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Review

Risk of tuberculosis with the use of anti-TNF medications in psoriasis: incidence, screening and management

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Abstract

Tumor necrosis factor (TNF) plays an important role in containing mycobacterial infections. With the rapidly increasing role of TNF inhibitors in dermatology, tuberculosis (TB) is becoming an important and worrisome concern to dermatologists. This paper aims to provide a comprehensive review on the incidence of TB in patients treated with anti-TNF, the variety of TB screening methods, and management of these cases. Various national recommendations have been highlighted. The monoclonal antibodies, infliximab and adalimumab, appear to be more associated with the risk of TB reactivation than the soluble receptor etanercept. Tuberculosis associated with TNF inhibitors, in contrast to classical TB, is more likely to be disseminated, atypical, extra pulmonary, and life threatening. Vigilance for typical and atypical presentations of active TB is mandatory until the end of therapy. Although tuberculin standard test (TST) has been the gold standard for screening of latent TB infection (LTBI) for close to a century, it has several inadequacies and may be unreliable in patients with widespread psoriasis. Interferon gamma release assays (IGRAs) with better diagnostic specificity and sensitivity are a promising adjunct to diagnose LTBI at present. Although appropriate screening and treatment of LTBI will lower the risk of reactivation to a great extent, no chemoprophylactic regimen is fully protective.

Keywords: Psoriasis, tuberculosis, anti-TNF, biologics, screening

Introduction

Tumor necrosis factor alpha (TNF-α) is a master cytokine in the pathogenesis of psoriasis. By binding to its specific p55 and p75 receptors, it triggers an inflammatory cytokine cascade that inhibits keratinocyte apoptosis, induces keratinocyte

hyperproliferation in the skin, and causes inflammation and destruction in the joints [1]. TNF-α levels are elevated in psoriatic plaques, serum, and synovial fluid of patients with psoriasis and the levels correlate positively with disease severity [1-3]. Under physiological conditions, TNF-α plays a crucial role in the formation and maintenance of granulomas that contain mycobacterial infections, which cannot otherwise be eradicated by the host defence mechanisms [4]. In tuberculosis (TB), the bacilli are sequestered within granulomas where they are contained in a viable but dormant or latent state via TNF mediated activation of antigen specific T-cells, recruitment of macrophages, and secretion of inflammatory cytokines. This important role of TNF-α in host defences against TB has been demonstrated in animal models in which inhibition of TNF-α led to loss of ability to control primary infection, breakdown of granulomas and release of mycobacteria, and rapid progression to active disease [4]. In humans, studies based on post-marketing surveillance of adverse drug reactions and biologic registries have shown a consistent risk of reactivation of latent tuberculosis in individuals being treated with TNF-α blockade therapies [5-9].

Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis*. Globally, it is second only to the human immunodeficiency virus (HIV) as the leading infectious cause of death. According to the last WHO estimates, 8.7 million new cases of TB and 1.4 million TB deaths occurred in the year 2011 [10]. Following primary infection, 95% of patients are able to effectively contain the bacterium in a state of latency by mediating a robust cell-mediated immune response. These individuals are then said to have latent tuberculosis infection (LTBI) and are asymptomatic and non-infectious; they mostly remain free of disease for their lifetimes unless the immunological balance between the host and pathogen is perturbed in some way [4,11]. About one-third of the world's population is latently infected, with a 5-10% lifetime risk of progression from LTBI to active disease [12]. Factors that drive progression include HIV infection, diabetes, chronic renal failure, silicosis, organ transplants, and immunosuppressive medications such as systemic corticosteroids and TNF antagonists [4,11,12].

Until as recently as a decade ago, diagnosis and treatment of non-cutaneous TB were outside the realm of regular dermatological practice. However, with the advent of anti-TNF therapies for psoriasis, patients treated with these drugs have become a new high risk group for developing TB and it is now imperative for dermatologists to have in-depth knowledge and understanding of the immunopathogenesis, clinical presentation, screening methods, and management of TB in this group of patients; this papers aims to provide summaries of these. PubMed, the Cochrane library, Google Scholar, and Medline via Ovid (1946 to August 2013) were searched using the keywords: *tuberculosis, biologics, screening* and *tumour necrosis factor*. The search was limited to papers in the English language and individual search hits were combined with "and". Reference lists of relevant papers were also searched for related studies resulting in a total of 61 records.

Incidence of tuberculosis with anti-TNF therapy

Data from a number of studies and biologic registries, mostly in the rheumatoid arthritis (RA) population, have tried to establish the incidence of TB associated with TNF inhibitor therapy (Table 1). Based on data from the BIOBADASER, a national biologics registry established by the Spanish society of Rheumatology, Gomez-Reino et al [7] reported an extremely high TB incidence rate (IR) in patients treated with infliximab in the year 2000, prior to implementation of screening recommendations (IR= 1893 per 100,000 patient-years vs. only 21/100,000 patient-years in the general population) [risk ratio (RR) = 90.1 (95% CI 58.8 to 146.0)]. Similarly, Tubach et al [8] reported 69 cases of TB in patients treated with infliximab, adalimumab and etanercept between 2004 and 2006, translating to an IR of 116.7/100,000 patient-years (95% CI 10.6 to 222.9); this is about 12 times greater than the rate in the general French population [standard incidence ratio (SIR) = 12.2 (95% CI 9.7 to 15.5; p < 0.0001)].

Recently, Dixon et al [9] carried out a prospective observational study using the British Society for Rheumatology Biologics Registry (BSRBR) to explore drug-specific risk of TB in patients treated with anti-TNF between 2001 and 2008. A total of 39 cases of TB associated with the three TNF inhibitors were identified translating to an IR of 118/100,000 patient-years (95% CI 84 to 160); this is over 8 times greater than the rate in the general UK population [8].

