %	κ	Concordant results		Discordant results	
									TST+/IGRA+ n (%)	TST-/IGRA- n (%)	TST-/IGRA+ n (%)	TST+/IGRA- n (%)
Cobanoglu [**143**]	Turkey	QFT-G IT	10	68 cases	>65% RA+AS	100	10.3	0.14	8 (13.1)	23 (37.7)	1 (1.6)	29 (47.5)
				38 controls			5.3	-0.05	0	23 (63.8)	1 (2.8)	12 (33.3)
Matulis [**144**][¶]	Switzerland	QFT-G IT	5	142	>65% RA+SA	83	6	0.16	10 (7)	60 (44.7)	5 (3.5)	34 (25.4)
Dinser [**132**]	Germany	Flow cytometric assay	5	97	>50% RA	5.1	0	0.31	6 (6.2)	74 (76.3)	10 (10.3)	7 (7.2)
Ponce de Leon [**145**]	Peru	QFT-G IT	5	101 cases	RA	80.2	1.9	0.37	21 (20.8)	50 (49.5)	24 (23.8)	6 (5.9)
				93 controls		80.6	0	0.55	16 (17.2)	61 (65.6)	5 (5.4)	11 (11.8)
Vassiloupolos [**146**]	Greece	T-SPOT.*TB*	5	70	>85% RA+AS+PA	40	0	0.38	12 (17.1)	39 (55.7)	4 (5.7)	15 (21.5)
Bocchino [**147**]	Italy	QFT-G IT	5	69	RA+IBD+PA	2.8	2.8	0.57	14 (20.9)	41 (61.2)	8 (11.9)	4 (6)
		T-SPOT.*TB*		69			5.8	0.48	12 (18.5)	39 (60)	(13.8)	5 (7.7)
Bartalesi [**148**]	Italy	QFT-G IT	[ƒ]	398	>85% RA+PA+AS	4.1	1.5	0.55	39 (10)	306 (77.8)	13 (3.3)	35 (8.9)
Murakami [**149**]	Japan	ELISPOT[§]	5	71	RA	100	0	0.18	4 (5.7)	50 (71.4)	6 (8.4)	11 (15.5)
Martin [**150**][+]	Ireland	T-SPOT.*TB*	5	150	RA+PA+AS	82	4.7	0.2	6 (4.2)	110 (77)	8 (5.6)	19 (13.2)
		QFT-G		72			2.8	NA[++]	NA[++]	NA[++]	NA[++]	NA[++]
Behar [**151**]	USA	T-SPOT.*TB*	5[##]	179	>80% RA	4.7	0	-0.019	0 (0)	167 (93.3)	10 (5.6)	2 (1.1)
Laffitte [**152**]	Switzerland	T-SPOT.*TB*	5	50	SP	90	0	0.33	8 (16)	28 (56)	2 (4)	12 (24)
Soborg [**153**]	Denmark	QFT-G	[¶¶]	234	>50% RA	76	5	0.2	9 (4)	180 (77)	9 (4)	36 (15)
Inanc [**154**]	Turkey	QFT-G	5	140	RA+AS	84	5.7	0.29	41 (31)	40 (30)	5 (4)	46 (35)

BCG: bacillus Calmette–Guérin; QFT-G IT: QuantiFERON TB Gold In-tube; QFT-G: QuantiFERON TB Gold; RA: rheumatoid arthritis; AS: ankylosing spondylitis; SA: spondylarthropathies; PA: psoriatic arthritis; SP: severe psoriasis; IBD: inflammatory bowel disease; NA: not available. [#]: refers to the TST cut-off in the IMID subjects (and not in the controls, where present); [¶]: TST analysed retrospectively; the median time between performing the TST and the QFT assay was 102 days (range 7–184 days); [+]: concordance between QFT-G and T-SPOT.*TB* 98.4% (agreement: k=0.9); [§]: in-house ELISPOT with antigens CFP-10 and ESAT-6; [ƒ]: TST cut-off >5, >10 or >15, stratified by groups at risk and risk factors for *Mycobacterium tuberculosis* infection; [##]: TST was read, after instruction, by the patients themselves; [¶¶]: TST cut-off ⩾12 for BCG vaccinated and ⩾6 for unvaccinated; [++]: data on discordant results between two tests not available.

class compared to those not receiving it was, nevertheless, remarkably modest in a comprehensive study in Sweden [4].

