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Diagnosis and Management of Tuberculosis in Candidates for Tumor Necrosis Factor Alpha Antagonists: An Experts Survey

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Abstract

Background: There are some controversies regarding the management of latent tuberculosis infection and tuberculosis in patients with rheumatologic indications for biologic therapy.

Objectives: To describe current expert opinions and preferences regarding the evaluation and management of latent tuberculosis infection and tuberculosis in candidates and recipients of tumor-necrosis factor-alpha blocking therapy.

Methods: A questionnaire addressing preferences related to management and treatment of latent tuberculosis infection and active tuberculosis in tumor-necrosis factor-alpha blocking candidates was distributed to tuberculosis and rheumatology experts across the United States between August 18, 2009, and June 21, 2010. Survey responses were formulated as a 5-point Likert scale (strongly disagree to strongly agree), or as a priority rank order list (1 to 6 or 7), and data were analyzed for percent agreement and median rankings.

Measurements and main results: The tuberculin skin test and interferon-gamma release assays for latent tuberculosis infection screening were highly accepted among tuberculosis and rheumatology experts. Most participants supported the use of daily isoniazid for 9 months for latent tuberculosis infection therapy, but responses were mixed regarding timing to initiation of tumor-necrosis factor-alpha blocking therapy. Most tuberculosis experts supported standard anti-tuberculosis therapy for treatment of tuberculosis, but preferences varied among rheumatologists. In contrast, most rheumatologists believed tumor-necrosis factor-alpha blocking therapy should be stopped in individuals with active tuberculosis, while opinions varied among tuberculosis experts.

Conclusions: Agreement among experts was common regarding preferences for diagnosis and management of latent tuberculosis infection and tuberculosis under hypothetical but likely common clinical scenarios, but some differences exist.

Keywords: Anti-TNF therapy; Expert; Immunosuppression; Rheumatoid arthritis; Survey; Tuberculosis

Introduction

Inflammatory diseases such as rheumatoid arthritis, inflammatory bowel diseases, and psoriasis are characterized by the deleterious effects of inflammatory cytokines such as tumor-necrosis factor-alpha (TNF-α). Accordingly, several therapeutic biologic agents have been developed to inhibit the effects of TNF-α in disease refractory to other standard immunosuppressive treatments [1]. Unfortunately, TNF-α blocking (TNFAB) therapy increases the risk for the development of active tuberculosis (TB) and other opportunistic infections, as an effective host immune response against TB relies on Th-1 cytokines, including TNF-α. While the incidence of TB has been declining in industrialized countries, individuals receiving TNFAB therapy have been found to have higher rates of the disease than the general population or individuals with inflammatory conditions who have not received biologic therapy [2,3]. Despite this well-recognized risk, evidence regarding the prevention and treatment of TB in TNFAB candidates is limited.

Several national guidelines have been published, but controversy exists regarding the management of Latent Tuberculosis Infection (LTBI) and TB in patients with rheumatologic indications for biologic therapy. In order to evaluate current clinical practices, the American College of Chest Physicians sponsored a national survey of TB specialists and rheumatologists to describe expert opinions and preferences regarding the evaluation and treatment of LTBI and TB in this population.

Methods

Study participants

Participants were selected based on recent contributions to the field identified by publication or practice in a US referral center. The survey was distributed to 61 pulmonary or Infectious Diseases (ID) TB experts and to 30 rheumatologists from academic medical centers across

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the United States. Twenty-nine TB experts and 12 rheumatologists completed the voluntary survey.

This work was based on a web-based survey to expert physicians. Our survey work was determined to be exempt (45 CFR 46.101, item 2) from review by the Mayo Clinic Institutional Review Board (IRB) (IRB application #09-000883). Invited physicians participated voluntarily and no informed consent was necessary for these survey procedures.

