The risk of tuberculosis related to TNF antagonist therapies:
A TBNET consensus statement

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Abstract

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Anti-tumour necrosis factor (TNF) monoclonal antibodies or soluble TNF receptor 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 increased risk of reactivating latent infections, especially tuberculosis. Following TNF antagonist therapy, the relative risk for tuberculosis 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 for the presence of latent infection with *M. 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. Consequent 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 tuberculosis. This TBNET consensus statement summarizes current knowledge and expert opinions and provides evidence-based recommendations to reduce the tuberculosis risk among candidates for TNF antagonist therapy.

1 Introduction

Tumor 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 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 tuberculosis 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 tuberculosis. Following TNF antagonist therapy, the relative risk for tuberculosis 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 tuberculosis related to TNF antagonist therapies occur in close temporal proximity to 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 tuberculosis 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 tuberculosis in individuals undergoing TNF antagonist therapies, the risk in individuals who exhibited positive immune responses in a 2-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, Interferon-γ release assays (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 *M. 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 tuberculosis is accordingly superior compared to that of a tuberculin skin test [18].

Because of the superior performance of IGRA 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 IGRA 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 tuberculosis following TNF antagonist therapy who should be offered preventive therapy.

There is a substantial uncertainty among clinicians about the management of patients undergoing TNF antagonist therapies and the best strategies for the prevention of tuberculosis. 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 summarizes the current knowledge of the risk of tuberculosis following TNF antagonist therapies and provides evidence graded recommendations (evidence categories A-D, see **Table 1**) for the screening for latent infection

with *M. tuberculosis* and for preventive chemotherapies in individuals undergoing TNF antagonist therapies.

2 TNF and TNF antagonist therapies: mode of action and side effects

2.1 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 proinflammatory 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 synergizing with interferon (IFN)-γ [22]. Neutralization 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 caused by *L. monocytogenes*, *M. tuberculosis* or *H. capsulatum* [25-27]. TNF stimulates the production of chemokines such as CCL2,CCL3,CCL4,CCL5,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 mal-organized, leading to inefficient containment of infectious foci [29]. Similarly, neutralization 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 Th1-type cytokine and chemokine expression, but – in the absence of sTNF – is insufficient to provide lasting anti mycobacterial protection [30, 31] (**Figure 1**). TNF has long been postulated to be directly involved in caseation necrosis, because infection of cells with *M. tuberculosis* render 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 serves 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 *M. 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 iNOS, therefore also serves to downregulate an exacerbated inflammatory response, in part by inducing apoptosis of effector T cells [35].

TNF thus 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 as alone to support granuloma formation in the absence of TNF [36-38]. On the other hand, LTα$_3$ is necessary for establishing the proper architecture of the granuloma, since, in the absence of LTα$_3$, T cells do not migrate into the granulomatous lesion, but only accumulate in perivascular cuffs [24] (**Figure 1**).

2.2 TNF antagonists

Four monoclonal anti-TNF antibodies are presently in clinical use: infliximab, adalimumab, golimumab, and certolizumab pegol (**Figure 2**; [reviewed in 21, 39]). Infliximab is comprised of human IgG1 constant regions and murine variable regions, whereas adalimumab and golimumab have both human IgG1 constant and variable regions. Certolizumab pegol is a pegylated, humanized 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 μg/ml. Adalimumab, certolizumab, and golimumab are administered by subcutaneous injection. Peak blood concentrations of 10 μg/ml have been reported for adalimumab, 90 μg/ml for certolizumab, and 2.5 μg/ml for golimumab.
Etanercept is the only soluble TNF receptor presently 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 μg/ml.

2.3 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 (reviewed in [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 more than 90% of bound cytokine within two to three hours; 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 neutralization 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. Bruns et al, for example, found that numbers of circulating effector memory CD8 T cells were reduced by infliximab treatment [49].
Experience with the Fab' TNF antibody fragment certolizumab pegol, however, 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 tuberculosis (see section 5 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].

2.4 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 tuberculosis. 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 vs. transmembrane TNF may account for some of the observed differences in reactivating tuberculosis following treatment with anti-TNF antibodies vs. soluble TNF receptor constructs.

3 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 licenced for the treatment of rheumatoid arthritis while their approval status for other rheumatic diseases differs (**Table 2**).

3.1 Rheumatoid arthritis

Rheumatoid arthritis is the most common inflammatory rheumatic disease characterized by chronic synovial inflammation and progressive erosive polyarticular joint damage. Data from the first randomized 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 improve not only signs and symptoms, and health related quality of life but also retard 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 MTX 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 licenced only in combination with methotrexate. A clinically significant improvement with TNF antagonists in combination with MTX 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 (ACR) 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 (EULAR) recommends initial therapy with methotrexate in early rheumatoid arthritis, because of a favourable benefit/to risk ratio and its cost-effectiveness [60].

Randomized clinical trials comparing the efficacy of the different TNF blocking agent 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].

3.2 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 (BASDAI) and the Bath Ankylosing Spondylitis Functional Index (BASFI) 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 demonstrated superiority of one over the other TNF antagonists in the improvement of signs and symptoms [63] (**Table 2**).

3.3 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 [66] (**Table 2**).

3.4 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 around 60% of patients in articular manifestations and uveitis [67, 68]. However, only 25% of patients attain remission, and disease flares occur in around 50% once in remission [69].

3.5 Summary

- In rheumatoid arthritis, TNF antagonists not only improve signs and symptoms and health related quality of life, but also retard 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 yet no evidence that one TNF antagonist is significantly superior over the other.

