

ORIGINAL ARTICLE

Evaluation of screening methods for identification of patients with chronic rheumatological disease requiring tuberculosis chemoprophylaxis prior to commencement of TNF- α antagonist therapy

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ABSTRACT

Background Patients undergoing tumour necrosis factor (TNF)- α antagonist therapy are at increased risk of latent tuberculosis infection (LTBI) reactivation. The aim of this study was to determine the optimum available screening strategy for identifying patients for tuberculosis (TB) chemoprophylaxis.

Methods We conducted a prospective observational study of consecutive adults with chronic rheumatological disease referred for LTBI screening prior to commencement of TNF- α antagonist therapy. All patients included had calculation of TB risk according to age, ethnicity and year of UK entry, as described in the 2005 British Thoracic Society (BTS) guidelines and measurement of tuberculin skin test (TST) and T.Spot.TB.

Results There were 187 patients included in the study, with 157 patients (84%) taking immunosuppressants. 137 patients would require further risk stratification according to the BTS algorithm, with 110 (80.3%) classified as being at low risk of having LTBI. There were 39 patients (35.5%) who were categorised as low risk but were either TST and/or T.Spot positive and would not have received chemoprophylaxis according to the BTS algorithm. Combination of all three methods (risk stratification and/or positive T.Spot and/or positive TST) identified 66 patients out of 137 who would potentially be offered chemoprophylaxis, which was greater than any single test or two-test combination.

Conclusion Performing both a TST and T.Spot in patients on immunosuppressants prior to commencement of TNF- α antagonist therapy gives an additional yield of potential LTBI compared with use of risk stratification tables alone. Our results suggest that use of all three screening modalities gives the highest yield of patients potentially requiring chemoprophylaxis.

INTRODUCTION

Tumour necrosis factor (TNF)- α inhibitors are frequently used to treat immune-mediated inflammatory diseases and are recommended for a range of rheumatological conditions. However, patients undergoing TNF- α inhibitor therapy are at increased risk of developing serious opportunistic infections, including reactivation of latent tuberculosis infection (LTBI).^{1–3} Crucially, treatment with chemoprophylaxis in patients who are diagnosed with LTBI prior to commencement of TNF- α

Key messages

What is the key question?

- What is the optimum screening method for identification of patients who require tuberculosis (TB) chemoprophylaxis prior to commencement of tumour necrosis factor- α (TNF- α) antagonist therapy?

What is the bottom line?

- Performing both a tuberculin skin test (TST) and T.Spot in patients on immunosuppressants prior to commencement of TNF- α antagonist gives an additional yield of potential latent tuberculosis infection compared with use of risk stratification tables or either test alone.

Why read on?

- This study aims to determine the optimum screening strategy, and this is of clinical importance, given that there is significant increased risk of TB reactivation associated with use of TNF- α antagonist therapy.

inhibitor therapy is associated with a 74% reduction in risk of tuberculosis (TB) reactivation.⁴

Screening for LTBI prior to initiation of TNF- α inhibitors is now part of routine care in the UK, and specific guidance exists in the form of the 2005 British Thoracic Society (BTS) guidelines.⁵ The optimum screening strategy remains unclear with different countries recommending varying approaches based on using risk stratification as a surrogate for LTBI and/or one or a combination of interferon- γ release assay (IGRA) and tuberculin skin testing (TST).^{2 6–10} The BTS recommend a specific algorithm and advocate sole use of risk stratification tables based on age, ethnicity and year of UK entry to guide chemoprophylaxis decisions for patients on immunosuppressant therapy due to the fact that the TST may be falsely negative in the setting of immunosuppressants.¹¹ The guidelines recommend chemoprophylaxis decisions based on balancing the population risk of LTBI in different groups using age and ethnicity with the risk of therapy-induced serious hepatotoxicity, and

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assume equivalence between the significance of the two potential complications of LTBI reactivation and hepatotoxicity. Additionally, since the publication of the BTS guidance, routine IGRA testing is now becoming more widely available to clinicians as an alternative method of assessing for LTBI.

A number of previous studies have assessed the correlation between IGRAs and TST in LTBI screening prior to TNF- α antagonist therapy,^{12–16} but no study has directly compared the performance of these tests with the risk stratification method advocated by the BTS. Only a small number of studies have taken into account whether the patient is on immunosuppressant medication.^{17–18} At our centre, we adopt an alternative unique approach of undertaking ‘triple testing’ (combined BTS risk stratification, TST and T.Spot TB) in all patients referred for LTBI screening prior to commencement of TNF- α antagonist therapy. The aim of our study was, therefore, to compare the performance of the BTS risk stratification approach with use of the T. Spot and/or TST in order to determine the optimal screening strategy in patients with rheumatological disease being considered for TNF- α inhibitor therapy.