Differences in TB risk by type of TNF antagonist

Epidemiologically more meaningful, despite remaining methodological problems, have been intra-class comparisons, evaluating the relative impact on TB incidence by type of compound. The incidence rate ratio during the first 90 days of treatment (to exclude super-imposed recent infection), was approximately nine-fold among US patients [39]. However, drawing definite conclusions about the risk difference remains potentially biased because the conditions differ for which the two agents are preferentially prescribed.

General criteria to define indication for preventive chemotherapy

An objective strategy to define patient categories for whom preventive therapy should routinely be considered takes the remaining life-time risk relative to expected toxicity from the intervention into account, *e.g.* children have a larger life-time risk and tolerate drugs better than adults.

A second consideration concerns adults. Among these, a critical threshold relative risk warranting preventive chemotherapy, compared to persons with a long-lasting infection (in whom preventive chemotherapy is not recommended as a routine) should be defined. This seems to be largely absent from relevant statements and position papers. The American Thoracic Society recommends that persons with a recently acquired infection warrant preventive chemotherapy at any age [157] as does the British Thoracic Society [158]. The relative risk of progression to TB in a recently infected person is ~10-fold increased compared to that in a person with a long-standing infection. Implicitly and explicitly, patients with equal or stronger risk factors (patients with fibrotic lesions, diabetes, silicosis, HIV infection, *etc.*) are thus eligible for preventive chemotherapy irrespective of their age. Patients with weaker, but nevertheless recognised risk factors (such as smoking or underweight) are not generally considered for preventive chemotherapy, although the American Thoracic Society remains ambiguous on the issue of age [157].

Consequences for preventive chemotherapy among patients treated with TNF antagonists

No properly designed, population-based study has ever demonstrated a relative risk of TB in excess of 10 among patients treated with etanercept, even if the comparison group was the general population. The indication for preventive therapy with soluble TNF fusion protein is thus, compared with other risk factors that are clearly warranting preventive therapy, much less convincing. However, should the differential analysis [39] on the two main classes of TNF antagonists hold true, then monoclonal antibody-based TNF antagonists entail a relatively higher risk of progression from latent infection to active TB than patients receiving a soluble receptor-based compound.

In addition, given that the patient population receiving TNF antagonists commonly has an underlying risk that is elevated compared to the general population, patients started on therapy with TNF antagonists warrant strong consideration for preventive chemotherapy.

Type and duration of preventive chemotherapy for persons treated with TNF antagonists

There is no clinical trial evidence but information from a carefully conducted observational study has determined the effectiveness of preventive chemotherapy in this population [14, 115]. In this study from Spain, after implementation of official recommendations to prescribe isoniazid preventive therapy for 9 months, the incidence rate of TB was reduced by 80% compared to the period prior to the recommendations. However, the confidence intervals for the risk reduction were very large because of the small number of events [14]. Concerns have been raised that treatment with TNF antagonists may result in an immune reconstitution syndrome similar to that observed among patients treated with antiretroviral therapy [159, 160]. It is not known to what extent and whether such observation should influence treatment decisions with preventive chemotherapy.

Summary

In summary, implementation of local guidelines tailored to background to deal with latent infection with *M. tuberculosis* before starting TNF antagonists significantly decreases the number of active TB cases during treatment (evidence level C). Treatment of latent infection with *M. tuberculosis* for 9 months with 300 mg of isoniazid daily is recommended by most national guidelines and the US Centers for Disease Control and Prevention. In this case, delaying the start of TNF antagonists for 4 weeks is a safe approach (evidence level D).