Table 1. Major Studies Reporting Tuberculosis Associated With TNF-α Inhibitor Therapy in RA

AUTHOR	COUNTRY	SOURCE OF DATA	TB IR with anti-TNF /100,000 PATIENT-YEARS (95% CI)			TB IR in RA POPULATION / 100,000 PATIENT-YEARS
			Etanercept	Infliximab	Adalimumab	
Keane, 2001 [5]	USA and Europe	FDAAERS	-	24.4 (95% CI 0.6 - 34.0)	-	6.2
Mohan, 2004 [58]	USA	FDAAERS	10	-	-	6.2

Wallis, 2004 [13,14]	USA	FDAAERS	28	54	-	5.6
Wolfe, 2004 [6]	USA	National Database for Rheumatic Diseases	-	52.5 (95% CI 14.3 - 134.4).	-	6.2
Askling, 2005 [15]	Sweden	Swedish registry	80	145	-	-
Gomez –Reino, 2007 [31]	Spain	Spanish register BIOBADASER	114	383	176	-
Tubach, 2009 [8]	France	French register RATIO	9.3	187.5	215	8.7
Dixon, 2010 [9]	UK	British registry BSRBR	39 (95% CI 13 -92)	136 (95% CI 68 - 244)	144 (95% CI 72 - 258)	-

TB: Tuberculosis; IR: incidence rate; TNF: tumour necrosis factor; 95% CI: confidence interval; RA: Rheumatoid arthritis; FDAAERS: Food and Drug Administration Adverse Events Reporting System; RATIO: French Research Axed on Tolerance to Biotherapies; BSRBR: British Society for Rheumatology Biologics Registry

Although the risk of reactivation is common to all TNF inhibitors, the monoclonal antibodies infliximab and adalimumab appear to portend a much higher risk compared to the soluble TNF receptor etanercept [5,8,9,13,14] (Table 1). In a large review based on cases reported voluntarily to the Food and Drug Administration Adverse Events Reporting System (FDAAERS) between January 1998 and September 2002, Wallis et al [13,14] reported higher rates of granulomatous infections associated with infliximab (54/100,000) than with etanercept (28/100,000) in cases restricted to the United States. However, pharmaco-vigilance based on voluntary reporting is prone to inherent flaws like physician underreporting and reporter bias. Also, other differences such as the local prevalence rates of TB, pattern of drug use (preferential use of infliximab in Europe where TB prevalence rates are higher), severity of the underlying disease, concomitant medications and medical comorbidities may all potentially confound the analysis of differential risks between these drugs [11]. A recent analysis of data from the British Society for Rheumatology Biologics Registry (BSRBR) [9] controlled for these confounders and showed high tuberculosis IR of 144 /100,000 patient-years for adalimumab (95% CI 72 to 258) and 136 /100,000 patient-years for infliximab (95% CI 68 to 244) vs. only 39 /100,000 patient-years for etanercept (95% CI 13 to 92). Likewise, data analysis from the French registry RATIO [8] also controlled for differences and showed that most cases of TB were associated with the use of adalimumab [SIR = 29.3 (95% CI 20.3-42.4; p< 0.0001)] and infliximab [SIR= 18.6 (95% CI 13.4 to 25.8; p< 0.0001)] rather than etanercept [SIR=1.8 (95% CI 0.7 to 4.3; p= 0.20)]. Although the exact mechanisms remain unclear, differences in the pharmacodynamic properties and mechanism of action of these drugs have been proposed to explain this disparity [11].

Although this large body of epidemiological evidence supports the biological plausibility that LTBI reactivation can occur with TNF-α inhibition, most of this data relates to the use of these drugs in RA, which itself is associated with an increased risk of TB. Also, drugs like methotrexate and corticosteroids used in the management of RA may further contribute to the immunosuppressed state [15, 16]. Currently, the proportion of risk that stems from the immunological disease itself, the concomitant medications or the synergy between these drugs, rather than the TNF inhibitor therapy itself is unknown [16,17]. Whereas there have been anecdotal reports of TB associated with the use of methotrexate in RA and psoriasis, this risk has not been confirmed by any large studies [18-20]. On the other hand, prolonged use of corticosteroids at doses 15-20 mg/day has been shown to increase the risk of tuberculosis independent of other risk factors [21-23]. Although dermatologists should benefit from the rheumatology experience, extrapolating this data to patients with psoriasis may overestimate the potential risks because TNFα inhibitors are typically given as monotherapy in psoriasis. This risk of TB activation with anti-TNF monotherapy in psoriasis was examined in some case reports [24-26], which found that active cases of TB, although few in number, were continuously reported with the use of these drugs in psoriasis. Another analysis of the risks associated with TNF inhibitors in psoriasis reported a lifetime risk of tuberculosis of 0-17% in patients using TNF inhibitors versus 0.3% in those without [27].

Development of active TB in patients undergoing anti-TNF-α therapy

Unlike TB in immunocompetent individuals, TB associated with anti-TNF therapies is often atypical, extra pulmonary, and disseminated [4, 5,11]. The diagnosis is commonly delayed owing to the altered presentation and the disease may initially be refractory to treatment because of the lingering of anti-TNFα in the system [28]. All these factors confer a high degree of morbidity and associated mortality in these patients. In one study [5], over half of the reported cases had extra-pulmonary disease

and in more than a quarter it was disseminated. Additionally, most cases associated with TNFα inhibitors occurred in close proximity to the initiation of therapy and progressed rapidly, suggesting reactivation of latent infection rather than new disease. The estimated median time from initiation of therapy to diagnosis of TB is 3 months for infliximab, 4-6 months for adalimumab, and 11.5 months for etanercept [28]. Nevertheless, TB occurred in a few patients 7.1 - 13.9 months after discontinuation of mononuclear antibodies infliximab (n=3) and adalimumab (n=1) [8].