METHODS

We conducted a prospective observational study of consecutive adult patients (>16 years) with chronic rheumatological disease referred for LTBI screening prior to commencement of TNF- α inhibitor therapy at St Mary’s Hospital, London, between September 2009 and September 2012. The study was approved by the Local Joint Research Office.

Information about demographics, including age, ethnicity, rheumatological diagnosis, Bacille Calmette-Guerin (BCG) vaccination status and, if appropriate, year of entry to the UK, were recorded on a standardised pro forma. A clinical history was taken from all patients with specific enquiry about symptoms of active TB (cough, fever, weight loss and night sweats) and drug history including current use of immunosuppressant medications. Enquiry was also made about previous history of active TB and treatment received and any previous close contact with TB-infected persons was recorded, as previously described.¹⁰

All patients had calculation of TB risk according to age, ethnicity and year of UK entry, as described in the 2005 BTS guidelines (see online supplementary material for details). A chest radiograph to assess for signs of active TB or previous TB (eg, apical scarring, calcified granulomata) was also carried out.

Interferon γ ELISPOT and TST

The T.Spot.TB test (Oxford Immunotech, Oxford UK) was measured as previously described.¹⁹ Peripheral venous blood samples were collected and assays were carried out in accordance with the manufacturer’s instructions. Results were defined as positive, negative or indeterminate depending on the manufacturer’s criteria.

The TST was undertaken, according to the Mantoux method, by trained TB specialist nurses. A 0.1 mL dose (2 IU) of tuberculin purified protein derivative (PPD RT23; Statens Serum Institute, Copenhagen, Denmark) was injected intradermally, according to standard guidelines. The main diameter of skin induration was then recorded 48–72 h after inoculation and result was recorded. A transverse diameter of ≥ 6 mm in the absence of previous BCG vaccination or ≥ 15 mm in the presence of previous BCG vaccination was considered positive. Patients who had no visible BCG scar and were unable to recall history of receiving BCG were assumed to have not received it.

Exclusion criteria

Patients who did not receive TST and T.Spot tests, or in whom either test was declined or not successfully completed were excluded from the study.

Statistical analysis

All data were analysed using SPSS 13.0 for windows (Chicago, Illinois, USA). The χ^2 test was used to compare the proportions of factors of interest in patients categorised as high risk versus low risk, patients with positive T.Spot versus those with negative T.Spot, and patients with positive TST versus those with negative TST. The Mann–Whitney U test was used to compare the median age as a continuous variable between patients categorised as high risk versus low risk, patients with positive T.Spot versus those with negative T.Spot and patients with positive TST versus those with negative TST. All analyses were undertaken using two-tailed tests with a $p < 0.05$ considered to be statistically significant.

RESULTS

There were 187 patients included in the study. Figure 1 shows patient entry into the study. Baseline demographics of the study population are shown in table 1. There were 157 patients (84.0%) taking immunosuppressants at the time of LTBI screening. There was a non-statistically significant trend towards patients on immunosuppressants being less likely to have positive TST results (40.0% vs 22.9%; $p = 0.09$), but no differences between the proportion of patients who were high risk according to BTS risk tables or who were T.Spot positive (table 1, see online supplement).

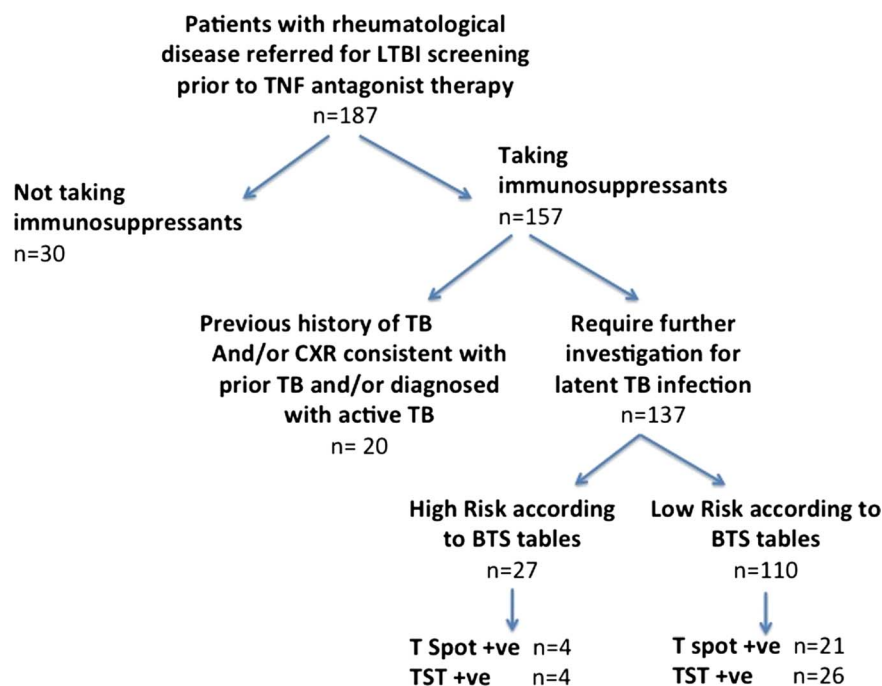
EVALUATION OF RISK STRATIFICATION ALONE AS A METHOD OF IDENTIFYING PATIENTS REQUIRING CHEMOPROPHYLAXIS

