ABSTRACT Treatment with biologic agents, in particular tumor necrosis factor alpha (TNF-α) inhibitors, is associated with an increased risk of tuberculosis (TB), and screening and treatment for latent TB infection (LTBI) in patients undergoing such treatment is therefore indicated. The risk of TB associated with different biologics varies significantly, with the highest relative risks, 29.3 and 18.6, associated with adalimumab and infliximab, respectively. The risk of TB with newer TNF-α inhibitors and other biologics appears to be lower. Performance of LTBI screening tests is affected by immune-mediated inflammatory diseases and immunosuppressive therapy in patients due to commence TNF-α inhibitor treatment. Interferon gamma release assays (IGRAs) have a higher specificity than the tuberculin skin test (TST) in patients with Bacillus Calmette–Guérin (BCG) vaccination and have probably a better sensitivity than TST in immunosuppressed patients. LTBI screening programs prior to commencement of anti-TNF-α treatment significantly reduce the incidence of TB, but the optimal screening algorithm, in particular the question of whether a combination of IGRA and TST or a single test only should be used, is a matter of ongoing debate. Use of TST in combination with IGRA is justified to increase sensitivity. Repeat testing for LTBI should be limited to patients at increased risk of TB. If TB develops during anti-TNF-α treatment, it is more likely to be disseminated and extrapulmonary than are other TB cases. Discontinuation of anti-TNF-α treatment in patients diagnosed with TB is associated with an increased risk of immune reconstitution inflammatory syndrome, which is probably best managed by reintroduction of anti-TNF-α treatment.

INTRODUCTION
In recent years, the market of biopharmaceuticals has been growing at a fast pace due to increased availability of targets for biologic agents, approval of biologic agents for new and expanded indications, and increased use of these medications. Biopharmaceuticals, also known as biologic products or agents, biologics, or biologicals, are drugs that are produced through biological processes rather than chemical synthesis. These include recombinant proteins, monoclonal and polyclonal antibodies, peptides, antisense oligonucleotides, therapeutic genes, and recombinant and DNA vaccines. Biopharmaceuticals usually require infusion or injection rather than oral application.

The medical community has been well aware of the increased risk of tuberculosis (TB) reactivation associated with treatment with tumor necrosis factor alpha (TNF-α) inhibitors since the beginning of this century (1). In this chapter, the risk of TB associated with different biologic agents (especially TNF-α inhibitors), pretreatment strategies, observation during treatment with TNF-α inhibitors, and the management of active TB in patients on biologic agents are reviewed.

TB RISK ASSOCIATED WITH BIOLOGIC AGENTS
A study published in 2001 reviewed reports of TB in patients on the TNF-α inhibitor infliximab since its licensure in 1998 from the U.S. Food and Drug Administration’s (FDA) Adverse Event Reporting System (1) and brought awareness to the association between treatment with biologic agents and the risk of TB. The study found 70 reported cases of TB after treatment with infliximab for a median of 12 weeks, of which...
48 patients developed TB after three or fewer infusions. Before this clinical observation, data from animal studies had already demonstrated a central role of TNF in TB immunity (2).

Subsequent studies aimed to establish the relative risk (RR) of TB in patients using TNF-α inhibitors (and other biologics) compared to that in the general population. Registries for patients on biologics have provided a valuable resource for studies that aimed to determine the risk of TB associated with these therapies. Table 1 gives an overview of the estimated RR of TB associated with the use of different biologics (3–10).

**Drug-Specific RRs of TB**

Anti-TNF-α monoclonal antibodies (e.g., adalimumab and infliximab) are associated with a higher risk of TB than is soluble TNF-α receptor therapy (etanercept) (3, 11–13). Data from the FDA’s Adverse Event Reporting System from 1998 to 2002 showed estimated TB rates of 54 and 28 per 100,000 patients who started therapy with infliximab and etanercept, respectively, during the study period (12, 14). The overall TB incidence of TB in the United States at the time of the study was 5.8 per 100,000 person-years (14). Data from the Spanish Society of Rheumatology Database on Biologic Products (BIOBADASER) showed crude incidence rate ratios for TB of 90.1 (95% confidence interval [CI], 58.8 to 146.0) in the year 2000 and 53.0 (95% CI, 34.5 to 89.0) in the year 2001 among patients with rheumatic diseases treated with infliximab compared to that in the general Spanish population (15). A French study using the RATIO registry (16) found age- and sex-standardized incidence ratios (SIR) for infliximab, adalimumab, and etanercept of 18.6 (95% CI, 13.4 to 25.8), 29.3 (95% CI, 20.3 to 42.4), and 1.8 (95% CI, 0.7 to 4.3), respectively, compared to that in the general population (3). A study using data from the British Society for Rheumatology Biologics Register (BSRBR) confirmed an increased risk of TB associated with anti-TNF-α monoclonal antibodies, showing three- and four-fold risks of TB with infliximab and adalimumab, respectively, compared to that with etanercept (SIR, 3.1, and 95% CI, 1.0 to 9.5, for infliximab and SIR, 4.2, and 95% CI, 1.4 to 12.4, for adalimumab) (11).

