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Clinical Study

Targeted Screening for Latent TB Infection prior to Biologic Therapy to Improve Patient Safety and Reduce Costs: A Prospective Observational Study

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Objective. Our current practice of screening for latent TB infection (LTBI) using universal T-SPOT assays is not in line with British Thoracic Society (BTS) recommendations. We set out to determine the clinical benefit and cost effectiveness of blanket TSPOT.TB (T-SPOT) testing as a screening tool for patients awaiting anti-TNF-α therapy. *Methods*. 130 consecutive rheumatology patients were investigated for LTBI before commencing anti-TNFα therapy at Gartnavel General Hospital, Glasgow, an area of low TB prevalence and high BCG vaccination. Chest radiograph and clinical interview were used to identify risk factors for LTBI. The annual risk of TB was calculated using tables from BTS recommendations and then compared to the risk of drug-induced hepatitis. All patients were given a T-SPOT according to current local policy. Indeterminate T-SPOTs were recorded and repeated. *Results*. For 130 patients, a total of 160 tests were required resulting in a cost of £24,000. 99 (76%) patients had no TB risk factors and a total of 22 repeat tests were required before returning negative results. This equates 121 T-SPOTs and potential cost savings of £18,150. *Conclusion*. In the absence of risk factors for TB and an abnormal chest radiograph, the use of T-SPOT as a first line test for LTBI may result in unnecessary risk of TB chemoprophylaxis-induced hepatitis, increased costs, and a delay in early anti-TNFα therapy.

1. Introduction

It has been estimated that a third of the world's population has been exposed to tuberculosis (TB); however, it is well established that only a minority of these individuals ever develop active TB infection. When an individual is infected with the causative organism of TB, *Mycobacterium tuberculosis* (*M. tuberculosis*), the bacilli are believed to exist in a subclinical state with minimum replication, in which they are unable to produce active disease. However, upon a shift in the person's immunological status the bacteria are able to multiply further resulting in disease, which manifests as active TB [1, 2]. It is estimated that there is a 10% lifetime risk of progressing to active infection and patients with latent TB infection (LTBI) may experience reactivation decades after exposure.

Due to the central role of TNF-α in the pathogenesis of chronic inflammatory disease, its inhibition with anti-TNF-α agents has revolutionised the treatment of a broad spectrum of rheumatic diseases such as rheumatoid arthritis (RA), psoriatic arthritis, and ankylosing spondylitis. However, TNF-α also has an essential role in host defence mechanisms, and, as such, therapeutic inhibition of TNF-α may increase the risk of opportunistic infections, in particular, TB [3]. The increased incidence of TB infection in patients receiving anti-TNF-α agents is a continued concern for rheumatologists, particularly as the use of biologic therapies is increasingly popular. The fivefold increased risk of TB following commencement of anti-TNF-α treatment [4, 5] is presumed to stem from the adverse effects of TNF-α inhibition on granuloma formation and maintenance, which is important for compartmentalising *M. tuberculosis* bacilli during infection [6–8].

LTBI is by definition an asymptomatic condition and as such steps must be taken in order to identify LTBI in patients at risk of reactivation. The two main categories of diagnostic TB tests currently available are the tuberculin skin test (TST)

Table 1: Risk factors for prior TB exposure.

Close contact with individuals known to have TB including
(i) family members
(ii) people sharing a living space
Birth or extended residence in a country with a high prevalence of tuberculosis
History of living or working within congregate settings where tuberculosis is more common including the following:
(i) prison
(ii) homeless shelters
(iii) healthcare environments where TB patients are treated
History suggestive of prior LTBI diagnosis including the following:
(i) previous positive screening tests
(ii) chest radiograph findings associated with prior tuberculosis (i.e., fibronodular opacities)