SPECIAL CONSIDERATIONS IN CHILDREN

As increasing numbers of children are successfully treated with TNF antagonists, mainly for juvenile idiopathic arthritis and Crohn's disease, we have also gained more experience with regards to the frequency of adverse drug events with their use [161]. In adults there is compelling evidence of increased rates of TB and this has been translated into similar concerns and a belief that the same risk is true for children. This, however, is not substantiated by relevant scientific publications, and there is a distinct lack of good surveillance data in children, unlike adults, on adverse drug events and infection risk of long-term TNF antagonist treatment.

Most evidence has accumulated around the use of etanercept, which has proven efficacy in juvenile idiopathic arthritis. Initial trials found no documented cases of TB [162] and more recent long-term follow-up has confirmed that very few cases occur. The largest, a German registry of 504 children followed for >1 yr [163], as well as a Dutch registry of 146 children followed for up to 4 yrs [164] and a US study of 69 children, 26 of whom completed 8-yr follow-up [165], revealed only two children developed TB on etanercept. One, a 9-yr-old female from the UK developed TB septic arthritis [166], the other a 9-yr-old female from the Netherlands initially received etanercept, then infliximab after which she developed extrapulmonary TB [167]. There are even fewer published data regarding the use of infliximab in juvenile idiopathic arthritis and in inflammatory bowel disease [168, 169] with, however, only one documented case of a child developing TB whilst on infliximab for juvenile idiopathic arthritis [170]. Adaluzimab and abatacept have so far only included trials with <200 children with juvenile idiopathic arthritis, but they had relatively short

follow-up. No cases of TB have been reported [171]. The existing data support a clear difference in the risk of developing TB between adults and children who receive TNF antagonist therapies in industrialised countries. This is likely to result from the lower prevalence of latent infection with *M. tuberculosis* in these children compared to adults, and not because they are less likely to reactivate *M. tuberculosis* where it is present. Because they are perceived as having a low risk, children are not always screened for latent infection with *M. tuberculosis* prior to embarking on TNF antagonist therapy.

Diagnosis of TB/latent infection with M. tuberculosis *in children*

The diagnosis of TB in any young child is difficult, due to the nature of primary childhood TB, the paucity of bacteria and the inability of most children to produce sputum [172]. Using a positive tuberculin skin test as the diagnostic marker for latent infection in young children is unreliable because of the possible interference with a more recent BCG immunisation and the higher percentage of anergy in young children, even if not receiving immunosuppressive therapy. Current data suggest that IGRA are probably more accurate in diagnosing latent infection in children than the skin test. They do, however, seem to perform relatively poorly in children with (recent) active disease. Moreover there are insufficient data regarding the reliability of IGRA in children <2 yrs of age [173–175].

Immunodiagnostic performance in immunosuppressed children

Over the past decade we have learnt that genetic defects in T-cell mediated immune pathways impose a higher risk of developing mycobacterial disease [172], but such defects are rare. The tuberculin skin test is recognised to be unreliable if there is immunosuppression such as might be the case with corticosteroid therapy or in children with measles, varicella or with HIV-infection. Most recent studies assessing the performance of the newer immunodiagnostics in immunosuppressed children are carried out in HIV-infected children in high incidence settings, which is arguably not the most appropriate model for children receiving TNF antagonists or representing rates of latent infection in Europe.

One recent study suggests that the QuantiFERON TB Gold in-tube assay (Cellestis Ltd) does not provide a determinate result in a substantial proportion of children with a variety of primary and acquired immunodeficiencies, including children treated for auto-inflammmatory disorders [176].

Current practice

There are currently no published (inter)national guidelines for TB screening for children about to embark on TNF antagonist therapy. However, most institutions have developed local protocols, usually modelled on adult guidelines.

Summary

In summary, there appears to be a smaller risk of developing mycobacterial disease in children receiving TNF antagonist therapies than in adults, most probably explained by the fact that latent infection with *M. tuberculosis* is more prevalent amongst adults in countries where these therapies are given. A risk assessment on the basis of country of origin, known TB contacts, travel history and age, still remains the important cornerstone of the diagnosis of infection with *M. tuberculosis* in children. Combining results of both tuberculin skin tests and IGRA may yield more accurate information, although there are currently no validated ''scoring-systems'' available for children and herein age seems to be an important confounder. The current paucity of available paediatric information makes it imperative that data are collected, and an international effort in this direction will certainly lead to better understanding and more knowledge in this field.