Survey methodology

A seven-member steering committee of pulmonary and ID specialists, including TB experts affiliated with the Centers for Disease Control and Prevention funded National TB Centers, prepared the study questionnaire. Survey questions were validated and evaluated for clarity by administration to physicians without specific expertise in the subject. The resulting eleven-question, web-based survey addressed practice preferences and hypothetical clinical scenarios including: 1) diagnostic value of the Tuberculin Skin Test (TST), Interferon-Gamma Release Assay (IGRA), and Chest Radiographs (CXR), respectively, prior to TNFAB therapy; 2) treatment of LTBI in TNFAB candidates; and 3) diagnosis and treatment of active TB in TNFAB recipients. Survey responses were formulated either as a 5-point Likert scale (strongly disagree to strongly agree), or as a priority rank order list (1 to 6 or 7). Respondents were also permitted to add free text comments in response to each question. Between August 18, 2009, and June 21, 2010, an e-mail invitation with a link to the survey was simultaneously sent to participants. The survey was originally developed as a Delphi survey, but after a longer-than-anticipated time to collect the initial round of information, the steering committee completed the study with data generated during the first round.

Statistical analysis

Data were analyzed using JMP software, 9.0.1. version (SAS Institute, Cary, NC). Median values (IQR) were calculated for responses on the Likert scale. Frequency of occurrence was determined for data in the rank order lists. Agreement among experts in each group was expressed as median ranking and percent agreement as indicated by the selection of "agree" or "strongly agree" on the Likert scale. Unless otherwise specified, Wilcoxon one-way analysis of variance by ranks was used to compare median responses between TB and rheumatology experts. For selected questions, "agree" and "strongly agree" as well as "disagree" and "strongly disagree" responses were grouped together, and "neutral" responses were excluded. A P value <.05 was considered significant.

Results

Screening for LTBI in patients with rheumatologic indications for TNFAB

Respondents were asked their opinion of the diagnostic value of screening tests including the TST, IGRAs, and CXR. Eleven of 12 rheumatologists (92%) agreed TST is of diagnostic value, while 1 disagreed. Twenty-five of 29 TB experts (86%) agreed TST was of diagnostic value, while 3 (10%) were neutral and 1 (3%) disagreed. The median answer was 4 ("agree") among both rheumatology and TB experts (P=.30).

Ten of 12 rheumatologists (83%) agreed IGRA is of diagnostic value, while 1 (8%) was neutral and 1 (8%) disagreed. Twenty-four of 29 TB experts (83%) agreed IGRA is of diagnostic value, while 4 (14%) were neutral and 1 (3%) disagreed. The median response was "agree" among both rheumatology and TB experts (P=.76).

Only 4 of 12 rheumatologists (33%) agreed that CXR should routinely be used to screen candidates for TNFAB therapy, while 1 (8%) was neutral and 7 (58%) disagreed. In contrast, 18 of 29 TB experts (62%) agreed with the routine use of CXR, while 5 (17%) were neutral and 6 (20%) disagreed. The median response was 2 ("disagree") among rheumatology experts and 4 ("agree") among TB experts. This did not reach a significant difference by the Wilcoxon one-way analysis of variance by ranks but approached significance by the Fisher exact test, excluding "neutral" responses (P=.33 and P=.06 respectively) (Table 1).

Treatment of LTBI in patients with rheumatologic indications for TNFAB

Daily isoniazid (INH) for 9 months was preferred for treatment of LTBI, ranked first by 8 of 12 rheumatologists (67%) and 25 of 29 TB experts (86%) (P=.34). Rifampin with or without INH for 4 months was the second choice among TB experts (16/29; 55%), while daily INH for 6 months was the second choice among rheumatologists (3/12; 25%). Responses were mixed regarding the remaining treatment options (Figure 1).

Among those recommending INH for 9 months, 5 of 12 rheumatologists (42%) recommended treatment for 1 month prior to initiating TNFAB therapy, while 10 of 29 TB experts (34%) favored 2 months of treatment. Some TB experts (4/29; 14%) recommended completing LTBI treatment before initiating TNFAB therapy. Responses varied among the remaining options (Figure 2).