The BTS advocates use of a risk-stratification approach alone for patients who are on immunosuppressants, and therefore, we assessed the yield of this method. Of the subgroup on immunosuppressants, 20 patients had either previous history of TB and/or chest radiograph consistent with prior TB, and/or were diagnosed with active TB at the time of screening. This left a total of 137 patients who, according to the BTS algorithm, would require further risk stratification. Two patients had a history of previous contact with an active TB case. Of the subgroup on immunosuppressants requiring further risk stratification, 27 (19.7%) patients were categorised as high risk. Table 2 shows a comparison between patients classified as high and low risk.

There were 26 out of 110 patients (23.6%) who were categorised as low risk, but had a positive TST. Twenty-six out of 31 (83.9%) of all patients with positive TST were categorised as low risk and would not have received chemoprophylaxis according to the BTS algorithm. In these low-risk patients with a positive TST, the median TST reaction size was 20 mm (15.5–20.5 mm). Fourteen out of 26 (53.8%) patients had strongly positive TST (≥ 20 mm). Of these 14 patients, nine (64.3%) had been previously vaccinated with BCG. There were 21 out of 110 patients (19.1%) who were categorised as low risk according to the BTS but had a positive T.Spot; 21 out of 25 (84.0%) of all patients with positive T.Spot were categorised as low risk and would not have received chemoprophylaxis according to the BTS algorithm.

In total, there were 39 patients (35.5%) who were categorised as low risk but had either TST and/or T.Spot positive and would not have received chemoprophylaxis according to the BTS algorithm.

Figure 1 Flow chart of patient entry into study. Abbreviations: BTS, British Thoracic Society; CXR, chest radiograph; TB, tuberculosis; TNF, tumour necrosis factor; TST, tuberculin skin test.



EVALUATION OF T.SPOT ALONE OR TST ALONE AS METHODS FOR IDENTIFYING PATIENTS REQUIRING CHEMOPROPHYLAXIS

The subgroup on immunosuppressants who would require further stratification according to the BTS algorithm (n=137) were assessed regarding their T.Spot positivity (n=136 due to one patient having indeterminate T.Spot) or TST positivity to assess the proportion of patients who would be identified as having LTBI using either test alone. Table 2 shows comparison between patients who were T.Spot positive and negative, and between those who were TST positive and negative. There were 25 patients who were T.Spot positive. In the T.Spot negative group, there were 23 patients (20.7%) who were classified as high risk and would have received chemoprophylaxis according to the BTS algorithm, and 22 patients (19.8%) patients who were TST positive.

There were 31 patients who were TST positive (according to threshold of ≥ 15 mm in presence of BCG or ≥ 6 mm in absence of BCG). If a lower threshold of ≥ 6 mm in all immunosuppressed patients was used (as advocated by some guidelines^{9, 20}), this would increase the total number to 56 patients with positive TST. In the TST negative group, there were 22 patients (20.8%) who were classified as high risk and 16 patients (15.1%) who were T.Spot positive.

COMPARISON BETWEEN RISK FACTOR APPROACH VERSUS T.SPOT ALONE OR TST ALONE, AND COMBINATIONS METHODS FOR IDENTIFYING PATIENTS FOR CHEMOPROPHYLAXIS

Table 3 shows numbers of patients that would be identified for chemoprophylaxis by each method alone and combinations of methods. Use of the BTS risk-factor approach, T.Spot or TST alone would lead to relatively similar numbers of patients being offered chemoprophylaxis and similar numbers of 'missed' patients (identified via the other two methods). TST alone identified slightly more patients for treatment with a higher sensitivity (compared with the 'gold standard' of triple combination testing) than sole use of either of the other two methods.

All three 'double test' combinations identified more patients for chemoprophylaxis than the remaining test alone. The best 'double test' combination method was risk stratification plus TST with a higher sensitivity than risk stratification and T.Spot combined or T.Spot and TST combined. Combination of all three methods identified 66 patients (48.2%) who would potentially be offered chemoprophylaxis, which was greater than any single test or any two-test combination. Figure 2 shows overlap between the yields for each test individually and the number of patients who were double and triple test positive (ie, both or all three tests mutually positive).