Pooled data from randomized controlled trials have not shown an increased TB risk with the newer anti-TNF-α monoclonal antibodies golimumab and certolizumab pegol compared to that with placebo (4, 5). A systematic review and meta-analysis of adverse events associated with certolizumab pegol treatment in patients with immune-mediated inflammatory diseases (IMIDs) found a trend towards an increased TB risk, but this was not statistically significant (RR, 2.83, 95% CI, 0.50 to 16.01, and P=0.24, in the certolizumab pegol 200-mg groups; RR, 3.02, 95% CI, 0.65 to 14.12, and P=0.16, in the certolizumab pegol 400-mg groups) (17). There is a paucity of data on the risk of TB with other biologic agents, such as rituximab, abatacept, tocilizumab, vedolizumab, and ustekinumab. The risk of serious infections appears to be significantly lower with these agents than with TNF-α inhibitors, and to date, they have not been associated with an increased risk of TB.

**Table 1** Drug-specific RR of TB

<table>
<thead>
<tr>
<th>Biologic</th>
<th>FDA-approved indications (as of 1 November 2016)</th>
<th>RR of TB compared to that in the general population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>AS, JIA, RA, Ps, PsA, Crohn’s, UC</td>
<td>29.3 (95% CI, 20.3–42.4) (5)</td>
</tr>
<tr>
<td>Infliximab</td>
<td>AS, RA, Ps, PsA, Crohn’s, UC</td>
<td>18.6 (95% CI, 13.4–25.8) (3)</td>
</tr>
<tr>
<td>Etanercept</td>
<td>AS, JIA, RA, Ps, PsA</td>
<td>1.8 (95% CI, 0.7–4.3) (3)</td>
</tr>
<tr>
<td>Certolizumab pegol</td>
<td>AS, RA, PsA, Crohn’s</td>
<td>No definite increase in RR in pooled data from RCTs (4)</td>
</tr>
<tr>
<td>Golimumab</td>
<td>AS, RA, PsA, UC</td>
<td>No definite increase in RR in pooled data from RCTs (5)</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Chronic lymphocytic leukemia, non-Hodgkin lymphomas, granulomatosis with polyangiitis, microscopic polyangiitis, RA</td>
<td>No definite increase in RR in pooled data from RCTs (6)</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>JIA, RA</td>
<td>No definite increase in RR in pooled data from RCTs (7)</td>
</tr>
<tr>
<td>Vedolizumab</td>
<td>UC, Crohn’s</td>
<td>No definite increase in RR from drug safety data (8)</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>Ps, PsA, Crohn’s</td>
<td>No definite increase in RR from drug safety data (9)</td>
</tr>
<tr>
<td>Abatacept</td>
<td>JIA, RA</td>
<td>No definite increase in RR in pooled data from RCTs (6)</td>
</tr>
</tbody>
</table>

*AS, ankylosing spondylitis; Crohn’s, Crohn’s disease; JIA, juvenile idiopathic arthritis; Ps, plaque psoriasis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RCTs, randomized controlled trials; UC, ulcerative colitis.*
reactivation \((8, 10, 18–20)\). Longer follow-up and more research (e.g., from existing registries for biologics) is, however, required before any definite conclusions regarding TB risk in these agents can be drawn \((21, 22)\).

**TB Risk Associated with Underlying Medical Conditions**

When trying to determine the RR of TB associated with the use of biologic agents, one needs to be aware that patients with IMIDs, for which biologics are prescribed, already have an increased risk of TB associated with their immunosuppressed disease state and often also have comorbidities and additional medications that themselves have an increased risk of TB compared to that of the general population \((23)\). It is therefore not possible to isolate the contribution of anti-TNF-\(\alpha\) agents to risk of TB among these patients compared to that of the general population by adjusting for age and sex alone. The isolated RR of TB associated with biologic agents can be determined only if the risk of TB in IMID patients with and without biologic treatment is known \((24)\). A Swedish study found that patients with rheumatoid arthritis (RA) who were not treated with TNF-\(\alpha\) inhibitors had an increased risk of TB compared to the general population (RR, 2.0; 95% CI, 1.2 to 3.4), and patients with RA on TNF-\(\alpha\) inhibitors had a four-fold-increased risk of TB (RR, 4.0; 95% CI, 1.3 to 12) over that of patients with RA not treated with TNF-\(\alpha\) inhibitors \((25)\). A Korean study showed a sex- and age-adjusted risk ratio of 8.9 (95% CI, 4.6 to 17.2) in RA patients not treated with TNF-\(\alpha\) inhibitors and a sex- and age-adjusted risk ratio of 30.1 (95% CI, 7.4 to 122.3) in those treated with infliximab, compared to that in the general Korean population \((26)\).