4 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) [74, 75] (**Table 2**). 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 approximately 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 about 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 disease (i.e. before patients have received oral immunosuppressants such as azathioprine which corresponds to a median disease duration of about 2.4 years) leads to a much higher level of efficacy [76], with almost 70% of Crohn's disease patients achieving corticosteroid-free remission as an endpoint after one year of therapy. This endpoint "corticosteroid free remission" historically has been 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 start of therapy. For the first time a correlation between Crohn's disease activity index (CDAI) and Crohn's disease endoscopic index of severity (CDEIS) 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 approximately 50% of cases over a one year 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 rates of disease related hospitalisation and surgery.

Infliximab is approved for use in paediatric Crohn's disease, too.

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 results from 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 tuberculosis) 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 the 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, glucocorticoids) or to poorly managed chronic active disease.

4.1 Summary

- Three different TNF antagonists with clinical efficacy (infliximab, adalimumab, certolizumab pegol) for remission induction and maintenance of remission are available and a fourth agent (golimumab) is in advanced clinical development.
- Efficacy endpoints 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.

5 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 proinflammatory 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.

5.1 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, adalimumab) in various forms of the disease.

Infliximab has been used in the treatment of psoriasis at doses of 3 to 10mg/kg and is now generally used at a dose of 5mg/kg 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 MTX 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 (PASI75) in over 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 to 50mg twice weekly are employed with typical PASI75 responses of 34 to 48% at 12 weeks [87]. Longer dosing periods result in increases in PASI75 response to 43 to 57% respectively. Etanercept has been shown to be effective in the treatment of psoriasis in children [88] and is licenced for use in children in the UK at a dose of up to 0.8mg/kg to a maximum of 50mg 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 80mg at week 0, followed by 40mg and 12 week PASI75 responses of 69 to 80% are 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 paper. 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.

5.2 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.

5.3 Summary

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

6 The risk of tuberculosis following TNF antagonist therapies

In Canada, Europe and Asia, the relative risk of tuberculosis in rheumatoid arthritis ranges between 2 and 16 owing to the disease itself and the use of non-biologic medications [4, 98-101]. In contrast, in one study from the US, and using non-standardized 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 tuberculosis 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 tuberculosis face several challenges, as tuberculosis 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 tuberculosis cases in patients treated with TNF antagonists that had been voluntarily reported to US FDA through its adverse event reporting system [12]. The tuberculosis risk posed by infliximab appeared twice that of etanercept. Risks of histoplasmosis and coccidioidomycosis were also increased by 6-7 fold. A study published in 2006 identified 51 tuberculosis 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 tuberculosis, and therefore likely misclassified latent infection with *M. tuberculosis* as tuberculosis [106, 107]. Another study from the BIOBADASER registry reported a not significantly different risk of active tuberculosis posed by all three TNF antagonits; a trend toward a 2-fold increased rate was noted for infliximab, but the study was limited in its statistical power [14]. A recent study identified 69 tuberculosis cases prospectively through the French RATIO registry [108]. The sex and age-adjusted tuberculosis incidence rate was 1.17 per 1000 patient-years, 12.2 times that of the general population. Nearly all of the excess risk was due to infliximab (standardized 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 tuberculosis cases that found the tuberculosis risk with anti-TNF antibodies 12-fold greater than with etanercept [109]. In the most recent study by the British Society for Rheumatology Biologics Register (BSRBR), the rate of tuberculosis in patients with rheumatoid arthritis treated with TNF antagonist therapies was three- to fourfold 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 tuberculosis 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, 111].

Most of the active tuberculosis cases in patients treated with TNF antagonists are due to reactivation of latent infection with *M. tuberculosis*. Tuberculosis 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 latent infection with *M. tuberculosis* before treatment with TNF antagonists [20, 112-117], 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 tuberculosis. The skin test has a low sensitivity in patients with rheumatoid arthritis [118], and may be falsely positive in patients with prior BCG vaccination or prior sensitization 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 tuberculosis 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 tuberculosis has a low incidence but the prevalence of prior BCG vaccination is high. IGRAs are proposed as an alternative for the tuberculin skin test [119]. The positive predictive value of an IGRA for the development of tuberculosis is most likely 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 tuberculosis infection cannot be made before more clinical data on their role in predicting tuberculosis become available.

Some patients have developed tuberculosis after receiving infliximab despite a negative initial skin test result [120]. Despite negative results of immunodiagnostic tests physicians should carefully question candidates for TNF antagonists therapies about prior exposure to tuberculosis. Chest radiographs may be helpful to identify radiographic evidence of prior tuberculosis or signs of current tuberculosis among such patients. When thus 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 4-drug therapy for tuberculosis should be started soon in all cases of suspected or documented active tuberculosis.

6.1 Summary

- The risk of active tuberculosis 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 tuberculosis cases in chronic inflammatory arthropathies.
- Tuberculin skin testing and preventive therapy is successful in programmes to prevent reactivation of tuberculosis in patients with chronic inflammatory rheumatic conditions (Evidence level C). Similar evidence concerning IGRA is lacking.