USE OF T.SPOT AND/OR TST IN LOW-RISK PATIENTS

Given that high-risk patients on immunosuppressants are recommended to receive treatment by the BTS algorithm without requirement for measurement of TST or T.Spot, we evaluated the yield of these tests in the subgroup classified as low risk (n=110). Again, TST identified more patients and missed fewer than T.Spot with double combination giving the highest yield (see table 4).

CLINICAL OUTCOMES IN PATIENTS WHO RECEIVED CHEMOPROPHYLAXIS

All patients who had positive results according to one or more of the three methods used (n=66) were offered chemoprophylaxis in the form of a 3-month course of rifampicin plus isoniazid (or a 6-month course of isoniazid alone if on maintenance steroids), as per BTS guidelines.⁵ One patient declined treatment, leaving a total of 65 patients who received treatment. Of these, two patients (3.1%) developed drug-induced hepatotoxicity requiring conversion to an alternative agent and three patients (4.6%) required alternative agents for other intolerance to therapy. There were no other therapy-related complications observed in the study.

DISCUSSION

Our study is the first to compare a risk-stratification method of identifying patients requiring chemoprophylaxis with tests to

Table 1 Baseline characteristics of study population

	Total cohort (n=187 patients)
Demographics	
Age (median (IQR))	54 (43–65)
Male sex	82 (43.9%)
Ethnicities	
Caucasian	109 (58.3%)
Black African	13 (7.0%)
Asian	23 (12.3%)
Other	42 (22.5%)
Comorbidities	
Chronic lung disease	13 (7.0%)
Ischaemic heart disease	8 (4.3%)
Diabetes mellitus	10 (5.3%)
HIV	1 (0.5%)
Inflammatory bowel disease	3 (1.6%)
Rheumatological diagnoses*	
Rheumatoid arthritis	113 (60.4%)
Ankylosing spondylitis	38 (20.3%)
Psoriatic arthropathy	23 (12.3%)
Juvenile idiopathic arthritis	2 (1.1%)
Other	13 (7.0%)
Immunosuppressants†	
Methotrexate	113 (60.4%)
Azathioprine	3 (1.6%)
Sulphasalazine	46 (24.6%)
Leflunomide	13 (7.0%)
Maintenance steroids	47 (25.1%)
Other	1 (0.5%)
LTBI screening	
BCG vaccinated	65 (34.8%)
T.Spot positive	42 (22.5%)
T.Spot indeterminate	1 (0.5%)
TST positive	48 (25.7%)
T.Spot and TST both positive	18 (9.6%)
High risk according to BTS risk tables	40 (21.4%)
CXR suggestive of previous TB	16 (8.6%)
Contact of active TB case	8 (4.3%)
Previously treated for TB	2 (1.1%)
Diagnosed with active TB	2 (1.1%)

Data presented as n (% of total cohort).

*Total exceeds 187 due to some patients having dual diagnoses.

†Total exceeds 187 due to some patients being on more than one immunosuppressant agent.

BCG, Bacille Calmette-Guérin; BTS, British Thoracic Society; CXR, chest radiograph; LTBI, latent tuberculosis infection; TB, tuberculosis; TST, tuberculin skin test.

directly identify LTBI prior to TNF- α inhibitor therapy. Our data show that use of risk-factor tables alone to guide treatment in patients taking immunosuppressants, as recommended by the BTS guidelines, misses a large number of predominantly Caucasian patients who have apparent LTBI as defined by a positive TST or T.Spot. Although deemed to be 'low risk' based on age and ethnicity, a total of 39 patients (35.5%) in this category had evidence of LTBI according to TST and/or T.Spot and these patients would not have been treated according to the BTS guidance.

We evaluated the yield of each test individually and also the yield of a combination of either (or all three) tests being positive. Use of TST alone identified slightly more patients with apparent LTBI with a higher sensitivity than either of the other tests alone, which is in keeping with some previous studies.^{13–14}

Use of combinations of any two methods gave higher yields than the missed yield from the remaining test. Overall, use of all three tests (any one or more being positive) led to the greatest yield of patients identified for treatment. Triple testing was performed in all patients in the current study. However, measurement of TST and T.Spot in those classified as high risk and on immunosuppression is unlikely to alter management, except to aid drug compliance and, in reality, such patients would be offered chemoprophylaxis regardless of the results of these tests. Therefore, in clinical practice, the most cost-effective strategy may be two-step: risk stratification in all with chemoprophylaxis offered to those who are high risk, followed by measurement of both T.Spot and TST in all low-risk patients (see online supplementary material for proposed alternative screening algorithm based on the results of this study). Prospective independent validation of this strategy is now required. It is also notable that in clinical practice, many centres are now using IGRA testing alone in preference to TST. According to our data, use of risk stratification followed by IGRA testing in low-risk patients would have a lower sensitivity for identification of patients requiring chemoprophylaxis than dual testing with IGRA and TST. However, given that the risk of reactivation in older patients with positive TST is likely to be low, dual testing with risk stratification followed by IGRA may still be an acceptable alternative strategy. Further prospective evaluation is required.