A systematic review of 40 randomized controlled trials found that the risk of developing TB was significantly higher when TNF-\(\alpha\) inhibitors were combined with methotrexate or azathioprine than with TNF-\(\alpha\) inhibitor monotherapy \((24/4,241 \text{ versus } 2/5,769; \text{ odds ratio [OR], } 13.3; 95\% \text{ CI, } 3.7 \text{ to } 100)\).

**Implications for Clinical Practice**

The fact that there are variable risks of TB reactivation associated with different biologic agents has important implications for clinical practice. In patients who have ongoing risk of TB exposure (e.g., traveling to areas where TB is endemic) or in patients who could not complete a course of treatment for latent TB infection (LTBI) (e.g., due to adverse reaction), clinicians should take the TB risk into consideration when choosing the optimal biologic treatment for their patients, preferably selecting a biologic other than adalimumab or infliximab, which are associated with the highest TB risk.

In settings with a high incidence of TB, early diagnosis and treatment with traditional disease-modifying anti-rheumatic drugs (DMARDs) should be the priority in patients with RA. It has been suggested that non-TNF-\(\alpha\) inhibitors should be considered as first-line biologics in DMARD-resistant RA in settings with a high incidence of TB \((27)\). This approach has been recommended, for example, in South Africa \((28)\). A similar approach seems reasonable in inflammatory bowel disease in settings with a high incidence of TB.

In summary, the risk of TB reactivation depends on the specific biologic agent used, with the highest risk associated with the anti-TNF-\(\alpha\) monoclonal antibodies adalimumab and infliximab. The newer TNF-\(\alpha\) inhibitors certolizumab pegol and golimumab, as well as non-TNF-\(\alpha\) inhibitor biologics, have not been associated with an increased risk of TB to date, but further observation is required before making any definite conclusions. Combining TNF-\(\alpha\) inhibitor treatment with methotrexate or azathioprine increases the risk of TB reactivation. In patients with ongoing risk of exposure to TB and in those who could not complete a course of LTBI treatment, clinicians should consider the risk of TB reactivation associated with different agents when determining the optimal treatment for their patients.

**PERFORMANCE OF SCREENING TESTS IN PATIENTS WITH IMIDS**

**Results of Screening Tests in Patients with IMIDs Compared to Healthy Controls**

Immunosuppressed states due to IMIDs as well as treatments for these conditions (e.g., steroids, thiopurines, methotrexate, calcineurin inhibitors, and biologics) potentially impact the performance of diagnostic tests for TB infection. When comparing the performances of the tuberculin skin test (TST) and interferon gamma (IFN-\(\gamma\)) release assays (IGRAs) for patients with IMIDS and healthy controls, results are heterogeneous. One study showed significantly lower rates of positive TSTs as well as IGRAs (QuantiFERON-TB Gold In-Tube [QFT-GIT]; Cellestis Limited, Carnegie, Victoria, Australia) for patients with IMIDs \((29)\), while other studies showed either no significant differences for both TST and QFT-GIT between the two groups \((30, 31)\) or lower rates of positive TSTs but not IGRAs for patients with IMIDs \((32)\). Agreement between TST and QFT-GIT was better for controls than for patients with IMIDs in one study \((32)\), while it was not significantly different in another \((30)\).
Sensitivity and Specificity of TST and IGRAs for Patients with IMIDs

The specificity of IGRAs, which are unaffected by Bacillus Calmette–Guérin (BCG) vaccination, is superior to that of TST in general (16). Increased specificity of IGRAs compared to that of TST has been demonstrated in patients with IMIDs as well. In a study with patients with rheumatic diseases starting anti-TNF-α therapy, of whom 76% (n = 81) had been vaccinated with BCG during adolescence or early adulthood, positive IGRAs (T-SPOT.TB test [Oxford Immunotec Limited, Abingdon, United Kingdom] and QFT-GIT) were less frequent than positive TSTs in the same cohort and showed a stronger correlation with established risk factors for TB than did the TST (33). While data for sensitivity are less clear, a meta-analysis showed that sensitivity of IGRAs is at least equal to or possibly superior (in particular for T-SPOT.TB) to that of TSTs for testing for LTBI in general (34). Most studies with patients with IMIDs without prior BCG vaccine showed more positive IGRA than TST results, possibly indicating superior sensitivity of IGRAs (35–37). Importantly, however, it appears that TST in addition to IGRA can increase sensitivity of LTBI testing and thus the diagnostic yield (38, 39).