PUBLISHED NATIONAL GUIDELINES

Since the recognition of an increased risk of reactivating TB with TNF antagonist treatment for inflammatory diseases, guidance for clinicians has been produced in several countries. This guidance has taken various forms from comprehensive evidence based guidelines (UK) to short statements of suggested practice (USA). Eight such statements or guidelines, published between 2003 and 2009, have been identified and are discussed and compared on factors affecting risk, definition of latent infection with *M. tuberculosis*, those eligible for preventive chemotherapy and recommended regimens, and time delay before commencement of TNF antagonist therapy. These publications are from the following countries: France [116], Germany [177], Ireland [117], Portugal [107], Spain (as outlined in [7, 115]), Switzerland [20], UK [113] and USA [114]. In addition, other national guidelines have recently become available in non-English languages, *e.g.* in Denmark.

The French publication is a response to the preliminary consensus guidelines elaborated at the Advances in targeted therapies IV meeting in 2002 [178], and is based on proposals by a multidisciplinary French co-operative group published in 2002 [179]. The Spanish documents published in 2003 and 2005 [7, 115] outline the measures initially proposed in 2002 by the Spanish Rheumatologic Society and the Spanish Health authority. Later on-line guidelines have become available in Spanish [180]. The Swiss recommendations are the result of a multidisciplinary workshop and are supported by a more recent article reviewing the indications and cautions before using TNF antagonists in patients with inflammatory bowel disease [181]. The US publication is not a guideline as such but a series of nine recommendations and refers to broader American Thoracic Society guidelines on tuberculin testing and treatment of latent infection with *M. tuberculosis* and TB. A summary of the main recommendations made in the different publications and in this TBNET consensus statement can be found in table 5.

Points of agreement

All guidelines recommend that every patient considered for TNF antagonist therapy should be screened for evidence of latent infection with *M. tuberculosis* or TB. A full clinical history and physical examination should be part of the initial assessment. This should include details of ethnicity, country of birth, history of recent exposure to TB, previous TB and treatment, together with any additional risk such as substance abuse. All patients should have a chest radiograph with either a tuberculin skin test or IGRA as investigations for evidence of latent infection. Several documents stress that even with a negative tuberculin skin test or IGRA, a history of past

TABLE 5 Comparison of recommendations of published national guidelines and of this TBNET consensus statement

Country/study [ref.][#]	Risk assessment examination CXR	TST	TST details	Positive TST	IGRA testing	Who should receive prophylaxis?	LTBI treatment[¶]	Time delay before TNF antagonist therapy	
								LTBI	Active TB
France [116]	All patients	All patients	One step	10 mm	No	TST+, history of TB treated before 1970 or not treated for min. 6 months; CXR lesions >1 cm^3 with no history of treatment	2RZ 3RH 9H	>3 weeks after starting prophylaxis	>2 months after completion of TB treatment
Germany [177]	All patients	Only if discrepancy between strong epidemiological evidence of prior TB exposure and negative IGRA		>5 mm	Yes	IGRA+, abnormal CXR suggestive of past TB inadequately treated; history of exposure	9H or 4R	1–2 months after starting prophylaxis	
Ireland [117]	All patients	All patients	One step	10 mm, 5 mm for IS, no change for BCG vaccinated	If available	TST+	9H 4R 4RH	As long as possible after starting prophylaxis	On completion of TB treatment
Portugal [107]	All patients	All patients	Two step	5 mm	In progress	TST+, consider prophylactic treatment in TST-negative patients	9H	1 month on prophylaxis	>2 months on TB treatment
Spain [7, 115]	All patients	All patients	Two step	5 mm	No	TST+, abnormal CXR suggestive of past TB inadequately treated; history of exposure	9H	1 month but consider days after or at same time as starting prophylaxis	
Switzerland [20]	All patients	Not recommended			Yes	IGRA+, abnormal CXR suggestive of past TB inadequately treated; history of exposure	9H or 4R	1 month after completion of prophylaxis	
UK [113]	All patients	Not for patients on IS as unreliable	One step	5 mm in unvaccinated, 15 mm in vaccinated	No (update due 2010 by NICE)	TST+ stratified for risk; previous TB inadequately treated or abnormal CXR; IS patients stratified for risk	6H or 3HR	If abnormal CXR or history of TB, complete prophylaxis. If normal CXR or IS can start concurrently	>2 months on TB treatment
USA [114]	All patients	All patients	One step	5 mm if IS, 10 mm if risks, *e.g.* new immigrant, drug users 15 mm if low risk	No	TST+ in presence of clinical suspicion, TST- if clinical or epidemiological risks	9H	Preferably complete prophylaxis	Preferably complete TB treatment
TBNET consensus statement	All patients	TST in individuals without a history of BCG vaccination	One step	⩾10 mm	Yes	IGRA+ or TST ⩾10 mm	9–12H or 3 RH	>4 weeks after initiation of prophylaxis	Preferably complete TB treatment