and the newer interferon-γ release assays (IGRA). The TST is a century-old test that was, until recently, the only diagnostic TB test used in clinical practice. It is normally performed by the Mantoux method and involves the intradermal injection of purified protein from *M. tuberculosis*. However, it is known to give false-positive test results, either due to previous Bacille Calmette-Guérin (BCG) vaccination, immunosuppressant medication or as a result of prior exposure to nontuberculous mycobacteria. False-negative TST results have also been reported in TB infected patients [9]. For this reason the more specific IGRAs tests were developed, such as the T-SPOT.TB (Oxford Immunotec), based on the detection of interferon-gamma (IFN-γ) released by T cells in response to the TB antigens specific to *M. tuberculosis*. The performance of T-SPOT.TB (T-SPOT) is consequently not influenced by previous BCG vaccination. The T-SPOT assay received Food and Drug Administration premarket approval in July 2008 and involves a simple blood test. Due to its high sensitivity (96%) and specificity (99%), the T-SPOT assay is used widely as part of the screening process for TB therapy [10]. However, IGRAs are more costly and may have a reduced sensitivity in immunosuppressed individuals [11].

Given the proven increased risk of TB activation, screening patients for LTBI should clearly take place before starting long-term immunosuppressive therapy. However, there is less clarity as to what the optimal screening strategy should be and no gold standard exists. Nevertheless, all screening strategies must take into account that the prophylactic therapy aimed at eradicating tuberculosis bacilli and reducing the likelihood of subsequent reactivation of disease is associated with a low, but not insignificant, risk of hepatotoxicity. The most recent recommendations from the British Thoracic Society (BTS) were published in 2005 before the advent of IGRAs. These guidelines do not recommend routine skin testing because of its reduced sensitivity in a setting of immunosuppression, including corticosteroid use [12]. Instead, the recommendation is that an individual risk assessment should be carried out for each patient and only when the annual risk of TB is greater than the risk of drug-induced hepatitis is chemoprophylaxis indicated [4].

As well as discussing current screening methodologies, this paper reports the results of a prospective observational study of 130 patients screened for LTBI prior to commencing anti-TNF-α treatment, at Gartnavel General Hospital, Glasgow, UK. In particular, we are questioning the clinical benefit of blanket T-SPOT testing over current BTS recommendations in the absence of risk factors for TB infection. Targeted TSPOT seems to be the best option, since universal screening using this method may result in unnecessary delay in early anti-TNF-α therapy and increase cost. We also aim to investigate the use of test for LTBI in this group in relation to the risk to patients of TB chemoprophylaxis-induced hepatitis.

2. Methods

Following our previous retrospective study [13], we performed a prospective observational study on 130 consecutive rheumatology patients who were investigated for LTBI prior to commencing anti-TNF-α therapy at Gartnavel General Hospital, Glasgow. Glasgow is an area of low TB prevalence and high BCG vaccination usage. The patients were seen between March 2010 and July 2012. All patients had risk stratification in line with the most recent BTS guidelines, which advocate that all candidates being considered for anti-TNF-α therapy should be screened for risk factors (Table 1). In addition to these risk factors, the risk of TB exposure also increases with age. Patients gave an extensive clinical history looking for the presence of these risk factors and details of their ethnic origin, place of birth, and number of years resident in UK were recorded. All patients also received a chest radiograph (CXR) to look for changes suggestive of TB. The BTS guidelines state that a diagnostic test would not add benefit for those with a normal CXR but rather that the individual patient data should be used to carry out a risk assessment to determine the annual risk of TB in these patients. However, all patients in this cohort did received a T-SPOT blood test as per the current local policy. The patient characteristics and the results of the tests performed are summarised in Table 2.

The patients were stratified into four age categories according to age (15–34, 35–74, 75–84, and ≥75). For each patient, the annual risk of TB was calculated using the appropriate table provided in the BTS recommendations [4]. This

Table 2: The patient characteristics and results of the test performed.

Characteristic	*N*	%
Gender		
Female	45	34.6
Male	85	65.4
Age (years)		
15–34	21	16.2
35–54	47	36.2
55–74	53	40.8
>75	9	6.9
Place of birth		
UK	124	95.4
Outside UK	6	4.6
Ethnic origin		
White	124	95.4
Black	1	0.8
ISC	3	2.3
Other	2	1.5
BCG vaccination		
Present	100	76.9
Absent	27	20.8
Uncertain	3	2.3
Self-reported history of TB contact		
Yes	21	16.2
No	109	83.8
TSPOT result		
Positive	5	3.8
Negative	125	96.2
Chest X-ray		
Normal	126	96.9
Abnormal	4	3.1

($n = 130$) (ISC: Indian subcontinent).

risk was then compared to the risk of hepatitis and a decision was recorded based on the benefits over the risks of TB prophylaxis to evaluate patients with a normal CXR. This enabled a comparison to be made between evaluation of patients by the current local policy of routine T-SPOT testing and that of risk stratification recommended by the BTS.