Screening for latent TB infection (LTBI)

Considering the high risk of reactivation of LTBI, fulminant course of TB disease, and morbidity and mortality associated with anti-TNF therapies, screening for tuberculosis before the initiation of these drugs is mandatory and should be considered the standard of care [11,28,29]. Screening should include a detailed medical history, chest X-ray, and tuberculin skin test (TST) and/or interferon-gamma release assay (IGRA) [29,30]. The history should include assessment of risk factors for tuberculosis, such as birth or residence in a country of high TB prevalence, recent travel to an area of high TB prevalence, recognised exposure to a patient with pulmonary TB, residence in a congregate setting (homeless shelters, prison, chronic care facilities, drug abusers), history of drug abuse, employment in facilities that treat tuberculosis, and any past history of adequately or inadequately treated tuberculosis [29,30]. Patients should also be questioned about symptoms like persistent cough, weight loss, night sweats, and fever to rule out active tuberculosis.

Several reports have documented the beneficial impact of screening and treatment of LTBI before anti-TNF therapy. Gomez-Reino et al [31] reported a fall in the tuberculosis IR from 472/ 100,000 patient-years (95%CI 384 to 642) to 43/ 100,000 patient-years (95% CI 11 to 175) when national screening recommendations were followed, compared to a 7-fold increase when they were not. The impact of screening has also been reported from Europe and North America [32] and Spain [33], which reported 85% and 83% decreases in the incidence of TB associated with adalimumab and infliximab therapy, respectively, following implementation of official recommendations on screening and treatment [incidence risk ratio (IRR) 1.0, (95% CI 0.02 to 8.2)].

Tuberculin skin test (TST)

The standard TST, using the Mantoux technique, involves the intradermal inoculation of 0.1ml of tuberculin- purified protein derivative (PPD), a crude mixture of more than 200 *M. tuberculosis* proteins, on the inner surface of the forearm. This stimulates a delayed (type IV) hypersensitivity reaction mediated by T-lymphocytes, leading to skin induration within 48 to 72 hours and rarely blistering and necrosis [11,21,34]. The greater the reaction, the more likely it is that an individual is infected with *M. tuberculosis*. Mantoux technique has largely replaced multiple-puncture methods such as the Tine test and Heaf test which are often unreliable because it is not possible to accurately control the amount of tuberculin.

The Mantoux test is read by measuring the size of induration (not erythema) 48 to 72 hours after intradermal injection [11]. Results read after this time period may be less reliable. A TST with ≥15 mm of induration is considered positive in healthy individuals with no risk for TB [21]. However, according to the National Psoriasis Foundation (NPF) recommendations, in patients considered for anti-TNF therapy, an induration of 5mm or more should be interpreted as positive and preventive chemotherapy initiated if there are no epidemiological risk factors for tuberculosis [30]. Vesiculation, ulceration, and necrosis may occur with active infection or infection that has been treated in the past [11].

Although the TST is the most widely used tool to detect tuberculosis infections, it has several limitations. False negative reactions may occur with advanced immunosuppression, live viral vaccination, some viral infections, and improper tuberculin handling [11,35]. Further, because many of the antigens in PPD cross-react with environmental mycobacteria and the BCG vaccine strain, false positive reactions may occur in BCG vaccinated individuals and those with non-tuberculous mycobacteriosis (NTM), resulting in poor specificity [11,12,34]. In addition, the logistical inconvenience of multiple visits, operator variability in the administering and reading of the test, and the lack of a standard value at which TST is considered positive are factors that limit its usefulness.

In psoriasis, the TST may be particularly unreliable and may overestimate the incidence of LTBI because the proinflammatory state of the skin results in enhanced immune responses and false positive TST reactions [36-38]. In an attempt to evaluate the effect of psoriasis on TST results, Tsouri et al [36] compared TST results in consecutive dermatology and internal medicine patients. Patients with psoriasis had significantly larger TST reactions compared to internal medicine patients (p< 0.0001) and were more likely to be treated for latent infection. TST was also found to correlate positively with PASI score [36]. These findings were reflected in another study by Basukkas et al [37] who showed that patients with psoriasis were likely to be overdiagnosed and overtreated for LTBI than demographically matched patients with inflammatory bowel disease when evaluated by TST. Furthermore, TST may pose special challenges in patients with widespread skin diseases like psoriasis, in which it may be impossible to find lesion free skin appropriate for TST testing [38].

Interferon-gamma release assay (IGRA):

TST was the only commercially available immunologic test for the diagnosis of LTBI for close to a century [35]. However, over the last decade, *in vitro* whole blood tests that measure the production of interferon gamma (INF-γ) by T-cells in response to highly specific *M. tuberculosis* proteins, the interferon gamma release assays (IGRAs), have been approved by the FDA as alternative diagnostic aids for *M. tuberculosis* infections [12,35]. The QuantiFERON-TB test (QFT) and the QuantiFERON-TB Gold Test (QFT-G) were the earliest IGRAs approved by the FDA [12]. Currently, the two commercially available IGRAs in many countries are the QuantiFERON-TB Gold In-Tube (QFT-GIT) assay and T. SPOT.TB assay [12] (Table 2).