7 Immunodiagnostics to identify individuals at risk of developing tuberculosis on immunobiologicals

Infection with *M. tuberculosis* induces a strong Th1-type cellular immune response [8, 121, 122]. 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 tuberculosis [121, 123]. Two test principles are currently available to detect specific immunity. The tuberculin skin test

has been in use for more than a century [124] 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 reaction transverse to the long axis of the arm is measured 48 to 72 hours after antigen injection. Reliability of the measurement might be improved by using the "ballpoint technique" [125]. 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 IFN-γ release assays (IGRA) [126]. The percentage of blood cells releasing IFN-γ may be determined using an enzyme-linked immunospot (ELISPOT) assay [127, 128] or the amount of IFN-γ released into the supernatant may be quantified using an enzyme-linked immunosorbent assay (ELISA) [129]. Commercial tests are available for both formats (ELISPOT as T-SPOT.*TB* by Oxford Immunotec, UK, and ELISA as QuantiFERON TB Gold in-tube by Cellestis, Australia). Alternatively, IFN-γ may be accumulated intracellularly and detected using flow-cytometry [130-133]. 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 [126, 134, 135]. Among those, early secretory antigenic target 6 (ESAT-6), culture filtrate protein 10 (CFP-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 [128, 136], 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 [133, 137]. 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 as compared to studies that used ELISA [16, 138]. 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 non-specific 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 licenced for clinical use in many countries [136, 139-141]. Up to now, however, no blood-based test allows distinction of active tuberculosis 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 tuberculosis 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** [131, 142-153]. In general, results of IGRAs and tuberculin skin tests correspond poorly, although agreement is stronger in countries with low tuberculosis prevalence and low BCG vaccination coverage [147]. 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 (between 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 tuberculosis. However, up to now, the positive predictive value of IGRA responses for the development of tuberculosis in candidates undergoing therapy with TNF antagonists is not known. A study conducted among individuals with HIV-infection from a low endemic area for tuberculosis indicates a very high negative predictive value of IGRAs in immunocompromised patients [154]. Currently it is unknown, whether individuals with a negative IGRA result and a medical history of tuberculosis or with imaging study findings suggestive of past tuberculosis or individuals with reverting IGRA results run a lower risk of tuberculosis than those with persistently positive IGRA results. Moreover, it is 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, 143, 147]. Therefore, recommendations that favour the use of IGRA over tuberculin skin testing to evaluate the risk for progression to tuberculosis 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.

7.1 Summary

- TST 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 tuberculosis infection.
- IGRAs are *in vitro* tests that rely on the rapid production of IFN-γ by circulating mononuclear cells in response to antigens that 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 tuberculosis and a low percentage of indeterminate results.
- Further longitudinal studies are needed to estimate the risk for progression to tuberculosis after IGRA-based and/or tuberculin skin test-based diagnosis of latent infection with *M. tuberculosis* in patients undergoing therapy with TNF antagonists.

8 Preventive chemotherapy

Although adalimumab and infliximab share a higher risk for progression from latent infection to tuberculosis than soluble TNF receptor [12, 14, 105, 108, 155], preventive therapy is warranted in any case. The available evidence from a carefully assembled register-based observational study from Spain using a course of nine 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 tuberculosis imparted by a risk factor relative to a population that is similar in every respect except for the presence of that factor. Because tuberculosis 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 [123]. However, for a decision to recommend antibiotic therapy to prevent tuberculosis, knowledge about the timing of tuberculin skin test or IGRA conversion is very helpful as the risk for the development of tuberculosis is low (incidence of about one per 1,000-person-years) when infection with *M. tuberculosis* occurred more than seven years 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 tuberculosis 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 tuberculosis, 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 tuberculosis. However, the relative risk of 4 among patients with rheumatoid arthritis receiving any of the compounds from the entire class compared to those not receiving it was nevertheless remarkably modest in a comprehensive study in Sweden [4].

8.1 Differences in tuberculosis risk by type of TNF antagonists

Epidemiologically more meaningful, despite remaining methodological problems, have been intra-class comparisons, evaluating the relative impact on tuberculosis 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.

8.2 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] and the British Thoracic Society does likewise [158]. The relative risk of progression to tuberculosis in a recently infected person is about tenfold 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 recognized 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].

8.3 Consequences for preventive chemotherapy among patients treated with TNF antagonists

No properly designed, population-based study has ever demonstrated a relative risk of tuberculosis in excess of ten 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 tuberculosis than patients receiving a soluble receptor-based compound.

Given that the patient population receiving TNF antagonists in addition 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.

8.4 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 that has determined the effectiveness of preventive chemotherapy in this population [14, 114]. In this study from Spain, after implementation of official recommendations to prescribe isoniazid preventive therapy for nine months, the incidence rate of tuberculosis 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.

8.5 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 tuberculosis 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 CDC. In this case, delaying the starting of TNF antagonists for 4 weeks is a safe approach (Evidence level D).

9 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 tuberculosis 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 tuberculosis [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 over 1 year [163], as well as a Dutch registry of 146 children followed for up to 4 years [164] and a US study of 69 children, 26 of whom completed 8 year follow-up [165] revealed only 2 children developing tuberculosis on etanercept. One, a 9 year old girl from the UK developed tuberculosis septic arthritis [166], the other a 9 year old girl from the Netherlands initially received etanercept, then infliximab after which she developed extrapulmonary tuberculosis [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 1 documented case of a child developing tuberculosis whilst on infliximab for juvenile idiopathic arthritis [170]. Adaluzimab and abatacept have so far only included trials with fewer than 200 children with juvenile idiopathic arthritis, but they had relatively short follow-up. No cases of tuberculosis have been reported [171]. The existing data support a clear difference in the risk of developing tuberculosis 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.

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

The diagnosis of tuberculosis in any young child is difficult, due to the nature of primary childhood tuberculosis, 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 immunization 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 younger than 2 years of age [173-175].

9.2 Immunodiagnostics performance in immunosuppressed children

Over the past decade, we have learned 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 recognized 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 does not provide a determinate result in a substantial proportion of children with a variety of primary and acquired immunodeficiencies, including children treated for autoinflammmatory disorders [176].