3. Results

The total cohort consisted of 130 patients with an average age of 53 (range = 20–87 years; SD = 15.62) and a female to male ratio of approximately 2 : 1. No patients reported any symptoms suggestive of TB or any past history of TB infection. The majority (95%) of the patients in the cohort were white and UK born. Three patients (2%) were from the Indian subcontinent, one (1%) was black African, and two (2%) were of other ethnic origins.

Only four of the 130 patients had an abnormal CXR but all four had a negative TSPOT result. All four patients were UK born and had no previous history of TB contact. They were all thoroughly investigated and active TB was ruled out. These patients proceeded to receive anti-TNF-α treatment without the need for prophylactic therapy (Table 3).

Table 3: Table showing number of patients with positive T-SPOTs according to patient risk factors.

Risk factors	Number of patients	Positive	Negative
None	99	2	97
Hx of TB contact	21	3	18
Ethnicity	6	0	6
Abnormal chest X-ray	4	0	4

Of the 130 patients, 99 (76%) were UK born with no risk factors for LTBI and a normal CXR. Therefore, the only risk factor altering their annual risk of TB was their age. The risk of prophylaxis-induced hepatitis was higher than the risk of TB in these patients, and, therefore, the risk/benefit conclusion would be observation (Table 4). Of these 99 patients only two patients had a positive T-SPOT and subsequently received prophylactic treatment. 21 (16%) of the 130 patients had a history of TB contact. All were UK born with normal CXRs. Of these patients three had a positive T-SPOT result and received chemoprophylaxis (Table 3).

There were six patients in the cohort who were South Asian, Black, or, of other ethnicity (Table 5), all of whom reported no previous TB contact. All six patients were resident in the UK for more than five years and all patients had a normal CXR. Three of these six patients had indeterminate T-SPOT results but all eventually had a negative test result. The BTS says, in general, black African patients aged over 15 years and all South Asians born outside the UK should be considered for chemoprophylaxis in any case. As such, these patients qualified for TB prophylaxis as per BTS risk-benefit calculation. However, as these patients had a normal CXR and a negative T-SPOT they did not receive chemoprophylaxis in line with current local policy (Table 5).

Although indeterminate results are normally fairly infrequent with T-SPOT, they may occur more frequently in immunosuppressed patients. In this cohort 22 patients (13%) had an indeterminate T-SPOT result in the first instance and as a result the test needed to be repeated. Of these patients two needed to be repeated twice and three patients needed a third repeat T-SPOT test to be carried out before a valid result was returned. All patients eventually had a negative T-SPOT result.

4. Discussion

Since the first report in 2001, from Keane et al. [14], showing an increased risk of reactivation of LTBI following anti-TNF-α therapy, there has been growing evidence that anti-TNF-α agents are associated with rates of TB above that of the background UK population. Evidence has shown that there is variation in TB incidence across the anti-TNF-α agents. When compared to etanercept, studies have indicated that both infliximab and adalimumab are associated with a higher incidence of TB infection, with infliximab being associated with a faster onset of TB [5, 15–17].

Table 4: Risk stratification for patients with a normal chest X-ray and no additional risk factors for TB exposure (risk statistics derived from the BTS guidelines) [4].

Age group (years)	Number of patients	TB risk adjusted ×5 for anti-TNF effects/100 000	Risks of prophylaxis/100 000	Risk/benefit conclusion
15–34	19	10	278	Observation
35–54	34	20	278	Observation
55–74	40	35	278	Observation
>75	9	55	278	Observation

Table 5: Risk stratification for patients not born in the UK.

Number of patients	Ethnicity	TB risk adjusted ×5 for anti-TNF effects/100 000	Risks of prophylaxis/100 000	Risk/benefit conclusion
1	Black African	1570	278	Prophylaxis
3	ISC	540	278	Prophylaxis
2	Other	195	278	Observation

ISC: Indian subcontinent.