Table 2. FDA approved interferon gamma release assays (IGRAS) for the diagnosis of LTBI [12]

TEST	ASSAY FORMAT	MANUFACTURER	FDA APPROVAL
QuantiFERON -TB test (QFT)	ELISA	Cellestis, Carnegie, Australia	2001
QuantiFERON-TB Gold test (QFT-G)	ELISA	Cellestis, Carnegie, Australia	2005
QuantiFERON-TB Gold In-Tube test (QFT-GIT)	ELISA	Cellestis, Carnegie, Australia	2007
T-SPOT.TB test	ELISPOT	Oxford Immunotech, UK	2008

QFT-GIT uses an enzyme-linked immunosorbent assay (ELISA) to measure the amount of IFN-γ released by T-cells in response to three *M. tuberculosis* specific antigens (ESAT-6, CFP-10 and TB7.7). It uses specially designed heparinized blood collection tubes that are coated with these highly specific antigens along with positive and negative control tubes (Figure 1). These specific antigens are absent from all BCG strains and most NTM (except *M. szulgai*, *M. kansaii* and *M. marinum*). A test is considered positive if the IFN-γ concentration of the TB-antigen tube is above the test cut-off (after subtracting the IFN-γ value in the negative control tube) [12].

T.SPOT.TB uses an enzyme-linked immunospot assay (ELISPOT) to detect increases in the number of T-cells that secrete IFN-γ in response to stimulation with ESAT-6 and CFP-10 antigens. Peripheral blood mononuclear cells are incubated with the control materials and the ESAT-6 and CFP-10 antigens in specialised sodium citrate, sodium, or lithium heparin tubes. The result is reported as the increase in the number of IFN-γ producing T cells (spot forming cells). A test is positive if the spot counts in the TB-antigen wells exceed a specific threshold relative to the control wells [12].

IGRAs are more specific than TST because the antigens do not cross react with BCG strains and most NTM (except *M. szulgai*, *M. kansaii* and *M. marinum*) [12]. IGRAs are also more sensitive, especially in immunocompromised individuals [11,12]. In a recent meta-analysis, IGRAs were found to have more specificity, higher positive predictive value (PPV), and higher negative predictive value (NPV) compared to the TST in the diagnosis of LTBI [39]. Unlike TST, IGRAs do not require a follow up visit to complete the testing process and results can be available within 24 to 48 hours [35].

Information on the performance of IGRAs in psoriasis patients is just accumulating. In a retrospective study in Switzerland, Laffitte et al [40] assessed 50 psoriasis patients who were screened for LTBI using both TST and T-Spot.TB test. A positive T-SPOT.TB test was found to correlate strongly with a diagnosis of LTBI [odds ratio (OR) = 7.43 (95% CI 1.38 to 39.9)], although there was poor agreement between the two tests (κ = 0.33, SD 0.13). Those who tested TST positive and IGRA negative did not receive anti-TB treatment and did not develop TB during a median period of 64 weeks (44-188 weeks) of anti-TNF treatment. In 2012, results of a comparative study of IGRAs and TST in patients with psoriasis and musculoskeletal inflammatory disorders

demonstrated that IGRAs outperformed TST in both sensitivity and specificity [41]. These results led the authors to recommend that IGRAs should be used in place of TST as the optimal screening test for LTBI prior to anti-TNF therapy [40,41].

Like TST, IGRAs are not without limitations. They cannot distinguish between active TB disease and LTBI; they are expensive and not widely available. In addition, they have exacting requirements for blood collection and transportation, associated with a high percentage of indeterminate results and require specialized laboratory equipment and technical expertize to perform the assays [12,34,35,42]. Also, these tests have been in use for but a few years and the evidence to support their predictive value in the risk of progression from latent to active disease is still limited.

TST or IGRA?

Although it appears from the accumulating data that IGRAs may play an important role in LTBI detection, the lack of a gold standard for the diagnosis of LTBI and the lack of controlled trials comparing the TST and IGRAs make the understanding of their relative merits difficult. Most comparative studies have been retrospective and have been limited by low statistical power, heterogeneity in BCG status, differing underlying inflammatory conditions, and use of immunosuppressive therapies, all of which can affect the performance of the tests [43]. Moreover, the agreement between the TST and IGRAS, when applied simultaneously, has been found to be low [40,41,44,45]. In a large study in Germany, 1529 patients were evaluated for LTBI using TST and one form of IGRA (either TSPOT.TB or Quantiferon TB Gold); the concordance rate between the TST and IGRAs in this study was found to be only 89.5% (κ= 0.40 p< 0.001) [44]. Further, nearly 27 of 71 patients who had TST indurations of ≥15 mm and no prior history of BCG vaccination tested IGRA negative highlighting the potential pitfalls of relying on any single test as a screening tool for LTBI. Hsia et al [45] pooled data from five large RCTs of the TNF inhibitor golimumab in an autoimmune inflammatory disease population. Patients (n=2282) were evaluated for LTBI using TST and QFT-IT simultaneously. Like the previous study, entirely different sets of patients were identified by both tests and the concordance rates between the two tests was low even in individuals who had not undergone BCG vaccination, suggesting that the IGRA cannot as yet be used as a single test to rule out LTBI.

National guidelines currently vary in their recommendations on the use of TST and IGRA to screen for LTBI and these variations may be driven by the prevalent tuberculosis rates, BCG usage, and availability and affordability of the IGRAs in different parts of the world (Tables 3 and 4). Whereas the TST appears to be still favored in countries with high TB prevalence (where a positive TST would have a higher positive predictive value) and limited resources, the higher specificity and logistic convenience of the IGRAs appear to make these tests easy to adopt in low incidence countries with high BCG penetration and high resource settings [46]. A recent paper that reviewed 33 guidelines and 2 position papers from 25 countries and 2 supranational organizations found that there was lack of conclusive data to inform these guidelines and most (70%) did not use transparent and objective systems for guideline development [46].