Question	TB Experts (n=29)			Rheumatology Experts (n=12)			
	% Agreement[b]	Median	Range	% Agreement[b]	Median	Range	*P* Value[c]
The TST is of diagnostic value for LTBI in patients with rheumatologic indications for TNFAB	86	4	2-5	92	4	2-5	0.30
IGRAs are good diagnostic tests for LTBI in patients with rheumatologic indications for TNFAB	83	4	2-5	83	4	2-5	0.76
The routine use of CXR is valuable in the assessment of rheumatology patients who are candidates for TNFAB, regardless of TST results	62	4	2-5	33	2	2-5	0.33[d]

CXR: Chest Radiographs; IGRAs: Interferon-Gamma Release Assays; LTBI: Latent TB Infection; TB: Tuberculosis; TNFAB: TNF-α blocking; TST: Tuberculin Skin Test
[a]Likert Response: 1, strongly disagree; 2, disagree; 3, neutral; 4, agree; 5, strongly agree
[b]Percent of individuals within each group who select "agree" or "strongly agree"
[c]Comparison of distribution between groups by Wilcoxon one-way analysis of variance
[d]P=.057 by the Fisher exact test, excluding "neutral" responses

Table 1: Expert Opinion Regarding Assessment for LTBI[a].

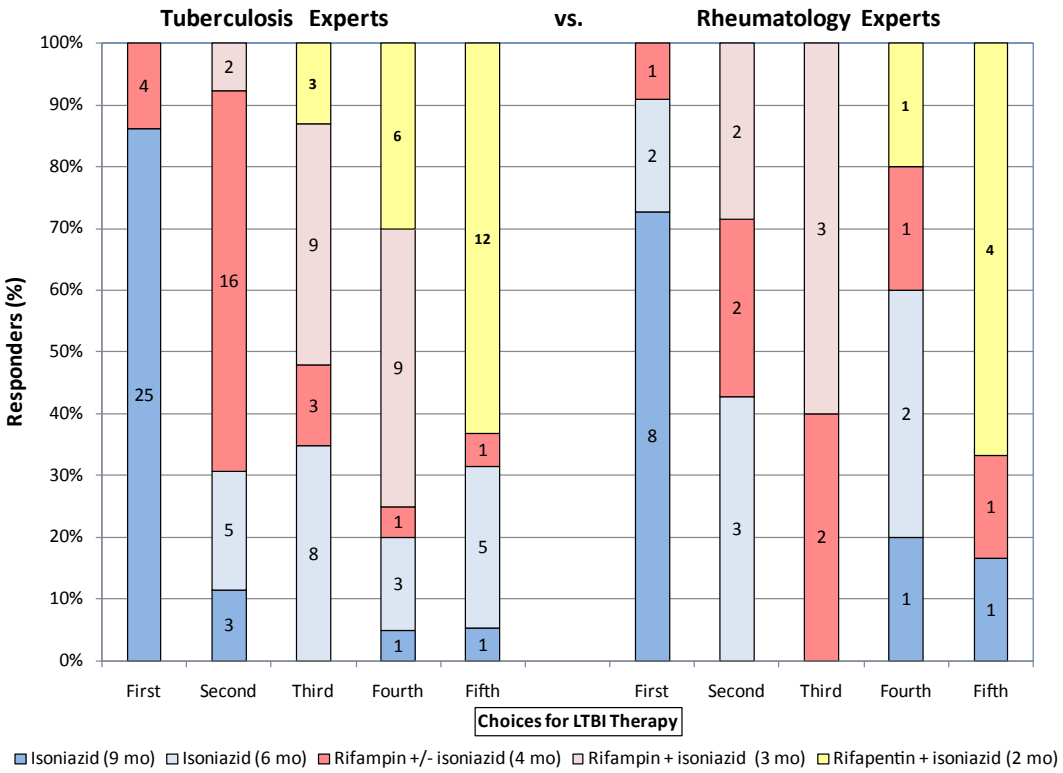

Figure 1: LTBI treatment preferences among TB and rheumatology experts.