CXR: chest radiograph; TST: tuberculin skin test; IGRA: interferon-γ release assay; LTBI: latent infection with *Mycobacterium tuberculosis*; TNF: tumour necrosis factor; TB: tuberculosis; IS: immunosuppressed/immunosuppression; BCG: bacille Calmette–Guérin; NICE: National Institute for Clinical Excellence; min.: minimum; RZ: rifampicin plus pyrazinamide; RH: rifampicin plus isoniazid; H: isoniazid: R: rifampicin. [#]: screening pre-TNF antagonist therapy; [¶]: the number denotes the number of months of LTBI treatment.

exposure or untreated TB should be an indication for preventive therapy. All recommend a whole course of treatment for active TB where present and preventive chemotherapy when latent infection with *M. tuberculosis* is diagnosed. The importance of maintaining vigilance for TB in all patients on TNF antagonist treatment is emphasised, even after a full course of preventive therapy has been completed.

Areas of difference

Guidelines for the diagnosis of latent infection with *M. tuberculosis* and recommendations for preventive chemotherapy regimens are not always consistent between different countries. Most guidelines except those from Switzerland and Germany recommend a tuberculin skin test for screening. Switzerland recommends using any of the two commercially available IGRA tests instead of the tuberculin skin test based on evidence by SELLAM *et al*. [182]. The German guidelines recommend using the tuberculin skin test only when proven exposure to an infectious case is not supported by a positive IGRA. The Portuguese guidelines are due to be updated and it is expected that a position for IGRA testing will be included for the first time. In the UK, the National Institute for Clinical Excellence will be publishing an evidence-based assessment for IGRA testing pre-TNF antagonist therapy in late 2010.

Interpretation of the tuberculin skin test result differs depending on the cut-off measurements for the intradermal test defining positivity, on the immune status of the patient and the likelihood of latent infection with *M. tuberculosis* based on previous exposure (table 5). Some guidelines recommend repeating the tuberculin skin test to increase test sensitivity. The Portuguese guidelines recommend skin testing before initiating any immunosuppressive treatment and then repeating screening prior to TNF antagonist therapy. Immunosuppression is defined as established disease, or treatment with corticosteroids of >10 mg·day^{-1}, methotrexate, cyclosporine, azathioprine, leflunomide or cyclophosphamide.

There are variations in the recommended preventive therapy regimens (table 5). In particular, the French guidelines are the only one to include the combination of rifampicin plus pyrazinamide as a possible regimen (table 5). Most countries, however, no longer use this combination due to the high incidence of severe drug-induced hepatic injury [183]. Further variations are found in the time suggested for both preventive chemotherapy and treatment for active disease before commencing therapy with TNF antagonists, varying from 3 weeks after initiation of preventive therapy to its completion, and 2 months after initiation of curative treatment to completion of therapy. The French guidelines are also unique in recommending long-term preventive therapy if TNF antagonist treatment is used at all after completion of treatment for active disease. The UK guidelines are probably the most comprehensive and cover several different clinical scenarios. Unique to these guidelines is an attempt to quantify risk of both reactivating TB and drug-induced hepatitis. In addition, according to the UK guidelines those with previously treated TB should continue to be monitored at 3-months intervals while on TNF antagonist therapy.