Thus critical gaps in our knowledge remain on the optimal screening strategy and the cost-effectiveness of the various suggested approaches. Given the vulnerability of this group of patients to develop serious and disseminated forms of the disease, some authors recommend that it may be prudent, until robust evidence based algorithms emerge, to use both the TST and IGRA as a dual-testing strategy to maximise diagnostic sensitivity and patient safety [34,43,48]. This approach, however, may result in overestimated positivity leading to unwarranted therapy with toxic drugs, especially in populations with low prevalence of tuberculosis. Therefore, the best strategy currently remains unclear.

There is also uncertainty and lack of consensus on the frequency of rescreening in patients established on anti-TNF therapies. Whereas annual screening for LTBI in all patients on TNF-α inhibitor therapy using TST or QTF-G is recommended in the U.S.A [11], yearly screening with any IGRA is only recommended in high risk patients by the BAD guidelines [28].

Table 3. Comparison of recommendations of national guidelines for the diagnosis and treatment of LTBI prior to TNF antagonist therapy.

COUNTRY	RECOMMENDED SCREENING MODALITY	RECOMMENDED PROPHYLACTIC REGIMEN	TIME DELAY BEFORE ANTI-TNF THERAPY
USA [12]	DETAILED IN TABLE 4	9H	Preferably after completion of chemotherapy

UK [59]	TST followed by IGRA if TST is positive	6H 3RH 4R	2 months
FRANCE [46,50]	IGRA alone	2RZ 3RH 9H	3 weeks
GERMANY [60]	IGRA alone	9H 4R	-
PORTUGAL [48]	Both TST and IGRA	9H	1 month
AUSTRALIA [61]	Either TST or IGRA	9H 4R	1-2 months
TBNET CONSENSUS [49]	Both TST and IGRA	9-12H 3RH	1 month

TST: Tuberculin standard test; **IGRA:** Interferon Gamma Release Assay; **H:** isoniazid; **RH:** rifampicin plus isoniazid; **R:** rifampicin; **RZ:** rifampicin plus pyrazinamide

Table 4. Centers of disease control and prevention guidelines on the selection of TST or IGRA for tuberculosis screening [12]

Situations where the TST or IGRA may be used without preference
- Contact Investigation
- Periodic screening and surveillance programmes (e.g. in healthcare workers)

Situations where the TST is preferred but IGRA is acceptable
- Child < 5 years

Situations where IGRA is preferred but TST is acceptable
- Groups with low rates of return to have TST read at 48 hours.
- BCG vaccinated individuals

Situations where both TST and IGRA may be considered
- When either test is negative, but the risk of tuberculosis infection is high and outcome poor.
- When either test is positive, but the risk of tuberculosis infection is low.
- When the initial IGRA is indeterminate

TST: Tuberculin standard test; **IGRA:** Interferon Gamma Release Assays

Chemoprophylaxis

Individuals diagnosed with LTBI should receive appropriate chemoprophylaxis in accordance with local recommendations or guidelines (Table 3). Given the profound morbidity and associated mortality of TB associated with TNF inhibitor therapy, a low threshold for prophylactic therapy is recommended [48,49]. There is general agreement that the potential hepatotoxicity associated with isoniazid should not prevent patients from receiving treatment for LTBI [21,48]. Instead, patient education, clinical monitoring, and baseline and monthly monitoring of liver enzymes should be undertaken to evaluate possible adverse effects that may occur during the course of therapy [21,48]. In patients in whom hepatotoxicity seriously limits use, other validated, albeit less effective, rifampicin based regimens should be considered.

The optimal time delay for initiating TNF inhibitors after LTBI therapy has not been established and guidelines vary widely in their recommendations with suggested time frames ranging from a 3-week delay in the French guidelines [50], to completion of a full 9-month course of preventive therapy in the NPF guidelines [30] (Table 3). However, there seems to be consensus among most guidelines that if the clinical condition warrants early treatment, anti-TNF therapy can be commenced after completion of 1-2 months of LTBI therapy provided adherence and tolerance to therapy are ensured (Table 3).

Although appropriate treatment will prevent the development of active disease in a majority of patients, no regimen is wholly effective in preventing reactivation [30]. Numerous case reports and series showed development of clinically active TB despite strict adherence to prophylactic recommendations, suggesting that the risk of TB persists in spite of adequate prophylaxis [51-53]. Evidence from systematic reviews and clinical trials of the various regimens commonly used in LTBI therapy showed that the efficacy in preventing TB reactivation was 90% with a 9 month isoniazid regimen, 69% with a 6 month isoniazid daily regimen, 65% with a 4 month rifampicin regimen, and 65% with a 2 month regimen of rifampicin and pyrazinamide [54]. A meta-analysis of 11 RCTs of 6-12 months of isoniazid preventive therapy involving 73,375 patients found that isoniazid was effective in preventing the development of TB in only about 60% patients who complete therapy, suggesting that chemoprophylaxis may not be fully protective [55].

Apart from efficacy, poor adherence to therapy remains another barrier to effective chemoprophylaxis. Current data suggest that completion rates are less than 50% over 9 months of therapy [54]. Patient education, the use of incentives and directly observed therapy (DOT) may improve adherence and lead to higher rates of completion [21,54].

Constant vigilance for typical and atypical manifestations of active TB is necessary during and for 6 months after completion of anti-TNF therapy [11, 28]. If patients do develop active TB, TNF therapy should be withdrawn and the patients referred to an appropriate physician for adequate management. Cases of paradoxical aggravation of TB have been reported in patients withdrawn from anti-TNF treatment. This response has been attributed to the immune reconstitution following withdrawal of iatrogenic immunosuppression, defined as the Immune Reconstitution Inflammatory Syndrome (IRIS), and may require treatment with corticosteroids and NSAIDs [56,57].