9.3 Current practice

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

9.4 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 tuberculosis 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 a better understanding and more knowledge in this field.

10 Published national guidelines

Since the recognition of an increased risk of reactivating tuberculosis 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. Only documents published in English have been included and all are hitherto referred to as "guidelines". These publications are from the following countries: France [115], Germany [177], Ireland [116], Portugal [155], Spain [as outlined in 7, 114], Switzerland [20], UK [112] and USA [113]. In addition, other national guidelines have recently become available in non-English languages, e.g. in Denmark (http://www.dsinfm.dk/).

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, 114] outline the measures initially proposed in 2002 by the Spanish Rheumatologic Society and the Spanish Health authority. Later on-line guidelines became 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 tuberculosis. A summary of the main recommendations made in the different publications and in this TBNET consensus statement can be found in **Table 5**.

10.1   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 tuberculosis. 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 tuberculosis, previous tuberculosis 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 exposure or untreated tuberculosis should be an indication for preventive therapy. All recommend a whole course of treatment for active tuberculosis where present and preventive chemotherapy when latent infection with *M. tuberculosis* is diagnosed. The importance of maintaining vigilance for tuberculosis in all

patients on TNF antagonist treatment is emphasised, even after a full course of preventive therapy has been completed.

10.2 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 2 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 (NICE) 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 immunsuppressive treatment and then repeating screening prior to TNF antagonist therapy. Immunosuppression is defined as established disease, or treatment with corticosteroids of >10mg/day, 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 three weeks after initiation of preventive therapy to its completion, and two 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 tuberculosis and drug-induced hepatitis. In addition, according to the UK guidelines those with previously treated tuberculosis should continue to be monitored at three months intervals while on TNF antagonist therapy.

10.3 Summary

- All eight national guidelines agree that every patient considered for TNF antagonist therapy should be screened for evidence of tuberculosis, 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 tuberculosis 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.

11 Consensus recommendations

The currently available evidence on the best management to prevent tuberculosis in patients receiving TNF antagonist therapies is limited. The recommendations summarised in this document represent a consensus of published evidence (for evidence levels see Table 1) and expert opinions to guide physicians to evaluate the risk for tuberculosis and to prevent tuberculosis 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.

1) **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 antagonists therapies should be questioned about a history of prior tuberculosis or tuberculosis contact and should have a chest radiograph to search for evidence of prior or active tuberculosis.

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

The risk of tuberculosis 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 tuberculosis (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).

3) **Should preventive therapy against tuberculosis be advised for all candidates undergoing TNF antagonist therapies with *M. tuberculosis* specific immune responses (latent infection with *M. tuberculosis*)? Is this valid also for those who are prescribed etanercept, where the risk of tuberculosis given latent infection is lower, compared to those treated with monoclonal antibodies against TNF?**

Preventive chemotherapy against tuberculosis 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).

4) Is a different management recommended based on different underlying disease (rheumatoid arthritis, psoriasis, inflammatory bowel disease)?

Screening for latent infection and preventive chemotherapy against tuberculosis should not be different for patients with different underlying disease (rheumatoid arthritis, psoriasis, inflammatory bowel disease) who are candidates for TNF antagonist therapies (Evidence level D).

5) Should latent infection with *M. tuberculosis* be diagnosed based on tuberculin skin testing or on IGRA testing or on 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 2-step tuberculin skin test predicts the development of tuberculosis 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 2-step tuberculin skin testing while expert opinion suggests that IGRAs are superior to the tuberculin skin test in identifying individuals at risk of developing tuberculosis.

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 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 tuberculosis. Where negative, however, these tests have a poor predictive value on their own (Evidence levels C and D).

6) 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 2 step approach be considered?

As there is limited evidence, at present, 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 2-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 ones, do recommend it based on empirical evidence (Evidence level C).

7) 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 over QuantiFERON TB Gold in-tube test 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).

8) 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 $\geq$ 10 mm, as generally recommended for other immunocompromised conditions (excluding HIV-infection) warranting preventive chemotherapy against tuberculosis, 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 $\geq$ 10 mm should not generally need confirmation by an IGRA.
Paediatric consensus is to provide preventive chemotherapy (i) if either the IGRA or the tuberculin skin test is positive and (ii) if only the tuberculin skin test is used, different cut-offs should be used for BCG-vaccinated ($\geq$10 mm) versus non-vaccinated ($\geq$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).

9) What decision should be taken when testing for latent infection yields discordant results (e.g. positive tuberculin skin test and negative IGRA test result) 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 (for children, see point 8) (Evidence level D).

10) When should TNF antagonist therapies be initiated following the induction of preventive

chemotherapy against tuberculosis?

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

11) Which preventive chemotherapy regimen is the most effective in reducing the risk of

developing tuberculosis in individuals with *M. tuberculosis* specific immune responses

undergoing TNF antagonist therapies?

Effectiveness of different chemotherapeutic regimens to prevent tuberculosis 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 three 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 tuberculosis 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 tuberculosis is substantially increased when adherence to guidelines for preventive chemotherapy against tuberculosis in individuals receiving TNF antagonist therapies is not strict.

12) How should patients who started preventive chemotherapy against tuberculosis be

followed especially in relation to the initiation of TNF antagonist therapies?

Patients should be educated about early signs and symptoms of tuberculosis 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 tuberculosis. However, In the presence of signs and symptoms compatible with active tuberculosis, chest radiography should be performed without delay. In cases of doubt, chest computerised tomography (CT)-scans should be performed, which are superior to chest radiography in detecting early radiological signs of active tuberculosis. Liver enzymes should be analyzed 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 tuberculosis 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).