Summary

In summary, all eight national guidelines agree that every patient considered for TNF antagonist therapy should be screened for evidence of TB, and where absent for latent infection. Investigations should include a chest radiograph with either a tuberculin skin test or an IGRA. A history of significant past exposure or untreated TB should be an indication for preventive chemotherapy even when tests for latent infection are negative. Recommended preventive chemotherapy regimens vary and include 6 or 9 months with isoniazid, 3 months of rifampicin plus isoniazid, and 4 months of rifampicin. There are variations in the recommendation for the duration of both preventive chemotherapy and treatment of active disease before commencing TNF antagonist therapy.

CONSENSUS RECOMMENDATIONS

The currently available evidence on the best management to prevent TB in patients receiving TNF antagonist therapies is limited. The recommendations summarised in this article represent a consensus of published evidence (for evidence levels see table 1) and expert opinions to guide physicians to evaluate the risk for TB and to prevent TB in patients with *M. tuberculosis* specific immune responses who are candidates for therapies with TNF antagonists. These recommendations shall be valid until further clinical evidence is available.

Who should be screened for latent infection with M. tuberculosis *prior to treatment with monoclonal antibodies against TNF?*

Prior to antibody-based anti-TNF therapies all candidates should be screened for the presence of *M. tuberculosis* specific immune responses (the best available proxy for latent infection with *M. tuberculosis*; evidence level C). All candidates for TNF antagonist therapies should be questioned about a history of prior TB or TB contact and should have a chest radiograph to search for evidence of prior or active TB.

Are persons receiving treatment with soluble TNF receptor-based antagonists with positive M. tuberculosis*-specific immune responses also at increased risk of developing TB?*

The risk of TB is increased in adults with positive *M. tuberculosis* specific immune responses (latent infection with *M. tuberculosis*) being treated with etanercept, a TNF receptor fusion protein. However, this risk of developing TB (given latent infection) has been shown to be lower in these individuals compared to individuals with latent infection with *M. tuberculosis* who are being treated with monoclonal antibodies against TNF (evidence level C).

Should preventive therapy against TB be advised for all candidates undergoing TNF antagonist therapies with M. tuberculosis*-specific immune responses (latent infection with* M. tuberculosis*)?*

Preventive chemotherapy against TB should be offered to all individuals before undergoing TNF antagonist therapies, including patients who receive etanercept, in the presence of evidence of latent infection with *M. tuberculosis* (evidence level C).

Is different management recommended based on different underlying diseases?

Screening for latent infection and preventive chemotherapy against TB should not be different for patients with different underlying disease (rheumatoid arthritis, psoriasis or inflammatory

bowel disease) who are candidates for TNF antagonist therapies (evidence level D).

Should latent infection with M. tuberculosis *be diagnosed based on tuberculin skin testing, IGRA testing or both?*

In general, IGRAs are superior to the tuberculin skin test in detecting anti-mycobacterial immune responses in immunocompromised individuals. In addition, mitogen controls in the IGRAs give an advantage over the tuberculin skin test as they can be used for discrimination between anergy and true negative-antigen specific immune responses. However, the only evidence available is that a positive result in a two-step tuberculin skin test predicts the development of TB in individuals undergoing TNF antagonist therapies. As IGRAs have not been evaluated in this context, the evidence is essentially indirect.

At this stage, the choice of immunodiagnostic test to detect latent infection with *M. tuberculosis* prior to TNF antagonist therapies is unclear. Published clinical evidence favours two-step tuberculin skin testing while expert opinion suggests that IGRAs are superior to the tuberculin skin test in identifying individuals at risk of developing TB.

For the diagnosis of *M. tuberculosis* specific immune responses (latent infection with *M. tuberculosis*) expert opinion suggests using the QuantiFERON TB Gold in-tube test or the T-SPOT.*TB* test (Oxford Immunotech) or, as an alternative, tuberculin skin testing in individuals without a history of BCG vaccination.