Due to the absence of a current gold standard for LTBI diagnosis, screening strategies and guidelines vary across different regions and patient groups, providing conflicting recommendations about the place of diagnostic screening tests. The recent National Institute for Health and Clinical Excellence (NICE) guidelines on the clinical diagnosis and management of TB contain only a small section on managing LTBI in immune-suppressed patients. It states that all patients should receive an IGRA alone or alongside a concurrent TST and following a positive result, a clinical assessment for active TB should be carried out followed by consideration of the need for LTBI treatment [18]. However, NICE provides no specific focused recommendation for patients taking or being screened for biologic therapy. In the United States, the TST is still routinely performed in all patients; however, the guidance emphasizes the importance of starting the screening process by taking a detailed history for TB risk factors. In Spain, there is a successful two-step TST screening process in place, which has reduced anti-TNF-α associated TB rates by 85% [19]. However, in Switzerland, all patients receive an IGRA [20]. The Canadian recommendations say that IGRAs may be used if the initial TST result is negative and there is concern about LTBI in an immune-suppressed patient [21]. As discussed, the recommendations from the BTS are different again, instead recommending the practice of risk stratification in biologic therapy candidates.

Following our previous retrospective study [13], we identified the need to determine the cost effectiveness of T-SPOT testing as a screening tool adding further to diagnostic and management decisions over and above current BTS recommendation of risk stratification. Since the BTS guidelines were written, IGRAs have become more widely available and evidence of their benefit over TST has increased. The sensitivity of IGRA and TST tests in the setting of immunosuppression is still debated. It has been suggested that IGRAs may be adversely affected by immunosuppression, giving a higher proportion of indeterminate results [22]. If two consecutive indeterminate IGRA results occur, clinicians are recommended to suspect anergy and are advised to rely on clinical history and investigation results [21]. Anergy is defined as a T-cell hyporesponsiveness to a previously exposed antigen as a result of immunosuppression, which may result in a false-negative TST or IGRA result [23]. In our cohort, indeterminate T-SPOT results clearly caused a delay to the commencement of early treatment with anti-TNF-α therapy as well as an increased total number of tests needed, resulting in an increased cost. Therefore, for 130 patients a total of 160 tests were required, at a cost of approximately £150 per test. This is a total cost of around £24,000 for these patients.

Isoniazid has been the front-line antituberculosis medication since 1952 but the hepatotoxicity associated with this drug ranges from asymptomatic elevation of transaminases to frank liver failure. It has been reported that up to 20% of patients who take Isoniazid experience mild, usually subclinical, hepatic injury. This is often evidenced by mildly elevated serum aminotransferases and liver biopsy shows minor hepatocellular damage [24, 25]. In UK born patients, lacking TB risk factors, it seems reasonable to presume such patients are uninfected and thus should be simply observed according to BTS risk stratification. As even with a positive T-SPOT the risk of TB chemoprophylaxis-induced hepatitis is higher than that of reactivation of TB. In this cohort, 99 patients had no risk factors that indicated the need for a T-SPOT according to the BTS guidelines. In addition, a total of 22 repeat tests were required for this group of patients before they all returned a negative result. This equates to a total of 121 T-SPOTs and a potential cost saving of £18,150 when targeted screening is followed instead of blanket T-SPOT testing. This is concerning given the current economic climate and the recent target announced for the NHS to save £15–20 billion in costs by 2014 [26].