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

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

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

Patients who have completed appropriate tuberculosis therapy do not appear to have an increased risk of tuberculosis 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 tuberculosis in the past, unless reinfection with *M. tuberculosis* is plausible (Evidence level D).

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

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

12 Conclusions

The introduction of TNF antagonist therapies into clinical practice has been a breakthrough in the history of 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 statement by the TBNET we have summarized the current knowledge of the risk of tuberculosis in relation to TNF antagonist therapies and we have provided detailed consensus recommendations for the most important clinical questions related to tuberculosis and TNF antagonist therapies in adults and children.

Tuberculosis 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 document will lead to a significant reduction in the number of cases of active tuberculosis in relation to TNF antagonist therapies.

13 Abbreviations

4R, 4 months rifampicin; 6H, 6 months isoniazid; 9H, 9 months isoniazid; 9-12H, 9-12 months isoniazid; 2RZ, 2 months rifampicin plus pyrazinamide; 3RH, 3 months rifampicin plus isoniazid; ACR, American College of Rheumatology; AS, ankylosing spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BCG, Bacille Calmette Guérin; BIOBADASER, a national registry of patients with different forms of chronic arthritis who are treated with biologics; CCL, chemokine ligand; CDAI, Crohn's disease activity index; CDC, Centre for Disease Control and Prevention; CDEIS, Crohn's disease endoscopic index of severity; CFP-10, culture filtrate protein 10; CXR, chest x-ray; CT, computerised tomography; DAS, disease activity score; DLQI, Dermatology Life Quality Index; DMARD, disease modifying antirheumatic drug; DTH delayed-type hypersensitivity; ELISPOT, enzyme-linked immunospot; EMEA, European Medicinal Agency; ESAT-6, early secretory antigenic target 6; EULAR, League against Rheumatism; FDA, Federal Drug Administration; HIV, Human Immunodeficiency Virus; IBD, inflammatory bowel disease; IFN-γ, interferon-γ; IgG, immunoglobulin G; IGRA, IFN-γ release assay; IMMID, immune-mediated inflammatory diseases; IPT, isoniazid preventive therapy; IR, incidence rate; IS, immunosuppressed/immunosuppression; LTBI, latent tuberculosis infection; LT, lymphotoxins; MTX, methotrexate; NICE, National Institute for Clinical Excellence; NSAID, non-steroidal anti-inflammatory drug; PASI, Psoriasis Area Severity Index; PPD, purified protein derivative; PUVA, Psoralen + UVA treatment; QFT-G: QuantiFERON TB Gold; QFG-IT, QuantiFERON-TB Gold in-tube; RATIO registry, a French registry designed by a multidisciplinary group to collect data on opportunistic and severe bacterial infections and lymphoma in patients treated with TNF antagonists (infliximab, etanercept and adalimumab); RD, regions of difference ; RR, adjusted rate ratio; SIR, standardized incidence ratio; SP, severe psoriasis; sTNF, soluble TNF; TNFR, TNF receptor; TACE, metalloproteinase; TB, tuberculosis; tmTNF, transmembrane protein TNF; TBNET, Tuberculosis Network European Trialsgroup; TST, tuberculin skin test; TNF, tumour necrosis factor.