Immunosuppressive therapy (IST) in patients with IMIDs has been associated with negative TST and QFT-GIT results and/or indeterminate QFT-GIT results in some studies (33, 40–43), but this appears to be less of an issue with T-SPOT.TB (33, 44–47). A systematic review in patients with inflammatory bowel disease found that immunosuppressive treatments negatively impacted positive QFT-GIT and TST results (P = 0.02 for both) (48). Prednisone therapy in particular has been associated with negative TST results (40, 45, 49, 50), negative QFT-GIT results (33, 40), and increased risk of indeterminate QFT-GIT results (49). Anti-TNF-α treatment has been associated with negative TST results (40) but had no impact on QFT-GIT results (40).

Discordant Screening Test Results

Discordant results between IGRAs and TST for patients with IMIDs are common (51). Concordance has ranged from 64% (33) to 89.5% (38), and Cohen’s kappa value (κ) has ranged from 0.15 (33) to 0.55 (40), indicating poor to fair or moderate concordance only. A meta-analysis with patients with inflammatory bowel disease showed pooled concordances of 85% (95% CI, 77% to 90%) between the TST and QFT-GIT and 72% (95% CI, 64% to 78%) between TST and T-SPOT.TB (48). A large multicenter study with patients with rheumatic diseases found a concordance of 89.5% between IGRAs and TST, but the κ was only 0.40 (fair). Concordances were 87.6% (κ = 0.34) between TST and QFT and 91.1% (κ = 0.44) between TST and T-SPOT (38). Discordant results in which patients have a positive IGRA and a negative TST are still not fully understood due to the fact that there is no gold standard to determine if a patient truly has LTBI. Once data on the estimated risk for progression to active disease in persons with discordant negative TST become available, we will hopefully gain a clearer understanding about the optimal clinical management of this group (31).

Correlation between Risk Factors for LBI and Positive Screening Tests

Similar to the case with TST, there is strong evidence for the correlation between risk factors for LTBI and a positive IGRA (QFT-GIT and T-SPOT.TB). Demographic and clinical risk factors for LTBI that have been linked to positive IGRAs include history of close contact with a patient with infectious TB (11, 38, 40, 48, 52, 53), older age (30, 33, 40), birth or residence in a country where TB is endemic (30, 33, 44, 52), chest X-ray findings suggestive of past TB (30, 44, 52), history of active TB (30, 52), prior prison stay (30), intravenous drug use (30), and being a health care worker (30). History of active TB, followed by chest X-ray findings suggestive of past TB, was associated with the highest odds for a positive IGRA result. Patients with IMIDs who had at least one risk factor for LTBI were 2.5 to 23.8 times more likely to have a positive QFT-GIT, 4.8 to 8.7 times more likely to have a positive T-SPOT.TB, and 1.6 to 6.2 times more likely to have a positive TST (51).

In summary, IGRAs (QFT-GIT and T-SPOT.TB) are more specific than TST for patients with BCG vaccination. IGRAs appear to be slightly more sensitive than TST for patients with IMIDs, but IST can be associated with false-negative and indeterminate QFT-GIT results. T-SPOT.TB appears to be less affected by IST and should be considered for patients on IST, in particular patients on prednisone.

SCREENING ALGORITHMS AND CURRENT GUIDELINES

Given that patients on TNF-α inhibitors have an increased risk of TB reactivation and an increased risk of poor outcomes if TB develops, screening for LTBI in this patient group is crucial. If there is evidence of LTBI, treatment for LTBI should be initiated before biologic...
therapy is started. Besides screening recommendations from the U.S. Centers for Disease Control and Prevention (CDC) (54), guidelines on LTBI screening in patients who are about to commence anti-TNF-α treatment have been issued by different national professional societies. While the newer TNF-α inhibitors golimumab and certolizumab pegol and non-TNF-α inhibitor biologics do not seem to be associated with the same risk of TB reactivation as earlier TNF-α inhibitors (5, 8, 18, 22), caution is warranted until longer-term data are available. Until then, it is appropriate to apply the same screening strategies as for traditional TNF-α inhibitors.

Screening should include a medical history, physical examination, TST and/or IGRA, and a chest X-ray for patients with a positive TST or IGRA as well as for patients with a clinical history or physical examination consistent with active TB or past TB (54, 55). Sputum samples should be sent for acid-fast bacillus smear and Mycobacterium tuberculosis culture, if there is any suggestion of possible TB on chest X-ray. Regarding the use of screening tests for LTBI, recommendations from different professional organizations and different countries are not consistent with each other, ranging from recommending TST or IGRA only to using a combination of TST and IGRA (23, 54–61) (Table 2). TST may be performed as a single-step or two-step test, and recommended cutoff levels to determine a positive TST vary between guidelines.