Moreover, paediatric practice suggests concomitantly using all three, tuberculin skin test, IGRA and chest radiography, and any positive result taken as evidence for latent infection, after exclusion of active TB. Where negative, however, these tests have a poor predictive value on their own (Evidence levels C and D).

If the tuberculin skin test is used for the diagnosis of latent infection with M. tuberculosis *prior to the initiation of TNF antagonist therapies, should a two-step approach be considered?*

At present, as there is limited evidence that sensitivity for true latent infection with *M. tuberculosis* is increased among persons who respond to a tuberculin skin test booster (but considerable evidence is available to show that this reduces specificity), the two-step approach is not generally recommended for the diagnosis of latent infection with *M. tuberculosis* prior to the initiation of TNF antagonist therapies, although some national guidelines, *e.g.* Spanish guidelines, do recommend it based on empirical evidence (evidence level C).

If IGRAs are used for the diagnosis of latent infection with M. tuberculosis *prior to the initiation of TNF antagonist therapies is there a preference for QuantiFERON TB Gold in-tube or T-SPOT.TB test in this specific situation?*

Although there is some evidence of increased sensitivity of the T-SPOT.*TB* test (Oxford Immunotech) over QuantiFERON TB Gold in-tube test (Cellestis Ltd) in severely immunocompromised patients in diagnosing *M. tuberculosis* specific immune responses (latent infection with *M. tuberculosis*), current clinical evidence from cross sectional and cohort studies, including patients undergoing TNF antagonist therapies does not clearly favour one test over the other. Both tests are advocated for the diagnosis of latent infection prior to the initiation of TNF antagonist therapies (evidence level D).

Which cut-offs should be used for the tuberculin skin test and IGRAs for the diagnosis of latent infection with M. tuberculosis *prior to the initiation of TNF antagonist therapies?*

For the tuberculin skin test, there is evidence that the loss in sensitivity by increasing the cut-off point from 5 to 10 mm to denote infection is marginal while there is a substantial gain in specificity. A tuberculin skin test cut-off of $\geqslant$10 mm, as generally recommended for other immunocompromised conditions (excluding HIV-infection) warranting preventive chemotherapy against TB, seems to be the most appropriate for the diagnosis of latent infection with *M. tuberculosis* prior to the initiation of TNF antagonist therapies. A tuberculin skin test result of $\geqslant$10 mm should not generally need confirmation by an IGRA.

Paediatric consensus is to provide preventive chemotherapy if either the IGRA or the tuberculin skin test is positive and if only the tuberculin skin test is used, different cut-offs should be used for BCG-vaccinated ($\geqslant$10 mm) *versus* non-vaccinated ($\geqslant$5 mm) children, taking epidemiological risk factors into account (evidence level C).

The cut-offs for IGRAs for the diagnosis of latent infection with *M. tuberculosis* prior to the initiation of TNF antagonist therapies should be used as recommended by the manufacturers for Europe (evidence level D).

What decision should be taken when testing for latent infection yields discordant results prior to the initiation of TNF antagonist therapies?

The role of patient history, origin and prior BCG vaccination status should guide interpretation of test results. IGRA tests should be preferred over tuberculin skin testing in individuals with a known history of BCG vaccination whenever possible. In individuals without a history of BCG vaccination, one positive test result (either tuberculin skin test or IGRA) should qualify for the individual to undergo preventive therapy (evidence level D).

When should TNF antagonist therapies be initiated following the induction of preventive chemotherapy against TB?

An induction period of 4 weeks is considered safe by most experts to start TNF antagonist therapy following the induction of preventive chemotherapy against TB (evidence level D).