14 Figures

Figure 1: TNF acts at multiple steps in antibacterial and inflammatory responses to *M. tuberculosis* infection. **A**. Macrophage-derived TNF acts as a co-stimulus for T cells. **B**. T-cell–derived TNF primes macrophages for mycobacteriocidal activity. **C**. Macrophage- and T-cell–derived TNF (together with 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. Figure reproduced with permission from ref. 10, copyright Infectious Diseases Society of America 2005.
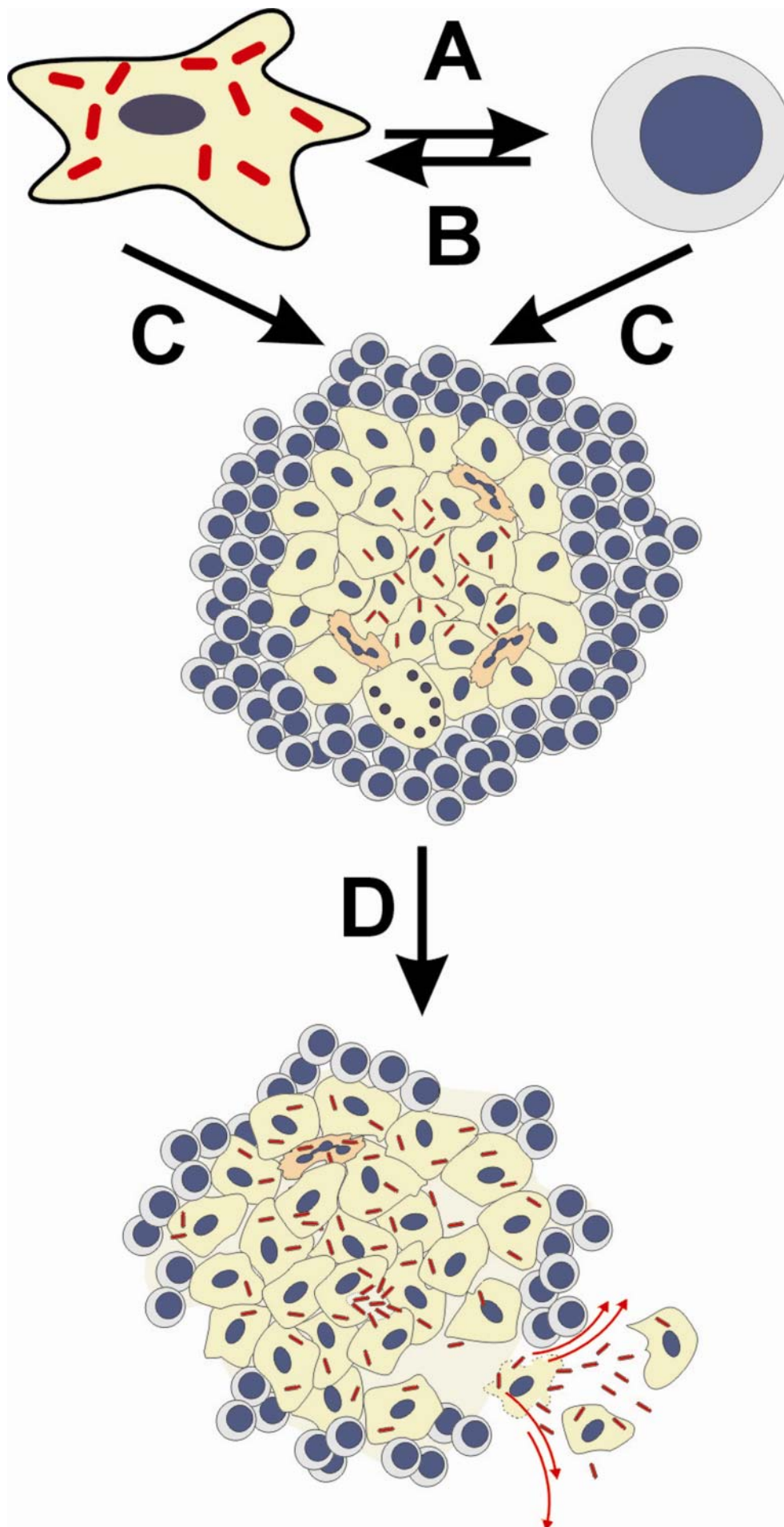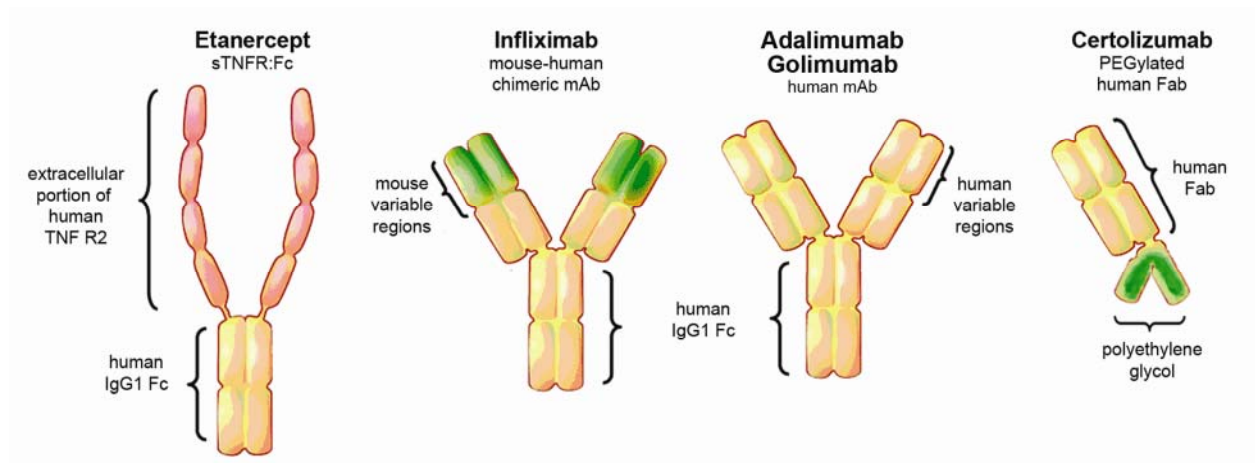
Figure 2: Structures of the TNF antagonists. Adapted with permission from reference [39].

15 Tables

Table 1: Description of levels of evidence

Evidence Category	Sources of Evidence	Definition
A	Randomised controlled trials (RCT) Rich body of data	Evidence is from endpoints of well-designed RCT 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 (RCT) Limited body of data	Evidence is from endpoints of intervention studies that include only a limited number of patients, post-hoc or subgroup analysis of RCT, or meta-analysis of RCT. 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.

Table 2: TNF antagonists: licenced indications, conditions for prescription, and dosing

Licenced Indications	Infliximab	Etanercept	Adalimumab	Golimumab	Certolizumab
Rheumatoid arthritis • active disease *and* inadequate response to DMARDS including MTX[3] • patients with severe and progressive/erosive disease without prior DMARD therapy[3] • patients with moderately to severely active disease[4]	+[1] +[1] Dosing: • 3 mg/kg i.v. week 0,2,6, then 8-weekly • Inadequate response: up to 7.5 mg/kg 8-weekly or 3mg/kg 4-weekly	+[1,2] +[1,2] Dosing: 25 mg s.c.2x/week *or* 50 mg s.c.1x/week	+[1,2] +[1,2] Dosing 40 mg s.c. 2-weekly	+[1] +[1] Dosing 50 mg s.c. 4-weekly	+[1,2] +[1,2] Dosing 400 mg s.c. week 0 and 2, then once-monthly
Ankylosing spondylitis • Inadequate response to conventional therapy (i.e. NSAID)[3] • active disease[4]	+ Dosing: 3 mg/kg i.v. week 0,2,6, then 6-8-weekly	+ Dosing: 25 mg s.c.2x/week *or* 50 mg s.c.1x/week	+ Dosing 40 mg s.c. 2-weekly	+ Dosing 50 mg s.c. 4-weekly	-
Psoriatic arthritis • active disease *and* inadequate response to DMARDS including MTX[3] • active arthritis[4]	+[1,2] Dosing: 3 mg/kg i.v. week 0,2,6, then 8-weekly	+ Dosing: 25 mg s.c. 2x/week *or* 50 mg s.c.1x/week	+ Dosing 40 mg s.c. 2-weekly	+[1,2] Dosing 50 mg s.c. 4-weekly	-
Juvenile idiopathic arthritis • age >4 and < 18 *and* active disease *and* inadequate response to or intolerance of DMARDS including MTX[3] • patients with moderately to severely active disease[4]	-	+ Dosing: 0.4 mg/kg s.c 2x/week	+ Dosing 40 mg s.c. 2-weekly	-	-
Crohn's disease	Dosing 5 mg/kg i.v. week 0,2,6, then 8-	Not used	Dosing 160 mg s.c.,	Not approved	Dosing 400 mg s.c. at