Conclusions

The introduction of biologics and the efficacy demonstrated by the TNFα inhibitors in particular have revolutionized the treatment of moderate to severe psoriasis. Because of the important role TNF plays in containing TB infection, the use of TNF inhibitors increases the incidence of active TB in various populations. The monoclonal antibodies infliximab and adalimumab appear to be more heavily associated with the risk of reactivation than the soluble receptor etanercept. TB associated with TNF inhibitor therapy, unlike classical disease, is often disseminated, atypical, extra pulmonary, and life threatening. Although appropriate screening and treatment of LTBI will lower the risk of reactivation to a large extent, no chemoprophylactic regimen is completely protective. It has been suggested that adherence to solely TST based guidelines may overestimate the risk of LTBI in patients with moderate to severe psoriasis. Whereas the performance characteristics of IGRAs are seemingly superior to the TST, they are not without limitations. Generally, a clear consensus on the optimal screening strategy is still needed.

References

1. Krueger G, Callis K. Potential of Tumor Necrosis Factor Inhibitors in Psoriasis and Psoriatic Arthritis. Arch Dermatol. 2004 Feb; 140(2):218-225. PMID: 14967799
2. Ettehadi P, Greaves MW, Wallach D, Aderka D, Camp RDR. Elevated tumour necrosis factor-alpha (TNF-α) biological activity in psoriatic skin lesions. Clinical and experimental immunology. 1994 Apr; 96(1): 146-51. PMID: 8149659
3. Victor FC, Gottlieb AB, Menter A. Changing Paradigms in Dermatology: Tumor Necrosis Factor Alpha (TNF- α) Blockade in Psoriasis and Psoriatic arthritis. Clinics in Dermatol. 2003 Sep/Oct; 21(5): 392-97. PMID: 14678719
4. Gardam MA, Keystone EC, Menzies R, Manners S, Skamene E, Long R et al. Anti-tumour necrosis factor agents and tuberculosis risk: mechanisms of action and clinical management. Lancet Infect Dis. 2003 Mar; 3: 148-55. PMID: 12614731
5. Keane J, Gershon S, Wise RD, Mirabile-Levens E, Kasznica J, Siegel JN et al. Tuberculosis associated with infliximab, a tumor necrosis factor (alpha)- neutralizing agent. N Engl J Med. 2001 Oct; 345(15): 1098-1104. PMID: 11596589
6. Wolfe F, Michaud K, Anderson J, Urbansky K. Tuberculosis infection in patients with rheumatoid arthritis and effect of infliximab therapy. Arthritis Rheum. 2004 Feb; 50(2): 372-79. PMID: 14872478
7. Gomez-Reino JJ, Carmona L, Valverde VR, Martin Mola E, Montero MD. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk. Arthritis Rheum. 2003 Aug; 48(8): 2122-27. PMID: 12905464
8. Tubach F, Salmon D, Ravaud P, Allanore Y, Goupille P, Breban M et al. Risk of tuberculosis is higher with anti-tumor necrosis factor monoclonal antibody therapy than with soluble tumor necrosis factor receptor therapy: the three year prospective French Research Axed on Tolerance of Biotherapies Registry. Arthritis Rheum. 2009 Jul; 60(7): 1884-94. PMID: 19565495
9. Dixon WG, Hyrich KL, Watson KD, Lunt M, Galloway J, Ustianowski A. Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register (BSRBR). Ann Rheum Dis. 2010 Mar; 69(3): 522-28. PMID: 19854715
10. World Health Organisation. Global tuberculosis report 2012. Geneva: WHO; 2012

11. Hernandez C, Cetner AS, Jordon E, Puangsuvan SN, Robinson JK. Tuberculosis in the age of biologic therapy. J Am Acad Dermatol. 2008 Sep; 59(3): 363-80. PMID: 18694676

12. Centers for Disease Control and Prevention. Updated guidelines for using Interferon Gamma Release Assays to detect Mycobacterium tuberculosis infection-United States, 2010. Morbidity and Mortality Weekly Report. 2010 June; 59: No RR-5

13. Wallis RS, Broder MS, Wong JY, Hanson ME, Beenhouwer DO. Granulomatous infectious diseases associated with tumor necrosis factor antagonists. Clin Infect Dis 2004 May; 38(9):1261-5. PMID: 15127338

14. Wallis RS, Broder MS, Wong Y, Beenhouwer DO. Granulomatous infectious diseases due to tumor necrosis factor blockade: correction. Clic Infect Dis. 2004 Oct; 39 (8): 1254-5. PMID: 15486857

15. Askling J, Fored CM, Brandt L, Baecklund E, Bertilsson L, Coster L et al. Risk and case characteristics of tuberculosis in rheumatoid arthritis associated with tumor necrosis factor antagonists in Sweden. Arthritis Rheum. 2005 Jul; 52(7): 1986-92. PMID: 15986370

16. Gardam M, Iverson K. Rheumatoid arthritis and tuberculosis: time to take notice. J Rheumatol. 2003 Jul; 30(7): 1397-9. PMID: 12858431

17. Keane J. TNF blocking agents and tuberculosis: new drugs illuminate an old topic. Rheumatology (Oxford). 2005 Jun; 44(6): 714-20. PMID 15741198

18. Smith JD, Knox JM. Psoriasis, methotrexate and tuberculosis. Br J Dermatol. 1971 Jun; 84(6): 590-3. PMID: 5557512

19. Binymin K, Cooper RG. Late reactivation of spinal tuberculosis by low-dose methotrexate therapy in a patient with rheumatoid arthritis. Rheumatology (Oxford). 2001 Mar; 40(3): 341-2. PMID: 11285384

20. Winthrop KL. Serious infections with antirheumatic therapy: are biologics worse?   Ann Rheum Dis. 2006 Nov; 65(Suppl 3): iii 54-7. PMID: 17038474

21. Centers for Disease Control and Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. Morbidity and Mortality Weekly Report. 2000 Jun; 49: No RR-6.