Our data shows low correlation between traditional risk factors for LTBI (age, ethnicity and UK year of entry) and T.Spot and TST positivity. We found that 86.7% of all patients on immunosuppressants with positive TST, and 84% with positive T.Spot were classified as low-risk according to the BTS risk-tables. This result was surprising as we would have expected a higher correlation, given that risk-stratification alone is the method recommended by the BTS for guiding chemoprophylaxis in these patients. The precise reasons for poor correlation in the high-risk group are unclear, although we speculate that it may be due to the effects of rheumatological disease processes and/or immunosuppressant medication perhaps reducing the likelihood of T.Spot or TST positivity in these high-risk ethnic groups.

Our data suggests that Caucasian patients may be wrongly denied chemoprophylaxis, given their automatic classification as low risk by the BTS risk tables. Of our cohort, 58.3% were of Caucasian ethnicity, but despite this, many had a positive T.Spot and/or TST. It is our belief that a Caucasian individual who has underlying immunosuppression due to medication and/or rheumatological disease cannot be considered to have an equivalent risk of acquisition of LTBI to a normal, immunocompetent Caucasian individual. Consequently, use of risk-factor tables based on ethnicity may not be an appropriate strategy to guide chemoprophylaxis in this patient cohort.

Matulis and colleagues previously assessed correlation between TST and Quantiferon with risk factors for LTBI in patients with rheumatologic disease on immunosuppressants.¹⁷ Similarly, they found a number of patients who were low risk but had positive IGRA (12%) or TST (57%). One possible explanation for these results is that in a low-prevalence population, the false positive rate of a test may increase and we do not yet have prospective longitudinal data to understand the clinical significance of positive T.Spot results in this specific cohort. However, it is notable that the regional endemic rate of TB in London is considerably higher than national UK rates,²¹ and this may contribute to the higher than expected frequency of LTBI seen in low-risk patients in our cohort. Risk-stratification

Table 2 Comparison of characteristics in patients on immunosuppressants classified according to risk stratification, tuberculin skin test (TST) positivity and T.Spot positivity

	High risk according to BTS n=27	Low risk according to BTS n=110	p Value	TST positive n=31	TST negative n=106	p Value	T.Spot positive n=25	T.Spot negative n=111*	p Value
Male sex (%)	15 (55.6)	45 (40.9)	0.197	18 (58.1)	42 (39.6)	0.099	14 (56.0)	46 (41.4)	0.265
Age	50 (44–60)	57 (45–68)	0.063	57 (49–68)	55 (44–65)	0.530	56 (46–68)	55.5 (44–66)	0.624
Ethnicity									
Caucasian (%)	0 (0)	83 (75.5)	<0.001	19 (61.3)	64 (60.4)	1.0	16 (64.0)	67 (60.4)	0.823
Black African (%)	8 (29.6)	0 (0)	<0.001	2 (6.5)	6 (5.7)	1.0	3 (12.0)	5 (4.5)	0.163
Asian (%)	15 (55.6)	0 (0)	<0.001	3 (9.7)	12 (11.3)	1.0	1 (4.0)	14 (12.6)	0.304
Other (%)	4 (14.8)	27 (24.5)	0.441	7 (22.6)	24 (22.6)	1.0	5 (20.0)	25 (22.5)	1.0
High risk according to BTS (%)	–	–	–	5 (16.1)	22 (20.8)	0.798	4 (16.0)	23 (20.7%)	0.783
TST positive (%)	4 (14.8)	26 (23.6)	0.439	–	–	–	9 (36.0)	22 (19.8)	0.112
T.Spot positive (%)	4 (14.8)	21 (19.1)	0.783	9 (29.0)	16 (15.1)	0.110	–	–	–
Indeterminate T.Spot (%)	0 (0)	1 (0.9)	1.0	–	–	–	–	–	–
T.Spot and TST both positive (%)	1 (3.7)	8 (7.3)	0.688	–	–	–	–	–	–
Either T.Spot and/or TST positive (%)	7 (25.9)	39 (35.5)	0.496	–	–	–	–	–	–

*Total=136 due to one patient having indeterminate T.Spot result.

Data presented as median (IQR) or n (%); p values show comparison of proportions between groups or median values for continuous variables. BTS, British Thoracic Society.

tables based on national statistics such as those advocated in the BTS guideline may, therefore, not be applicable to regions with higher endemic TB rates. Interestingly, the BTS document does not discuss prior contact with an active TB case as a possible risk factor for LTBI. In our study, only two patients in the subgroup on immunosuppressants gave a history of prior contact with an active TB case and both these patients were classified as high risk on basis of risk-factor tables. It may be possible that a greater number of patients in the low-risk category had been exposed to an active TB case without their knowledge, and this may explain the relatively high TST and T.Spot positivity in so-called 'low risk' individuals.