There are different views on whether TST should be single step or two-step when screening patients with IMIDs due to start anti-TNF-α therapy. Authors of a Spanish study argued that using a screening algorithm incorporating a single-step rather than a two-step TST, combined with QFT-GIT, would reduce the need for LTBI screening while not increasing the risk of development of TB (62). In this study, 726 patients were screened prior to anti-TNF-α therapy using 1 of 3 diagnostic strategies over three consecutive periods: (i) a two-step TST, (ii) a two-step TST plus QFT-GIT (two-step TST/QFT-GIT), and (iii) a single-step TST plus QFT-GIT (TST/QFT-GIT). Patients with evidence of LTBI were offered preventive therapy. The incidences of TB did not differ significantly between the three screening strategy groups. The study was, however, likely underpowered, as there were only four patients who developed TB, three of whom had tested negative for LTBI (one with a two-step TST/QFT-GIT screening approach and two with the single-step TST/QFT-GIT approach). While different cutoff levels for positive TST results have been promoted, the most commonly recommended TST cutoff (also recommended by the CDC) in candidates for a TNF-α inhibitor is 5 mm (54).

The 2010 CDC guidelines do not recommend routine testing with both a TST and an IGRA, but state that a combination of the two tests might be useful when the initial test (either TST or IGRA) is negative and the risk for either infection, progression to active TB, or a poor outcome is increased (55). Patients who are to commence on anti-TNF-α therapy have an increased risk of progression from LTBI to active disease and an increased risk of poor outcome. Increasing sensitivity of LTBI screening is therefore important, and a screening strategy that combines IGRA and TST (and interpretation as evidence of LTBI if either test is positive) has been recommended in different countries and by different specialty medical societies. The “either test positive” strategy using TST and T-SPOT.TB was evaluated in a prospective cohort study in Korea, which found a cumulative incidence of TB of 0.9% (n = 4) among patients on TNF-α inhibitor treatment, of whom 46% (198/430) had commenced LTBI treatment following screening (63). However, no comparison with other screening strategies was made, and therefore, the study results did not allow any conclusions about whether the combined TST-IGRA method is superior to a single test method. The optimal screening strategy for LTBI in patients due to commence TNF-α inhibitor treatment therefore remains a matter of debate.

The British Thoracic Society guidelines recommend the use of TB risk stratification tables (based on age, ethnicity, and year of entry into the United Kingdom) to guide the LTBI treatment decision without additional TST or IGRA for patients on IST due to start anti-TNF-α treatment (64). However, a British study showed that 35.5% of patients categorized as being at low risk of having LTBI based on these risk stratification tables had a positive TST and/or T-SPOT.TB and would not have received treatment for LTBI according to the British Thoracic Society guidelines (65). A British group subsequently advocated a “triple testing” approach using a combination of risk stratification according to the British Thoracic Society guidelines, TST, and IGRA (T-SPOT.TB) to achieve maximum sensitivity (by accepting a positive result from any screening modality as indication for LTBI treatment) (66).

An alternative screening algorithm that takes into account the pretest probability of having LTBI as well as current immunosuppression in patients to be tested (and thus the risk of obtaining a false-negative result) to determine the optimal test strategy seems promising (67). In this scenario, patients with a high pretest probability
**TABLE 2** Recommendations for LTBI screening and treatment in different countries

<table>
<thead>
<tr>
<th>Agency and/or country or region, year</th>
<th>LTBI screening tests</th>
<th>LTBI treatment regimen (duration in months, medication)</th>
<th>Anti-TNF-α starting delay</th>
<th>Repeat testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centers for Disease Control and Prevention, United States, 2004 and 2010 (update) (54, 55)</td>
<td>TST or IGRA, combined use of TST and IGRA supported Positive TST: ≥5 mm</td>
<td>9H</td>
<td>No definite recommendation, completion of LTBI treatment before anti-TNF-α therapy, if possible</td>
<td>Only in individuals at increased risk for TB infection</td>
</tr>
<tr>
<td>American College of Rheumatology, United States (56)</td>
<td>TST or IGRA</td>
<td>Not specified</td>
<td>1 mo</td>
<td>Annually in individuals with risk factor for future or ongoing TB exposure</td>
</tr>
<tr>
<td>Canada, 2013 (57)</td>
<td>TST or IGRA, combined (sequential) use of TST and IGRA supported</td>
<td>9H</td>
<td>No recommendation</td>
<td>Only in individuals at increased risk for TB infection</td>
</tr>
<tr>
<td>British Thoracic Society, United Kingdom, 2005 (58)</td>
<td>Use of risk stratification tables (and chest X ray) for patients on IST. TST performed only in patients not on IST (positive TST is ≥15 mm in BCG-vaccinated patients and ≥5 mm in non-BCG-vaccinated patients)</td>
<td>6H 3RH</td>
<td>≥2 mo Delay until completed LTBI treatment if abnormal chest X ray, history of TB</td>
<td>Not specified</td>
</tr>
<tr>
<td>France, 2003 (59, 60)</td>
<td>TST only Positive TST: ≥10 mm</td>
<td>2RZ 3RH 9H</td>
<td>≥3 wks</td>
<td>Not specified</td>
</tr>
<tr>
<td>Switzerland, 2007 (61)</td>
<td>IGRA only</td>
<td>9H 4R</td>
<td>1 mo</td>
<td>Not specified</td>
</tr>
<tr>
<td>TBNET International consensus, Europe (23)</td>
<td>TST or IGRA. TST performed only in patients without BCG. Positive TST: ≥10 mm</td>
<td>9–12H 3RH</td>
<td>4 wks</td>
<td>Not specified</td>
</tr>
</tbody>
</table>