Which preventive chemotherapy regimen is the most effective in reducing the risk of developing TB in individuals with M. tuberculosis*-specific immune responses undergoing TNF antagonist therapies?*

Effectiveness of different chemotherapeutic regimens to prevent TB in individuals with *M. tuberculosis* specific immune responses undergoing TNF antagonist therapies has not been evaluated. The best clinical evidence of efficacy (evidence level A) in other populations supports a choice between two preventive therapy regimens: 12 months of isoniazid and

3 months of isoniazid plus rifampicin. The efficacy of both regimens exceeds 90%. However, in most countries 9 months isoniazid regimens are currently recommended to prevent TB in individuals with latent infection. Alternative regimens with likely lower efficacy and effectiveness, but reduced incidence of significant adverse drug events, are isoniazid for 6 months (which is recommended in the UK) or rifampicin for 4 months. The probability of developing active TB is substantially increased when adherence to guidelines for preventive chemotherapy against TB in individuals receiving TNF antagonist therapies is not strict.

How should patients who started preventive chemotherapy against TB be followed especially in relation to the initiation of TNF antagonist therapies?

Patients should be educated about early signs and symptoms of TB and possible adverse drug events of the medication used for preventive therapy. Routine follow-up with chest radiography is not indicated in asymptomatic individuals treated with preventive chemotherapy against TB. However, In the presence of signs and symptoms compatible with active TB, chest radiography should be performed without delay. In cases of doubt, chest computer tomography scans should be performed, which are superior to chest radiography in detecting early radiological signs of active TB. Liver enzymes should be analysed prior to the initiation of preventive chemotherapy and may be re-evaluated every 3–4 weeks on treatment, or if the patient becomes symptomatic. Repeated testing for latent infection with *M. tuberculosis* (every year) may be considered in persons with ongoing risks of TB exposure (travel, work, *etc.*), but is not recommended to be done with the tuberculin skin test as results might be distorted by boosting (evidence level D).

When shall treatment with TNF antagonists be initiated (if indicated) in patients with active TB?

The optimal time-point for the initiation of treatment with TNF antagonists in individuals who are being treated for active TB is unclear. Expert opinion suggests to preferably initiate treatment with TNF antagonists when a full course of anti-TB treatment, according to international standards, has been completed (evidence level D).

Are patients with a history of TB, who have been adequately treated, at increased risk for TB reactivation when they receive TNF antagonist therapies?

Patients who have completed appropriate TB therapy do not appear to have an increased risk of TB when TNF antagonist therapy is started. Currently, preventive chemotherapy is not generally recommended for patients with positive *M. tuberculosis*-specific immune responses undergoing TNF antagonist therapies who have been adequately treated against TB in the past, unless re-infection with *M. tuberculosis* is plausible (evidence level D).

What is the optimal duration of anti-TB chemotherapy for patients who developed TB in relation to TNF antagonist therapies?

The optimal duration of anti-TB chemotherapy for patients who developed TB in relation to TNF antagonist therapies has not been defined. There is no evidence that the duration of anti-TB treatment needs to be prolonged, if TB developed in relation to TNF antagonist therapies (evidence level D).

CONCLUSIONS

The introduction of TNF antagonist therapies into clinical practice has been a breakthrough in the history of the treatment of inflammatory diseases such as rheumatoid arthritis, psoriatic arthritis, ankylosing spondylarthritis, juvenile idiopathic arthritis and inflammatory bowel disease. Blocking the action of TNF by anti-TNF antibodies or by a soluble TNF receptor leads to an inhibition of the pathological inflammatory process at multiple levels and it is currently the most effective treatment modality for these diseases.

A concerning common adverse event of TNF antagonist therapies is the reactivation of latent infection with *M. tuberculosis*. In this TBNET consensus statement we have summarised the current knowledge of the risk of TB in relation to TNF antagonist therapies and have provided detailed consensus recommendations for the most important clinical questions related to TB and TNF antagonist therapies in adults and children.

TB screening and preventive chemotherapy for all individuals with latent infection with *M. tuberculosis* should become the standard of care for all individuals undergoing TNF antagonist therapies. Following the guidelines of this article will lead to a significant reduction in the number of cases of active TB in relation to TNF antagonist therapies.

STATEMENT OF INTEREST

Statements of interest for J.J. Gomez-Reino, H.J. Milburn, R.S. Walis, D. Goletti, R. Diel, L. Carmona, F. Bartalesi, P. Ravn and C. Lange can be found at www.erj.ersournals.com/site/misc/statements.xhtml

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