22. Kim HA, Yoo CD, Baek HJ, Lee EB, Ahn C, Han JS et al. Mycobacterium tuberculosis infection in a corticosteroid-treated rheumatic disease patient population. Clin Exp Rheumatol. 1998 Jan-Feb; 16(1): 9-13. PMID: 9543555

23. Jick SS, Lieberman ES, Rahman MU, Choi HK. Glucocorticoid use, other associated factors and the risk of tuberculosis. Arthritis Rheum. 2006 Feb; 55(1): 19-26. PMID: 16463407

24. Shaikha SA, Mansour K, Riad H. Reactivation of tuberculosis in three cases of psoriasis after inititation of Anti-TNF therapy. Case Rep Dermatol. 2012 Jan; 4(1): 41-6. PMID: 22529801

25. Perlmutter A, Mittal A, Menter A. Tuberculosis and tumour necrosis factor-α inhibitor therapy: a report of three cases in patients with psoriasis. Comprehensive screening and therapeutic guidelines for clinicians. Br J Dermatol. 2009 Jan; 160(1): 8-15. PMID: 19016693

26. Solovan C, Chiticariu E. Psoriasis, anti-tumor necrosis factor therapy, and tuberculosis: Report of three challenging cases and literature review. Infect Dis Ther. 2013 Jun; 2(1): 59-73.

27. Kaminska E, Patel I, Dabade TS, Chang J, Qureshi AA, O'Neill JL et al. Comparing the lifetime risks of TNF-alpha inhibitor use to common benchmarks of risk. J Dermatol Treat. 2013 Apr; 24(2): 101-6. PMID: 21756157

28. Smith CH, Anstey AV, Barker JNWN, Burden AD, Chalmers RJG, Chandler DA et al. British Association of Dermatologists' guidelines for biologic interventions for psoriasis. Br J Dermatol. 2009 Nov; 161 (5): 987-1019. PMID: 19857207

29. Centers for Disease Control and Prevention. Tuberculosis associated with blocking agents against tumor necrosis factor-alpha—California, 2002-2003. Morbidity and Mortality weekly report. 2004 Aug; Vol 53 (No 30): 683-6.

30. Doherty SD, Voorhees AV, Lebwoh MG, Korman NJ, Young MS, Hsu S. National Psoriasis Foundation consensus statement on screening for latent tuberculosis infection in patients with psoriasis treated with systemic and biologic agents. J Am Acad Dermatol. 2008 Aug; 59(2): 209-17. PMID: 18485527

31. Gomez Reino J, Carmona L, Descalzo MA. Risk of tuberculosis in patients treated with tumor necrosis factor antagonists due to incomplete prevention of reactivation of latent infection. Arthritis Rheum. 2007 Jun; 57(5): 756-61. PMID: 17530674

32. Perez JL, Kupper H, Spencer-Green GT. Impact of screening for latent TB prior to initiating anti-TNF therapy in North America and Europe. Annual European Congress of Rheumatology. EULAR. 2005 [abstract OP0093]

33. Carmona L, Gomez-Reino JJ, Valverde VR, Montero D, Pascaul-Gomez E, Mola ME et al. Effectiveness of recommendations to prevent reactivation of latent tuberculosis infection in patients treated with tumor necrosis factor antagonists. Arthritis Rheum. 2005 Jun; 52(6): 1766-72. PMID: 15934089

34. Lalvani A, Millington KA. Screening for tuberculosis infection prior to initiation of anti-TNF therapy. Autoimmunity Rev. 2008 Dec; 8(2): 147-52. PMID: 18706526

35. Kardos M, Kimball AB. Time for a change? Updated guidelines using interferon gamma release assays for detection of latent tuberculosis infection in the office setting. J Am Acad Dermatol. 2012 Jan; 66(1): 148-52. PMID: 22177633

36. Tsiouri G, Gaitanis G, Kiorpelidou D, Dionysiou A, Efthymiou A, Daskalopoulos G et al. Tuberculin skin test overestimates tuberculosis hypersensitivity in adult patients with psoriasis. Dermatology. 2009 Aug; 219(2): 119-25. PMID: 19478478

37. Bassukas ID, Kosmidou M, Gaitanis G, Tsiouri G, Tsianos E. Patients with psoriasis more likely to be treated for latent tuberculosis infection prior to biologics than patients with inflammatory bowel disease. Acta Derm Venereol. 2011 Jun; 91(4): 444-46. PMID: 21547342

38. Chiu HY, Hsueh PR, Tsai TF. Clinical experience of QuantiFERON®-TB Gold testing in patients with psoriasis treated with tumour necrosis factor blockers in Taiwan. Br J Dermatol. 2011 Mar; 164(3): 553-59. PMID: 21083541

39. Diel R, Goletti D, Ferrara G, Bothamley G, Cirillo D, Kampmann B et al. Interferon-γ release assays for the diagnosis of latent Mycobacterium tuberculosis infection: a systematic review and meta-analysis. Eur Resp J. 2011 Jan; 37(1): 88-99. PMID: 21030451

40. Laffitte E, Janssens JP, Roux-Lombard P, Thielen AM, Barde C, Marazza G et al. Tuberculosis screening in patients with psoriasis before antitumour necrosis factor therapy: comparison of an interferon-γ release assay vs. tuberculin skin test. Br J Dermatol. 2009 Oct; 161(4): 797-800. PMID: 19659473