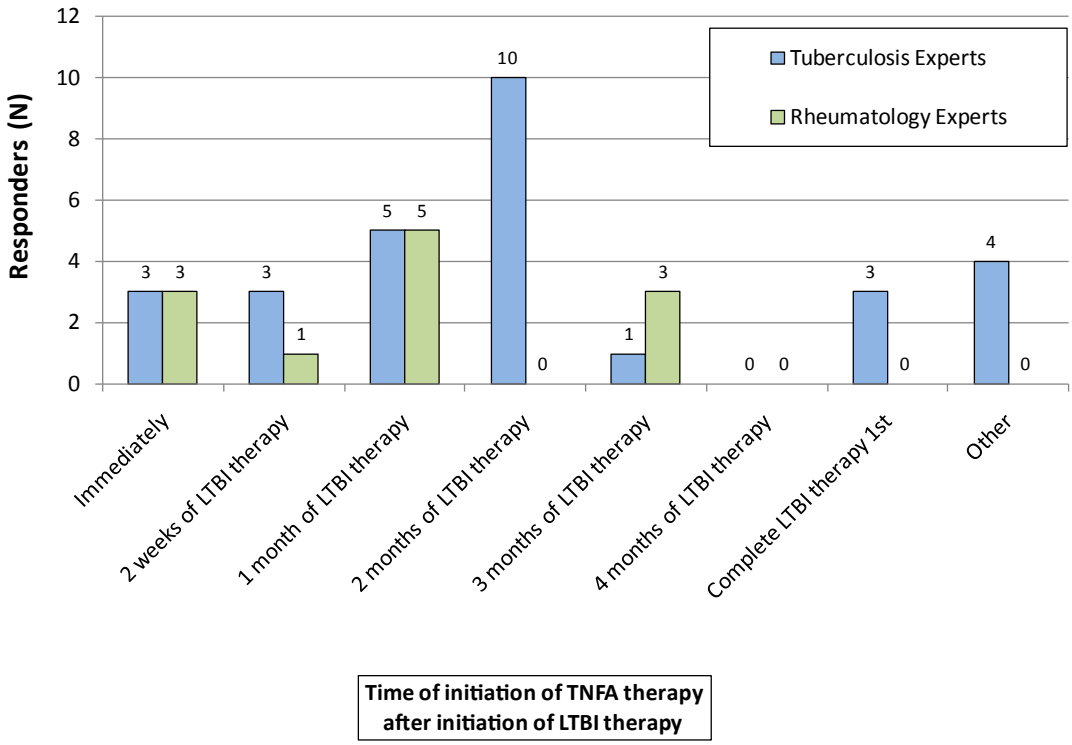

Figure 2: TB experts and rheumatologists' preferences for timing of TNFAB therapy following initiation of therapy for LTBI.

Diagnostic workup for suspected active pulmonary TB in Individuals undergoing TNFAB therapy

Eighteen of 28 TB experts (64%) agreed that 3 sputum acid-fast bacilli (AFB) smears with cultures was the preferred initial diagnostic test for TNFAB recipients presenting with signs and symptoms of pulmonary TB. Sputum induction was the second test of choice among most TB experts (13/28; 46%). Most rheumatologists also preferred either 3 sputum AFB smears and cultures (4/11; 36%) or sputum induction for AFB smear/culture (4/11; 36%).

Seventeen of 28 TB experts (61%) agreed that TNFAB therapy should be stopped for individuals with suspected TB, while 2 (7%) were neutral, 8 (29%) disagreed, and 1 (4%) strongly disagreed. The majority of rheumatologists (11/12; 92%) also agreed that TNFAB therapy should be stopped, with only 1 (8%) disagreeing. Although the percentage of experts who would stop TNFAB were different, there was not a statistical difference between these two groups (P=.18). Among TB experts, 18 of 28 (64%) agreed to start empiric therapy for suspected active TB, while 1 (4%) was neutral, and 9 (32%) disagreed. Seven of 12 rheumatology experts (58%) agreed with starting empiric therapy (P=.81), while 5 (42%) disagreed (Table 2).