Licenced Indications	Infliximab	Etanercept	Adalimumab	Golimumab	Certolizumab
	weekly, if ineffective increase to 10mg/kg every 8 weeks		followed by 80 mg s.c., then 40 mg every second week		weeks 0, 2 and 4 followed by 400 mg every 4 weeks (not yet approved in Europe)
Ulcerating colitis	Dosing 5 mg/kg i.v. week 0,2,6, then 8-weekly, if ineffective increase to 10mg/kg every 8 weeks	Not used	Not yet approved	Not yet approved	Not yet approved
Psoriasis • Very severe plaque psoriasis PASI >20, DLQI >18 and failure or contraindication to 2nd line drugs (MTX, cyclosporine, PUVA) • Severe plaque psoriasis PASI >10, DLQI >10 and failure or contraindication to 2nd line drugs (MTX, cyclosporine, PUVA)	Dosing 5mg/kg i.v. at weeks 0,2,6 and then every 8 weeks	Dosing 25mg sc 2x weekly or 50mg weekly to 24 weeks or 50mg 2x weekly to 12 weeks and weekly thereafter	Dosing 80 mg sc wk 0, 40mg week 1 and alternate weeks thereafter	No current data	No current data

[1]plus MTX; [2]without MTX if contraindicated or not tolerated; [3]European Medicinal Agency (EMEA) approved indication; Federal Drug Administration (FDA) approved indication, Abbreviations: MTX, methotrexate; DMARD, disease modifying antirheumatic drug, NSAID, non-steroidal antirheumatic drug.

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

	Country	Type of study	Adalimumab	Etanercept	Infliximab	Comments
Wallis et al. (2004) [12]	USA	Cases voluntarily reported to US FDA		IR 28/100,000	IR 54/100,000	Etanercept vs infliximab P<0.0001
Brassard et al. (2006) [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 et al. (2007) [14]	Spain	Data from Registry	IR 176 /100,000	IR 114 /100,000	IR 383 / 100,000	P= NS. Wide confidence interval
Tubach et al. (2009) [108]	France	Data from registry	IR 215.0 / 100,000	IR 9.3 /100,000	IR 187.5/ 100,000	SIR 29.3 for adalimumab SIR 1.8 for etanercept SIR 18.6 for infliximab. P< 0.0001
Fonseca et al. (2009) [155]	Portugal	Data from registry	4 cases / 171 patients	1 case / 333 patients	8 cases / 456 patients	Exposure is not provided

IR: incidence rate; RR: adjusted rate ratio; SIR: standardised incidence ratio

Table 4: Summary of studies analyzing the concordance of IGRA and tuberculin skin testing for the screening of tuberculosis infection in patients with chronic immune-mediated inflammatory diseases (IMID)

| Study (year) | Country | IGRA | TST Cut-off | Participants n° | IMID condition | BCG % | Indeterminate % | κ | Concordant results | | Discordant results | |
									TST+/IGRA+ N (%)	TST-/IGRA- N (%)	TST-/IGRA+ N (%)	TST+/IGRA- N (%)
Cobanoglu et al. (2007) [142]	Turkey	QFT-G IT	10 mm	68 cases 38 controls	>65% RA + AS	100	10.3 5.3	0.14 -0.05	8 (13.1) 0	23 (37.7) 23 (63.8)	1 (1.6) 1 (2.8)	29 (47.5) 12 (33.3)
Matulis et al.*‡ (2008) [143]	Switzerland	QFT-G IT	5 mm	142	>65% RA + S	83	6	0.16	10 (7)	60 (44.7)	5 (3.5)	34 (25.4)
Dinser et al. (2008) [131]	Germany	Flow cytometric assay	5 mm	97	>50% RA	5.1	0	0.31	6 (6.2)	74 (76.3)	10 (10.3)	7 (7.2)
Ponce de Leon et al. (2008) [144]	Peru	QFT-G IT	5 mm	101 cases 93 controls	RA	80.2 80.6	1.9 0	0.37 0.55	21 (20.8) 16 (17.2)	50 (49.5) 61 (65.6)	24 (23.8) 5 (5.4)	6 (5.9) 11 (11.8)
Vassiloupolos et al. (2008) [145]	Greece	T-SPOT.TB	5 mm	70	>85% RA + AS + PA	40	0	0.38	12 (17.1)	39 (55.7)	4 (5.7)	15 (21.5)
Bocchino et al. (2008) [146]	Italy	QFT-G IT T-SPOT.TB	5 mm	69 69	RA + IBD + PA	2.8 2.8	2.8 5.8	0.57 0.48	14 (20.9) 12 (18.5)	41 (61.2) 39 (60)	8 (11.9) 9 (13.8)	4 (6) 5 (7.7)
Bartalesi et al. (2009) [147]	Italy	QFT-G IT	**	398	>85% RA + PA + AS	4.1	1.5	0.55	39 (10)	306 (77.8)	13 (3.3)	35 (8.9)
Murakami et al. (2009) [148]	Japan	ELISPOT*	5 mm	71	RA	100	0	0.18	4 (5.7)	50 (71.4)	6 (8.4)	11 (15.5)
Martin et al.‖ (2010) [184]	Ireland	T-SPOT.TB QFT-G	5 mm	150 72	RA + PA + AS	82	4.7 2.8	0.2 na†	6 (4.2) na†	110 (77) na†	8 (5.6) na†	19 (13.2) na†
Behar et al. (2009) [150]	USA	T-SPOT.TB	5 mm#	179	>80% RA	4.7	0	-0.019	0 (0)	167 (93.3)	10 (5.6)	2 (1.1)
Laffitte et al. (2009) [151]	Switzerland	T-SPOT.TB	5 mm	50	PS	90	0	0.33	8 (16)	28 (56)	2 (4)	12 (24)
Soborg et al. (2009)	Denmark	QFT-G	***	234	>50% RA	76	5	0.2	9 (4)	180 (77)	9 (4)	36 (15)