We found a trend towards TST being less likely to be positive in patients on immunosuppressants compared with those who were not. Use of the TST as a modality for identifying LTBI in

immunosuppressed patients is not advocated by the BTS guidelines, since previous studies have suggested the possibility of false negative results.^{11–22} Previous studies have suggested that IGRAs, such as T.Spot, may be less affected by immune suppression, specifically in the context of HIV-infected patients,²³ and may also correlate better with LTBI risk factors in patients with inflammatory disorders taking immunosuppressants.¹⁷ In keeping with this, we found that T.Spot positivity was unaffected by immunosuppression in our cohort.

We still observed 36 patients (22.9%) who had a positive TST result despite immunosuppressant therapy. A potential known confounder of the TST is the possibility of false positive results, particularly in those with prior BCG vaccination or exposure to environmental mycobacteria.^{24–25} However, patients classified as low risk, according to the BTS tables, should be expected to

Table 3 Evaluation of yield of each test individually and combinations of tests

Approach	Number of patients identified for chemoprophylaxis (%)	Number of patients missed (would have been identified via other methods) (%)	Sensitivity versus triple combination testing (%)
Single test			
Risk factor approach alone	27 (19.7)	39 (28.5)	40.9 (29.0–53.7)
T.Spot positive alone	25 (18.2)	41 (29.9)	37.9 (26.2–50.7)
TST positive alone	31 (22.6)	35 (25.5)	47.0 (34.6–59.7)
Double test combinations			
Risk factor and/or T.Spot positive	48 (35.0)	18 (13.1)	72.7 (60.4–83.0)
Risk factor and/or TST positive	53 (38.7)	13 (9.5)	80.3 (68.7–89.1)
T.Spot positive and/or TST positive	47 (34.3)	19 (13.9)	71.2 (58.7–81.7)
Triple test combination			
Risk factor and/or T.Spot positive and/or TST positive	66 (48.2)	–	–

Data shown as n (% of total cohort 137) or sensitivity (95% CI). TST, tuberculin skin test.

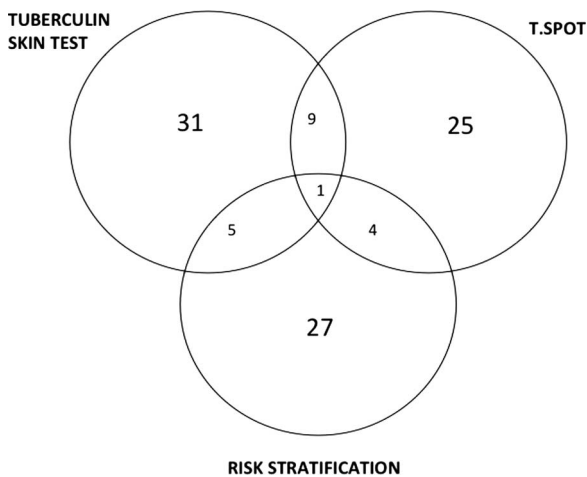


Figure 2 Overlapping yield for tests when mutually positive.

have low rates of TST positivity and, as previously discussed, the increased rate of positivity may be explained by higher regional endemic rates of TB in London than the national UK rates.

Previous studies have correlated increasing sizes of Mantoux reaction to increased risk of TB reactivation.²⁶ Furthermore, any TST positivity in the context of immunosuppression may be considered relevant.⁹ Studies have also shown that IGRAs have a higher positive and negative predictive value for progression to active TB compared with the TST.^{27–28} To date, the risk of reactivation according to TST or IGRA results, specifically in immunosuppressed patients, has not been extensively evaluated prospectively, except for one small study in patients with HIV.²⁹ There are no existing studies evaluating the predictive value of the BTS risk factor approach for LTBI reactivation.

In our low-risk subgroup, the median TST reaction size was 20 mm, with 14 out of 26 patients having strongly positive (≥ 20 mm) results. Of these 14 patients, 5 (35.7%) had no history of previous BCG vaccination. It is difficult to justify giving these patients TNF- α antagonist therapy without prior treatment with chemoprophylaxis, despite the poor correlation with T.Spot positivity in this group. Some guidelines advocate use of lower TST-positive thresholds (eg, >5 mm regardless of prior BCG in the context of immunosuppression.^{9–20}) This would have led to an even greater number of patients requiring therapy in our cohort (additional 25 patients). Our approach is to use standard thresholds with correction for prior BCG, to try

and reduce the number of patients treated unnecessarily for false positive results. However, if either risk stratification or T.Spot is positive in the context of a negative TST according to these thresholds, we recommend chemoprophylaxis.