*R, rifampin; H, isoniazid; Z, pyrazinamide; IST, immunosuppressive therapy.*
of having LTBI (based mainly on a history of contact with a case of active TB or birth or extended stay in a setting where TB is endemic) would have combined (sequential) screening with TST and IGRA, while patients with a low pretest probability of having LTBI would undergo combined screening only if they were immunosuppressed (poorly controlled IMID and IST). Non-immunosuppressed patients with a low pretest probability of having LTBI would have only an IGRA, because the negative predictive value of the IGRA is high in this context. This screening strategy could potentially increase the net benefit of an LTBI screening program in patients about to embark on treatment with a TNF-α inhibitor by reducing unnecessary treatment (and possible adverse events) in patients with low pretest probability for LTBI while ensuring that patients at risk are appropriately identified and receive treatment for LTBI.

TREATMENT OF LTBI
The effectiveness of a screening program for LTBI before starting TNF-α inhibitor therapy was documented in a study using the Spanish Society of Rheumatology Database on Biologic Products (BIOBADASER). The study showed a decrease of active TB rates among the BIOBADASER patients by 78% (incidence risk ratio, 0.22; 95% CI, 0.03 to 0.88; *P* = 0.008), after official recommendations on LTBI screening and treatment were issued (53).

In a retrospective cohort study from 2001 to 2011, Taiwanese researchers compared the incidence of TB in patients on anti-TNF-α treatment who had received LTBI treatment with the incidence of TB in patients on anti-TNF-α treatment who had not received LTBI treatment (68). Guidelines promoting screening for LTBI and treatment with 9 months of isoniazid, initiated 1 month prior to biologic therapy in the presence of LTBI, were introduced in Taiwan in 2010. The study found that none of the patients on etanercept (0/487) and rituximab (0/60) who received LTBI treatment developed TB, compared to 121 out of 26,880 and 2 out of 6,119 patients, respectively, who did not receive LTBI treatment. One patient on adalimumab who had received LTBI treatment (1/459) developed TB, compared to 66 patients with TB out of 10,713 patients on adalimumab who had not received treatment for LTBI.

A South Korean study compared completion rates and adverse events of different LTBI treatment regimens among 408 patients who received anti-TNF-α therapy (69). Patients received 9 months of isoniazid (9H), 4 months of rifampin (4R), or 3 months of isoniazid-rifampin (3HR). The treatment completion rate was highest in patients receiving 3HR (94.2%), while adverse drug reactions were similar in the three groups.

Commonly recommended LTBI treatment regimens in patients due to receive anti-TNF-α treatment are daily isoniazid for 6 to 9 months as well as rifampin and isoniazid for 3 months (Table 2). There are no trials that have examined how much time on treatment for LTBI ideally should have passed before commencing treatment with a biologic agent. The minimum time delay recommended is usually 1 month, and the benefit of earlier anti-TNF-α treatment improving the underlying disease has to be weighed against a potentially increased risk of TB reactivation if only a relatively short time has passed since commencement of LTBI treatment.

OBSERVATION DURING TREATMENT WITH TNF-α INHIBITORS
All patients receiving anti-TNF-α therapy should be monitored for signs and symptoms of TB at least until 6 months after cessation of treatment (58). There is no need to perform routine chest X-ray examination at certain intervals during treatment. A chest X-ray 3 months after commencing anti-TNF-α therapy is recommended for patients who had an abnormal chest X-ray at the time of initial TB screening or a history of TB or TB treatment but were deemed to have had previous adequate treatment by their TB specialist (58).

Some organizations, such as the National Psoriasis Foundation (NPF), recommend yearly TB screening (70) in patients on anti-TNF-α treatment, but the CDC and the American College of Rheumatology recommend annual TB testing only in individuals at increased risk for TB infection while they continue anti-TNF-α treatment (55, 56). Annual screening in these individuals includes a TST and/or IGRA if they previously tested negative, but repeating these tests for patients who had a positive TST or IGRA at baseline is not helpful to assess the risk of re-infection, as these tests often remain positive even after a full course of LTBI treatment (71, 72). The focus in these patients should be on assessing any new risk of exposure to TB (e.g., prolonged travel in settings with a high incidence of TB) and monitoring for clinical signs and symptoms of active TB.