41. Tavast E, Tuominen T, Pakkanen SH, Eriksson M, Kantele A, Jarvinen A et al. Immunosuppression adversely affects TST but not IGRAs in patients with psoriasis or inflammatory musculoskeletal diseases. Int J Rheumatol. 2012; 2012: 381929. PMID: 22666260

42. Centers for Disease Control and Prevention. Interferon- Gamma Release Assays (IGRAs) - Blood tests for TB infection. Fact Sheet. Available at http://www.cdc.gov/tb/publications/factsheets/testing/igra.htm (Accessed: 21 Feb 2014)

43. Winthrop KL, Weinblatt ME, Daley CL. You can't always get what you want, but if you try sometimes (with two tests – TST and IGRA – for tuberculosis) you get what you need. Ann Rheum Dis. 2012 Nov; 71(11): 1757-60. PMID: 22975752

44. Kleinert S, Tony HP, Krueger K, Detert J, Mielke F, Rockwitz K et al. Screening for latent tuberculosis infection: performance of tuberculin skin test and interferon-γ release assays under real life conditions. Ann Rheum Dis. 2012 Nov; 71(11): 1791-5. PMID: 22586160

45. Hsia EC, Schluger N, Cush JJ, Chaisson RE, Matesson EL, Xu S et al. Interferon-γ release assay versus tuberculin skin test prior to treatment with golimumab, a human anti-tumor necrosis factor antibody, in patients with rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis. Arthritis Rheum. 2012 Jul; 64(7): 2068-77. PMID: 22238071

46. Denkinger CM, Dheda K, Pai M. Guidelines on interferon-γ release assays for tuberculosis infection: concordance, discordance or confusion? Clin Microbiol Infect. 2011 Jun; 17(6): 806-14. PMID 21682801

47. Smith R, Cattamanchi A, Steingart KR, Denkinger C, Dheda K, Winthrop KL et al. Interferon-gamma release assays for diagnosis of latent tuberculosis infection: evidence in immune based inflammatory disorders. Curr Opin Rheumatol. 2011 Jul; 23(4): 377-84. PMID: 21519268

48. Duarte R, Campainha S, Cotter J, Rosa B, Varela P, Correia A et al. Position paper on tuberculosis screening in patients with immune mediated inflammatory diseases candidates for biological therapy. Acta Rheumatol Port. 2012 Jul- Sep; 37(3): 253-9. PMID: 23348114

49. Solovic I, Sester M, Gomez-Reino JJ, Rieder HL, Ehlers S, Milburn HJ et al. The risk of tuberculosis related to tumour necrosis factor antagonist therapies: a TBNET consensus statement. Eur Respir J. 2010 Nov; 36(5): 1185-1206. PMID 20530046

50. Mariette X, Salmon D. French guidelines for diagnosis and treating latent and active tuberculosis in patients with RA treated with TNF blockers. Ann Rheum Dis. 2003 Aug; 62(8): 791. PMID: 12860745

51. Calikoglu M, Sahin G, Aslan G. Two cases of tuberculosis complicating treatment with tumor necrosis factor-α inhibitors. Turkish Thoracic Journal. 2008 Sep; 9(3): 133-6

52. Sichletidis L, Settas L, Spyratos D, Chloros D, Patakas D. Tuberculosis in patients receiving anti-TNF agents despite chemoprophylaxis. Int J Tuberc Lung Dis. 2006; 10(10):1127-32. PMID: 17044206

53. Raychaudhuri S, Shmerlina R, Ermann J, Helfgott S. Development of active tuberculosis following initiation of infliximab despite appropriate prophylaxis. Rheumatology (Oxford). 2007 May; 46(5): 887-8. PMID: 17363399

54. Menzies D, Jahdali H, Otaibi B. Recent developments in treatment of latent tuberculosis infection. Indian J Med Res. 2011 Mar; 133( ): 257-66. PMID 21441678

55. Smieja M, Marchetti C, Cook D, Smaill FM. Isoniazid for preventing tuberculosis in non-HIV infected persons. Cochrane Database of systematic reviews. 1999; 1: CD 001363

56. Garcia Vidal C, Fernandez SR, Lacasa JM, Salavert M, Vidal R, Carballeira MR et al. Paradoxical response to antituberculous therapy in infliximab treated patients with disseminated tuberculosis. Clin Infect Dis. 2005 Mar; 40: 756-9. PMID: 15714425

57. Abounasr KK, Rogers L. A case of immune reconstitution syndrome secondary to discontinuation of anti-TNF agents in a patient with pulmonary tuberculosis. Chest. 2009 Oct; 136: 51S.

58. Mohan HK, Cote TR, Block JA, Manadan AM, Siegel JN, Braun MM. Tuberculosis following the use of etanercept, a tumor necrosis factor inhibitor. Clin Infect Dis.2004 Aug; 39(3): 295-9. PMID: 15306993

59. National Institute for Health and Clinical Excellence. Tuberculosis. Clinical diagnosis and management of tuberculosis and measures for its prevention and control. NICE clinical guidelines 117. Available at www.nice.org.uk/guidance/CG117 (Accessed: 21 Feb 2014)

60. Diel R, Hauer B, Loddenkemper R, Manger B, Kruger K. Recommendations for tuberculosis screening before initiation of TNF-α inhibitor treatment in rheumatic diseases. Pneumologie. 2009 Jun; 63(6): 329-334. PMID: 19517358

61. Screening for latent tuberculosis infection (LTBI) prior to use of biologic agents in Australia. Available at www.rheumatology.org.au/downloads/SCREENINGFORLATENTTUBERCULOSISINFECTION.pdf (Accessed 21 Feb 2013)