Overall, we advocate a two-step triple testing approach to screening prior to TNF α antagonist therapy, given that it identifies more patients requiring chemoprophylaxis than any other single test or double combination method. Similar strategies have previously been postulated,^{30–32} and our study offers supportive data for such approaches. Triple testing offers increased sensitivity to detect potential cases of LTBI and, although false positives may be more likely, we have no prognostic data for these tests in this setting. We believe that the risk associated with LTBI reactivation far outweighs the potential risks associated with therapy-induced hepatotoxicity, especially if adequate monitoring is in place.³³ The BTS guidelines assume an equivalence of clinical significance between these two complications. Notably, despite a higher number of patients being treated with chemoprophylaxis in our study than by recommended algorithms, we only observed treatment-limiting hepatotoxicity in two patients (3.1%). This is comparable with rates of drug-induced hepatotoxicity reported by other studies of rifampicin and isoniazid chemoprophylaxis for LTBI,³⁴ and therefore, in the current study, our strategy did not appear to lead to significantly increased risks of hepatotoxicity. Previous studies have also reported low rates of drug-induced hepatotoxicity in a similar setting.³⁵

Our study has limitations. First, the absence of a ‘gold standard’ for the diagnosis of LTBI makes it impossible to determine sensitivities and specificities for the screening methods evaluated, and the prognostic values of the risk factor approach, TST and IGRA in the setting of immunosuppression are unclear. A prospective follow-up study of patients classified as high or low risk according to the BTS tables is required for further evaluation. Second, our study has been carried out in an urban, ethnically diverse region and may not be applicable to other regions. Some authors advocate tailored screening strategies depending on the prevalence of TB disease and whether BCG is frequently used in the area.³² There are no existing studies that compare strategies in low-prevalence and high-prevalence areas.

In summary, performing a TST and T.Spot in patients on immunosuppressants prior to commencement of TNF- α antagonist therapy gives an additional yield of potential LTBI compared with use of risk stratification tables alone. Our results suggest that use of all three screening modalities gives the highest yield of patients potentially requiring chemoprophylaxis. Larger independent validation of this method is required along with development of more accurate composite risk-prediction models incorporating predictive biomarkers and other clinical risk factors.

Table 4 Evaluation of yield of T.Spot and tuberculin skin test (TST) in patients categorised as low risk

	Number of patients identified for chemoprophylaxis (%)	Number of patients missed (would have been identified via other methods) (%)	Sensitivity versus double testing combination (%)
T.Spot +ve	21 (19.1)	18 (16.4)	53.8 (37.2–69.9)
TST +ve	26 (23.6)	13 (11.8)	66.7 (49.8–80.9)
T.Spot and/or TST +ve	39 (35.5)	–	–

Data shown as n (% of low risk sub-group 110) or sensitivity (95% CI).

Contributors Conception and design: AS, SaS, AK, AL, MW, OMK. Data collection: AS, KM, PLM, DWC, PMG, SuS, AK. Analysis and interpretation: AS, SaS, MW, OMK. Drafting and editing manuscript: all authors. OMK is guarantor for the study.

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Competing interests Professor Lalvani is inventor for patents underpinning T-cell-based diagnosis. The ESAT-6/CFP-10 IFN- γ ELISpot assay was commercialised by an Oxford University spin-out company (T-SPOT.TB®). Oxford Immunotec Ltd, Abingdon, UK) in which the University of Oxford and Professor Lalvani have minority shares of equity and royalty entitlements.

Ethics approval Imperial College JRO.

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ONLINE SUPPLEMENT

The 2005 British Thoracic Society recommendations for TB screening in patients schedule for anti-TNF treatment

The BTS guidance document was published in 2005 and outlines an algorithm to provide guidance for screening of patients prior to commencement of TNF- α antagonist therapy.

The first consideration is whether the patient has symptoms of active TB, previous history of TB or abnormal chest radiograph consistent with prior or active TB. In such cases, a full work-up for active TB is recommended and the following recommendations are made:

-If the patient is confirmed to have active TB, it is recommended that they receive 6 months duration of standard quadruple therapy and start TNF- α antagonist therapy after at least 2 months

-If active TB is excluded, but the patients still has a history of previous TB or abnormal chest radiograph consistent with previous TB, an enquiry should be made about whether adequate chemotherapy was received. If adequate chemotherapy was received, it is recommended to monitor the patient during TNF- α antagonist therapy and reassess if symptoms develop. If adequate chemotherapy was not received, it is recommended to exclude activity with 6 months treatment if evidence of active disease or chemoprophylaxis for inactive disease.

If the patient has no symptoms of active TB/previous history of TB/abnormal chest radiograph, the next consideration is whether they are on immunosuppressant treatment. If this is the case, the algorithm states that the TST is unreliable, should not be performed and patients should be stratified for TB risk (see below)

In patients who are not on immunosuppressant treatment, a TST is recommended with interpretation based on presence or absence of prior BCG.