In patients on anti-TNF-α therapy with negative TST and IGRA results at baseline, the conversion rate in longitudinal studies has ranged from 0% to 37% for the TST, from 0% to 12% for QFT-GIT, and from 0% to 10.5% for T-SPOT.TB (73). A Greek study including 247 patients with various rheumatic diseases on anti-
TNF-α treatment who had negative baseline screening for TB infection by three different methods (TST, T-SPOT.TB, and QFT-GIT) showed that 21 to 29% of patients (depending on the criteria used for conversion definition) had conversion of at least one screening test after 1 year (73). Conversion rates were 7%, 10%, and 13% for QFT-GIT, T-SPOT.TB, and TST, respectively. While some of these conversions may indeed reflect true positive conversions consistent with TB infection, others may be false-positive results due to within-subject variations of the respective assays. Studies on serial IGRA testing have shown high rates of conversions and reversions, independent of exposure or treatment (74), and discordant results between initial and repeat tests even when using the same patient sample (75). In a study of North American health care workers, 65% (n = 169) had a reversion after a first positive QFT-GIT result (74).

A study from Italy of patients with rheumatic diseases found that among six patients who had a QFT-GIT conversion after 12 months on biologic therapy, only two had a repeat positive QFT-GIT 6 months later (76), indicating that within-subject variations of IGRA results are a potential problem in serial testing in patients on anti-TNF-α treatment.

Little is known about the effects of biologic agents on TST and IGRA results. Anti-TNF-α treatment has been associated with negative TST results but had no impact on QFT-GIT results in one study (36). The use of infliximab has been associated with a lower rate of IGRA and TST conversion (76), despite its increased risk for TB reactivation compared to that with etanercept (3). This may be due to its suppressive effect on IFN-γ responses measured in vitro, supported by the fact that mitogen-induced IFN-γ levels were lower after treatment than before (73).

Screening strategies among patients on anti-TNF-α treatment aim to increase sensitivity because of the increased risk of TB reactivation and poor outcome (fulminant TB or death from TB) in this patient group (55). Serial testing with two tests (TST and one IGRA) with interpretation of at least one positive result as indicative of TB infection could be justified on this basis. However, to avoid excessive false-positive results (and thus unnecessary risks associated with treatment of LTBI), it is important to repeat testing only for individuals with ongoing or new TB risk, in line with CDC recommendations (55).

There have been descriptions of TB developing in patients on anti-TNF-α treatment traveling to settings where TB is endemic (77). Current guidelines do not contain any specific recommendations regarding screening and TB chemoprophylaxis in this situation. Patients on anti-TNF-α treatment need to be made aware of the risk related to traveling to areas where TB is endemic. If at all possible, extended stays in such areas should be avoided by these patients. Repeat screening for TB infection after traveling to areas with a high incidence of TB should be considered. Further research is required to evaluate the potential benefit of chemoprophylaxis (preventive treatment given during and immediately after exposure without proof of infection as opposed to LTBI treatment where there is evidence of infection) in patients on anti-TNF-α treatment traveling to areas where TB is endemic.

**TB IN PATIENTS ON TNF-α INHIBITORS**

Persons receiving anti-TNF-α treatment not only have an increased risk of TB reactivation but also are at an increased risk for poor outcomes (e.g., meningitis, disseminated disease, fulminant disease, or death) if active TB develops. TB associated with anti-TNF-α therapy is more likely to involve extrapulmonary sites and to be disseminated at presentation than are other TB cases (54, 78). Thus, clinicians need to be vigilant and think of a TB diagnosis in patients on anti-TNF-α treatment who experience fever, night sweats, malaise, lack of appetite, and weight loss even in the absence of pulmonary symptoms. Anti-TB treatment needs to be initiated as soon as a clinical diagnosis of TB is suspected, even if patients previously tested negative for LTBI (79, 80) or have a history of LTBI treatment (81). Most authorities recommend that anti-TNF-α therapy be discontinued at the time of TB diagnosis, at least temporarily.