[152]												
Inanc et al. (2009) [153]	Turkey	QFT-G	5 mm	140	RA + AS	84	5.7	0.29	41 (31)	40 (30)	5 (4)	46 (35)

Abbreviations: IGRA: Interferon-γ release assay; QFT-G: QuantiFERON TB Gold (CFP-10 and ESAT-6); QFT-G IT: QuantiFERON TB Gold In-tube (CFP-10, ESAT-6 and TB7.7); BCG, Bacillus Calmette-Guérin; SP, severe psoriasis; RA, rheumatoid arthritis; PA, psoriatic arthritis; SA, spondylarthropathies; AS, ankylosing spondylitis; TST: tuberculin skin test

* In house made ELISPOT with antigens CFP-10 and ESAT-6.

† Data on discordant results between two tests not available

‡ TST analyzed retrospectively. The median time between performing the TST and the QFT assay was 102 days (range 7–184).

^ refers to the TST cut-off in the IMID subjects (and not in the controls, where present).

** Tuberculin skin test cut-off> 5, > 10, or > 15 mm, stratified by groups at risk and risk factors for *M. tuberculosis* infection.

*** Tuberculin skin test cut-off ≥ 12 mm for Bacille Calmette-Guérin vaccinated and ≥ 6 mm for unvaccinated.

TST was read, after instruction, by the patients themselves

|| Concordance between QFT-G and T-SPOT.*TB* 98.4% (agreement: k= 0.9)

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

National Guidelines for LTBI/active TB: Screening pre-TNF antagonist therapy	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 2003 [115]	All patients	All patients	One step	10mm	No	TST+ History of TB treated before 1970 or not treated for min 6 months; CXR lesions >1cm^3 with no history of treatment	2RZ 3RH 9H	> 3weeks after starting prophylaxis	>2 months after completion of TB treatment
Germany 2009 [177]	All patients	Only if discrepancy between strong epidemiologic evidence of prior TB exposure and negative IGRA	-	>5mm	Yes	IGRA+ Abnormal CXR suggestive of past TB inadequately treated; History of exposure	9H or 4R	1-2 months after starting prophylaxis	-
Ireland 2008 [116]	All patients	All patients	One step	10mm 5mm 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

National Guidelines for LTBI/active TB: Screening pre-TNF antagonist therapy	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
Portugal 2008 [155]	All patients	All patients	Two step	5mm	In progress	TST+ Consider prophylactic treatment in TST negative patients	9H	1 month on prophylaxis	>2 months on TB treatment
Spain 2003&2005 [7, 114]	All patients	All patients	Two step	5mm	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 2007 [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 2005 [112]	All patients	Not for patients on IS as unreliable	One step	5mm in unvaccinated 15mm in vaccinated	No (update due 2010 by NICE)	TST+ stratified for risk Previous TB inadequately treated or abnormal CXR;	6H or 3HR	If abnormal CXR or history of TB, complete prophylaxis. If normal CXR or	>2 months on TB treatment

National Guidelines for LTBI/active TB: Screening pre- TNF antagonist therapy	Risk Assessment Examination CXR	TST	TST details	Positive TST	IGRA testing	Who should receive prophylaxis?	LTBI treatment	Time delay before TNF antagonist therapy — LTBI	Time delay before TNF antagonist therapy — Active TB
						IS patients stratified for risk		IS can start concurrently	
USA 2004 [113]	All patients	All patients	One step	5mm if IS 10mm if risks e.g new immigrant, drug users 15mm 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	≥10mm	yes	IGRA+ or TST ≥10mm	9-12H or 3 RH	>4 weeks after initiation of prophylaxis	Preferably complete TB treatment

BCG, Bacille Calmette-Guérin; CXR, chest X-ray; IS, immunosuppressed/Immunosuppression; IGRA, IFN-γ release assay; 4R, 4 months rifampicin; 6H, 6 months isoniazid; 9H, 9 months isoniazid; 9-12H, 9-12 months isoniazid; 2RZ, 2 months rifampicin plus pyrazinamide; 3RH, 3 months rifampicin plus isoniazid; CXR, chest radiograph; LTBI, latent infection with *M. tuberculosis*; TST, tuberculin skin test; NICE (National Institute for Clinical Excellence).

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