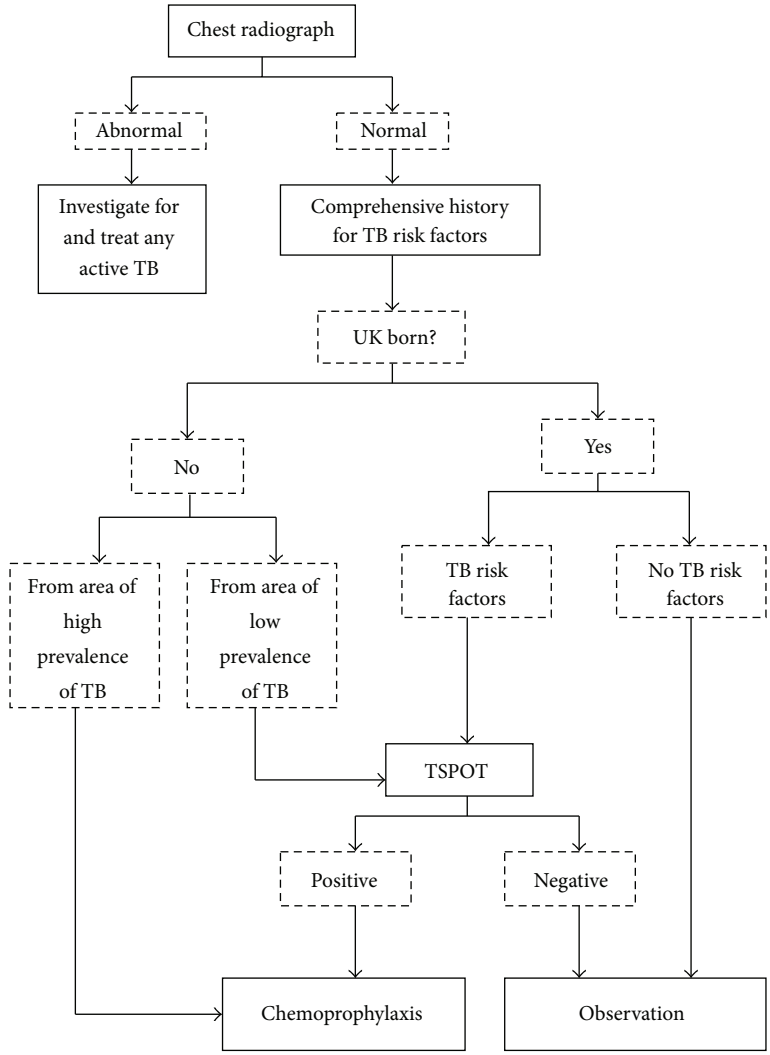

Figure 1: Authors' preferred screening strategy.

Given the importance of early effective treatment in inflammatory arthritic conditions such as rheumatoid arthritis, the delay resulting from T-SPOT testing and retesting where necessary, may compromise patient safety and prolong patient suffering before the start of effective treatment. In addition, following a diagnosis of LTBI, anti-TNF-α treatment can be delayed between four weeks and, preferably, until completion of a full course of antituberculosis treatment. Therefore, if patients are unnecessarily treated for LTBI, this further delays effective therapy.

The current local policy designates that, in the presence of a negative T-SPOT and a normal CXR, prophylactic treatment is not needed. However, three of the six patients born outside the UK were from areas with a high disease burden (i.e., Sub-Saharan Africa and Southeast Asia). These patients have a high likelihood of exposure and as such negative screening results should be treated with suspicion and empiric chemoprophylactic therapy should be considered. For those individuals with an abnormal CXR, appropriate investigations should be carried out in order to exclude active TB. For these patients and for those with a history of prior TB that was not adequately treated, chemoprophylaxis is recommended before commencing anti-TNF-α treatment.

The authors' preferred screening strategy, based on the results of this analysis, is illustrated in Figure 1. In essence, if a patient has risk factors for LTBI, a T-SPOT test should be performed. It should also be noted that screening does not act as a surrogate for clinical judgment and clinicians should use screening strategies only as an aide to diagnosis given the patients prior probability of TB exposure. No screening strategy is perfect and patients without risk factors, as well as patients correctly diagnosed and treated with TB chemoprophylaxis, can still develop TB while on anti-TNF-α therapy [23]. Therefore, patients must always be monitored for symptoms suggestive of TB while taking anti-TNF-α therapy and appropriate interventions should be taken. It is clear that there is a need for updated, specific recommendations for screening patients for LTBI prior to the commencement of biologic therapy in order to incorporate the recent developments in screening tests. Early arthritis clinics have been set up to rapidly gain control of patients' arthritis, yet we seem determined to put obstacles in the way

of prompt treatment. Targeted T-SPOT testing may be the answer but will still require further investigation. The debate for targeted T-SPOT testing versus blanket screening needs to be addressed not only to improve patient safety, but also to reduce morbidity and time off work and for increasing cost effectiveness, efficiency, and rapid control of symptoms.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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