The optimal timing of restarting TNF-α inhibitor treatment is unknown. To date, the only information on reinitiation of treatment comes from case series, which suggest that reinitiation of TNF-α inhibitor treatment appears to be safe in most patients with TB, but no conclusions regarding the optimal timing can be drawn from these reports. In a Turkish case series of nine patients who had developed TB on anti-TNF-α treatment, one was recommenced on anti-TNF-α treatment before anti-TB treatment was completed and eight patients restarted TNF-α inhibitor after completing anti-TB treatment (median, 1.3 months; interquartile range [IQR], 0.5 to 7.4 months) (82). The patient who was recommenced on anti-TNF-α treatment during the third month of anti-TB treatment for pulmonary TB completed a 6-month course of anti-TB treatment but developed clinical and radiological signs of TB meningitis (microbiologically negative) more than 12 months later. This was success-
fully treated with a 9-month course of anti-TB treatment. None of the other eight patients had recurrent TB. In a Portuguese cohort of 28 patients in whom anti-TNF-α treatment was discontinued when they developed TB, eight patients who restarted anti-TNF-α were prospectively followed up for a median of 2.5 years (1 to 65 months) (83). Anti-TNF-α treatment was reintroduced in five patients after TB treatment and in three patients during TB treatment, and none of the eight patients had microbiologically proven recurrent TB during the follow-up period. There was one case of meningitis 1 month after reintroduction of adalimumab, but the etiology remained unclear (suspicion of fungal infection). The patient was successfully treated with antifungal therapy and ongoing TB treatment.

In the absence of any more robust evidence, it seems reasonable based on these case series that TNF-α inhibitor treatment is reinitiated once drug susceptibility results are known and clinical improvement is evident. If patients were previously on a TNF-α inhibitor associated with a high risk of TB reactivation (e.g., adalimumab or infliximab), starting a TNF-α inhibitor associated with a lower TB risk (e.g., etanercept, golimumab, or certolizumab pegol) or a different biologic agent should be considered. Whether anti-TB treatment needs to be prolonged in patients on TNF-α inhibitors is not known. Considering a prolonged course (9 months) of anti-TB treatment may be prudent in these cases.

PARADOXICAL REACTIONS AND IRIS IN ANTI-TNF-α-ASSOCIATED TB

Paradoxical TB worsening, an example of the immune reconstitution inflammatory syndrome (IRIS), has been described for patients in whom anti-TNF-α treatment was discontinued due to anti-TNF-α-associated TB (84–86). To date, no cases of TB-IRIS have been described for patients treated with biologic agents other than TNF-α inhibitors. A case-control study based on data from the French RATIO registry examined risk factors associated with developing IRIS in 14 patients who developed TB while on anti-TNF-α treatment (87). Controls were patients who had anti-TNF-α treatment-associated TB but did not develop IRIS. IRIS occurred in 7% of all patients with anti-TNF-association in the RATIO registry (4/56 patients) and in 12.5% (0.0 to 28.7%) (2/16 patients) of patients with disseminated TB. IRIS-associated factors were as follows (OR [95% CI]): disseminated TB (11.4 [1.4 to 92.2]; P = 0.03), history of Mycobacterium tuberculosis exposure (12.7 [1.6 to 103.0]; P = 0.02), and steroid use after stopping anti-TNF agents at the time of TB diagnosis (4.6 [1.2 to 17.2]; P = 0.02). TB-IRIS developed within a median of 45 (IQR, 22 to 131) days after starting anti-TB therapy and 110 (IQR, 63 to 164) days after the last anti-TNF infusion. The latent period between commencing anti-TB treatment and the development of a paradoxical reaction can be explained with a prolonged effect (3 to 4 weeks) after infliximab therapy is ceased (35). Anti-TNF-α treatment was stopped at the time of TB diagnosis in all patients. IRIS treatment included steroids in nine patients (median 60 mg/day for a median of 11 [IQR, 7 to 12] months), a new anti-TB regimen in four patients, and rituximab in one patient (87). Anti-TB treatment lasted a median of 16 [IQR, 13 to 23] months in IRIS patients. Patients were cured within 375 (IQR, 146 to 813) days after IRIS diagnosis. IRIS symptom resolution took a median of 5 (range, 1 to 12) months after IRIS diagnosis.

The optimal treatment of TB-IRIS is still uncertain. While steroids are beneficial in symptomatic TB-IRIS associated with antiretroviral therapy in HIV (88), in the RATIO registry low-dose steroids could not prevent the onset of TNF-α-associated TB-IRIS (87). In fact, steroid use after anti-TNF-α treatment was withdrawn at the time of TB diagnosis appeared to be associated with the development of IRIS in this study, but the patient sample was small. In contrast, treatment with steroids once IRIS was apparent led to eventual cure in all patients on this treatment regimen in the RATIO registry study (87). A case report described a beneficial effect of infliximab therapy in a patient with steroid-resistant TB-IRIS involving the central nervous system who was not HIV infected and was previously not on anti-TNF-α treatment (89).

It has been suggested that reinitiation of anti-TNF-α treatment for severe IRIS symptoms and anti-TNF-α (low-dose) maintenance therapy in severely disseminated TB should be considered (84–86). Also, use of nonsteroidal anti-inflammatory drugs as well as prolongation of anti-TB treatment may be beneficial in TNF-α-associated TB-IRIS (84).

REFERENCES


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