Among those who would restart TNFAB therapy after discontinuation, responses varied regarding the length of time before resuming therapy. Five of 12 rheumatologists (42%) indicated they would wait for completion of treatment for active TB, while TB experts' responses were mixed among immediately restarting therapy (5/28; 18%), waiting 2 months (7/28; 25%), waiting until completion of TB treatment (6/28; 21%), and "other" (7/28; 25%). There was not a statistically significant difference between median responses after excluding from the analysis those who would never restart TNFAB and "other" (P=.17).

Treatment of active TB in individuals undergoing TNFAB therapy

For individuals with pansensitive and noncavitary TB and negative sputum cultures after 2 months of standard intensive-phase therapy (isoniazid, pyrazinamide, ethambutol, and rifampin), TB experts indicated a preference for continuing therapy with either INH and rifampin daily for 4 months (14/27; 52%), or INH and rifampin 3 times weekly for 4 months (13/27; 38%). Too few rheumatologists responded to clearly define a treatment preference.

For individuals with pansensitive and cavitary pulmonary TB disease with positive sputum culture results after 2 months of standard intensive-phase therapy, TB experts' first choice for continued therapy was INH and rifampin for 7 months; however, preference varied for dose frequency. Most TB experts preferred daily INH and rifampin (15/25; 65.2%), with a second first-choice preference for INH and rifampin 3 times weekly (7/25; 31.8%), and third first-choice preference for a twice-weekly regimen (3/25; 17.6%). Six of 8 rheumatologists (67%) selected INH and rifampin either daily or 3 times weekly for 7 months as a first choice, with mixed responses for the remaining choices.

Discussion

Screening for LTBI

Individuals with rheumatologic indications for TNFAB have a higher risk of developing active TB, but optimal screening is debated [4]. Similarly, survey respondents stressed the importance of screening prior to TNFAB therapy, with rheumatology and TB experts agreeing that TST and IGRAs are valuable screening tests. Although both TST and IGRAs had high rates of acceptance among both groups, several respondents commented that IGRAs were either as good as or better than the TST. Many also commented that the TST is more useful when positive than negative, and must be cautiously interpreted in immunocompromised patients. One reviewer mentioned that "many TNFAB candidates are already on significant immunosuppressant treatment at the time of TB evaluation, making any TB test less reliable."

The 2005 US Centers for Disease Control and Prevention guidelines for prevention of TB in the setting of TNFAB recommend screening with a one-step TST, with TST ≥5 mm considered positive in immunocompromised individuals [5]. Several European and the Australian guidelines also recommend screening with TST, but vary regarding the use of a one-step or two-step test, the diameter of a positive test, and the test's utility in the setting of prior immunosuppression or BCG vaccination [6-13]. The TST, however, is recognized to have limited sensitivity and specificity, particularly in immunocompromised individuals.

IGRAs have better specificity than the TST and are not affected by BCG vaccination or most strains of nontuberculous mycobacteria, both confounders of the TST [14]. However, the sensitivity of IGRAs in immunocompromised individuals is not entirely clear in the absence of a gold standard test for LTBI [14,15], and substantial rates of indeterminate results in this population have been reported in several studies [16-19]. Guidelines for LTBI screening with IGRAs in TNFAB candidates are mixed, with more recent guidelines giving increased support to IGRAs [7,11,13]. Recent studies and expert opinion also suggest the benefit of using both the TST and IGRAs to maximize testing sensitivity in immunosuppressed patients [18,20-25].

Evaluation with CXR is routinely recommended for immunocompetent individuals with a positive TST and/or IGRA prior to LTBI treatment [26]. In our survey, CXR prior to TNFAB therapy was better accepted among TB experts than rheumatologists, among whom opinion was mixed. In contrast, 62% of TB experts agreed CXR is useful. While it was stated that screening with CXR may detect many nonspecific abnormalities, rendering it less useful, it was also

Question	TB Experts (n=29)			Rheumatology Experts (n=12)			*P* Value[c]
	% Agreement[b]	Median	Range	% Agreement[b]	Median	Range	
I would stop therapy with TNFAB	61	4	1-5	92	4	1-5	0.18
I would start empiric therapy for TB	64	4	1-5	58	4	1-5	0.81
How long would you wait to start TNFAB therapy?	--	4	1-7	--	5	1-7	0.17