Tables to guide risks of TB and drug-induced hepatitis from chemoprophylaxis

In patients who require stratification for TB risk, it is recommended to consult tables contained within the guideline that allow calculation of the annual risk of TB disease/100,000 in England and Wales. These tables are based on the premise that the incidence of TB varies markedly within the UK, according to several factors: age, ethnic group and, for those not born in the UK, length of time since first entry. These tables can be consulted to calculate risk of TB for a particular patient and a separate table within the guideline can then be consulted to determine whether this risk exceeds the hepatotoxic risk of chemoprophylaxis /100,000. Chemoprophylaxis is advocated if the risk of TB exceeds the risk of hepatotoxicity. In general, Black Africans aged over 15 years and all South Asians born outside of the UK should receive chemoprophylaxis.

Comparison between patients on Immunosuppressants and those not on immunosuppressants

There were 157 patients taking immunosuppressants at the time of screening. eTable 1 shows characteristics in patients on immunosuppressants and those not on immunosuppressants.

	Patients on immunosuppressants (n=157)	Patients not on immunosuppressants (n=30)	p value
Age (years)	56 (45-66)	42 (34-54)	<0.0001
Male sex	69 (43.9%)	13 (43.3%)	1.0
BCG vaccinated	53 (33.8%)	12 (40%)	0.53
CXR features of previous TB	14 (8.9%)	2 (6.7%)	1.0
Previous treated TB	10 (6.4%)	2 (6.7%)	1.0
High risk according to BTS	34 (21.7%)	6 (20.0%)	1.0
T Spot positive	35 (22.3%)	7 (23.3%)	1.0
T spot indeterminate	1 (1.2%)	0 (0%)	1.0
TST positive	36 (22.9%)	12 (40.0%)	0.07
T spot and TST both positive	14 (8.9%)	4 (13.3%)	0.50
Tspot or TST positive	57 (36.3%)	15 (50%)	0.21
Active TB	2 (1.2%)	0 (0%)	1.0

Data presented as n (% of group) or median (IQR)

Proposed modified algorithm

eFigure 1 shows the current BTS screening algorithm and a proposed modified algorithm based on the findings of the current study.

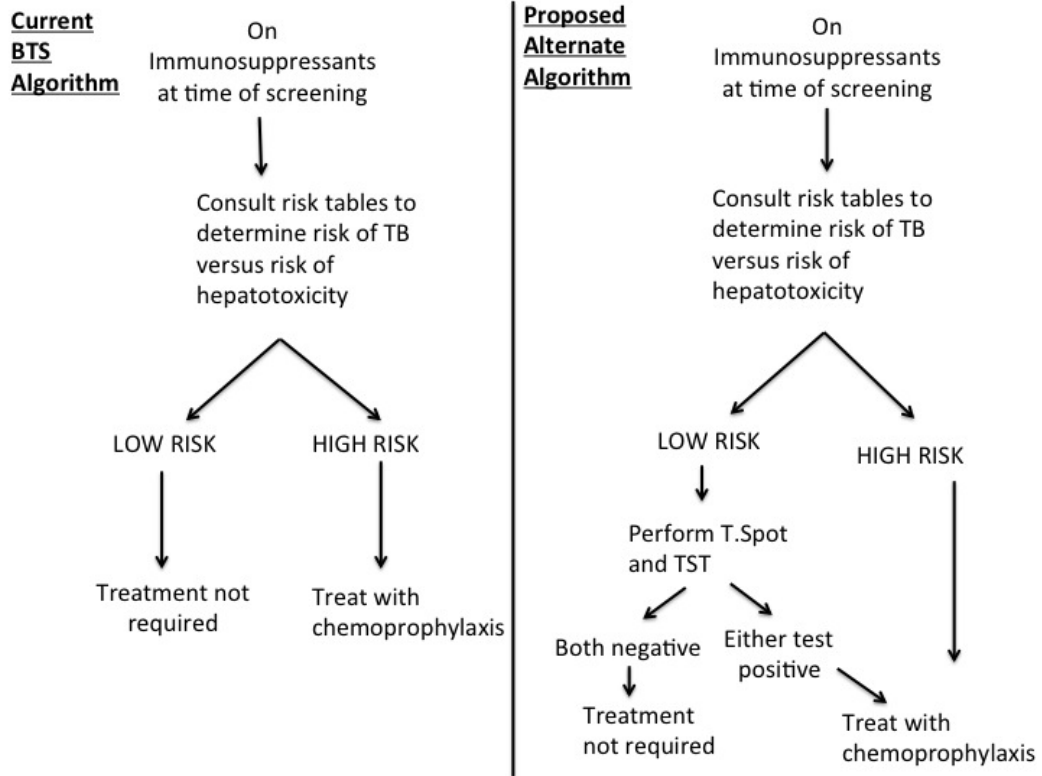


Figure 1: BTS Algorithm and Proposed modified algorithm