TNFAB: TNF-α blocking; TST: Tuberculin Skin Test

[a]Likert Response: 1, restart TNFAB immediate; 2, 2 weeks; 3, 1 month; 4, 2 months; 5, 3 months; 6, 4 months; 7,wait for completion of TB therapy (excluding from the analysis: 8, never restart TNFAB; 9, other[§])

[b]Percent of individuals within each group who select "agree" or "strongly agree"

[c]Comparison of distribution between groups by Wilcoxon one-way analysis of variance

Table 2: Expert Opinion Regarding TNFAB and Empiric TB Therapy for Individuals with Suspected TB While on TNFAB Therapy[a].

commented that the ability to detect additional abnormalities may lead to better management.

To our knowledge, the utility of using CXR for screening for TB in TNFAB candidates has not being rigorously tested, but CXR is often obtained with the TST and/or IGRA to rule out active pulmonary disease and to assess for evidence of previous infections. While CXR is often considered regardless of TST results, the high prevalence of extrapulmonary and disseminated disease as well as atypical pulmonary findings in immunocompromised individuals may lessen the ability of CXR to accurately detect specific abnormalities associated with TB [28,29]. Many published guidelines, however, recommend CXR prior to TNFAB therapy [6-8,11-13,29]. With lack of evidence to the contrary, it appears reasonable for clinicians to extrapolate current American Thoracic Society recommendations for CXR to evaluate this population prior to TNFAB therapy.

Treatment of LTBI prior to TNFAB therapy

LTBI treatment guidelines recommend INH daily for 9 months as the preferred regimen for both HIV-positive and HIV-negative individuals [26]. Similarly, both TB and rheumatology experts strongly favored INH daily for 9 months for TNFAB candidates (Figure 1). This regimen is recognized to have a lower risk of hepatotoxicity, although adherence must be assured.

There is little data, however, to guide how long to treat individuals before initiating TNFAB therapy. Some TB experts expressed the opinion that it is ideal to complete LTBI treatment prior to TNFAB therapy. When earlier initiation of TNFAB therapy is indicated due to the severity of the rheumatologic disease, many suggested it is preferable to wait at least 2 months. Rheumatology experts, however, had mixed responses, although the majority recommended at least 1 or more months of treatment prior to TNFAB therapy.

Similarly, published recommendations vary, from recommending concurrent therapy, to at least 1 month of INH before TNFAB therapy, to completing INH before TNFAB therapy [5,7,8,12,13,29]. The variability of responses among survey participants reflects variation in clinical scenarios and the uncertainty surrounding this question. Overall, although some prefer completion of INH prior to TNFAB therapy, an induction period of at least 2 months is widely accepted.

Evaluating for suspected active TB in individuals receiving TNFAB therapy

Diagnosing active TB in immunocompromised individuals can be difficult, as the lack of an appropriate immune response may lead to atypical findings, including extrapulmonary or disseminated disease [30,31]. However, for evaluation of patients on TNFAB therapy and presenting with a mild, nonproductive cough, fever, and CXR showing noncavitary pulmonary infiltrates, both TB and rheumatology experts preferred sputum sampling for AFB smear and cultures, either through routine collection or induction. In both groups, many selected pursuing diagnostic bronchoscopy only after exhausting other options for sputum evaluation.

Type and duration of anti-TB therapy for individuals who develop TB while receiving TNFAB therapy

An intensive phase of a 4-drug regimen for 2 months followed by INH and rifampin is widely accepted for the treatment of active TB regardless of immune status [32]. The duration of treatment for immunocompromised individuals is less certain, and recent European consensus guidelines on TB and TNFAB therapy have based recommendations on consensus judgment [13]. TB and rheumatology experts indicated their preferences under the following scenarios:

Treatment of a patient receiving TNFAB therapy who has been diagnosed with active TB and whose CXR shows noncavitary pulmonary infiltrates, and whose sputum AFB culture result is negative at 2 months of treatment: Most TB experts felt that treatment should continue for 4 months with daily INH and rifampin. Responses varied among rheumatologists, with many noting they would defer to their ID or pulmonary colleagues. In this scenario, therefore, standard 6-month therapy is accepted by those with experience treating TB.

Treatment of a patient receiving TNFAB therapy who has been diagnosed with active TB and whose CXR shows noncavitary pulmonary infiltrates, and whose sputum AFB culture result is positive at 2 months of treatment: This question was an internal validation control, as evidence supports the recommendation to extend the continuation phase from 4 to 7 months in individuals with cavitary disease and positive sputum culture at 2 months [33]. Accordingly, all TB experts indicated that after standard treatment for 2 months, treatment with INH and rifampin should continue for 7 months, assuming appropriate drug sensitivity. However, the frequency of dose administration varied, with a preference for daily and 3 times weekly regimens. Responses were somewhat mixed among rheumatologists, although three-fourths of those who responded selected 7-month treatment regimens for the continuation phase as their first choice. Those who did not respond with specific preferences commented that they would consult ID or pulmonary colleagues.

Continuation of TNFAB therapy for individuals with suspected active TB

Recommendations from the British Thoracic Society suggest, based on extrapolated evidence from case reports and expert opinion, that anti-TNF therapy can be continued for the duration of anti-TB therapy [34]. However, European consensus guidelines recommend, based on expert opinion, that a full course of anti-TB treatment should be completed prior to TNFAB therapy in TNFAB-naïve individuals [13]. In our survey, there were no statistical differences regarding discontinuation of TNFAB in the setting of active TB between the two group of experts. However, TB experts' responses were mixed, with one noting that the pulmonary process would have to be further defined, and another reporting experience with immune reconstitution inflammatory syndrome when TNFAB therapy is stopped. Most rheumatologists agreed that TNFAB therapy should be stopped if TB is suspected. There was not a clear trend within either group regarding how long to wait before restarting TNFAB therapy.

Responses also varied among rheumatology and TB experts regarding empiric therapy for suspected active TB; comments indicated some would start therapy after diagnostic workup was complete, would start therapy after sputum cultures had been obtained, or would rule out nontuberculous mycobacteria or fungal infection first. With data lacking, decisions regarding management of suspected TB appear highly dependent on individual clinical scenarios, with consideration of the degree of pulmonary disease, risk for immune reconstitution inflammatory syndrome, and risk for opportunistic infections.

Additional questions and limitations

This survey allows a descriptive summary of likely common clinical practices and physician experts' preferences in the management of TB in TNFAB candidates. Several questions remain, however, that were

beyond the scope of our survey but may impact future recommendations. There is evidence, for example, that risk of TB varies by TNFAB agent, with increased rates reported for monoclonal antibodies such as infliximab, compared to the soluble protein etanercept [35,36]. Other biological agents have also been introduced after the completion of this survey [37]. In addition, while most experts extrapolate current guidelines for the treatment of LTBI and TB in immunocompetent patients to this population, a new and shortened treatment regimen for LTBI (weekly INH and rifapentine for 3 months) was recommended by the Centers for Disease Control and Prevention after this survey, which may impact physicians' preferences [38,39]. Furthermore, prevalence and risk of TB varies by location, and practices for screening and treatment might vary accordingly. Although we noted trends among US experts, our sample size also limited statistical evaluation.

Finally, our survey focused on pulmonary TB, but TB associated with TNFAB therapy is commonly extrapulmonary or disseminated [35]. Prior immunosuppression may also affect evaluation, as many individuals are on immunosuppressive therapy demonstrated to alter TB risk prior to TNFAB therapy [40]. The overall risk of TB, and therefore the impact of screening, varies based on rheumatologic treatment, type of TNFAB therapy, local prevalence, and exposure history; and these factors, among others, should be considered when evaluating for LTBI and TB [1].

Conclusion

This study does not intend to provide specific guidelines or recommendations, but attempts to evaluate current practices from medical experts in areas of uncertainty regarding LTBI and TB in TNFAB candidates. Surveys of TB and rheumatology experts assessed preferences for diagnosis and management of LTBI and TB under hypothetical but likely common clinical scenarios. Agreement among experts was common, but some differences exist.

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