Does an interferon-gamma release assay change practice in possible latent tuberculosis?

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Summary

Background and Aims: Suspected latent tuberculosis infection (LTBI) is a common reason for referral to TB clinics. Interferon-gamma release assays (IGRAs) are more specific than tuberculin skin tests (TSTs) for diagnosing LTBI. The aim of this study is to determine if IGRA changes practice in the management of cases referred to a TB clinic for possible LTBI.

Design and Methods: A prospective study was performed over 29 months. All adult patients who had TST, CXR & IGRA were included. The original decision regarding TB chemoprophylaxis was made by TB team consensus, based on clinical history and TST. Cases were then analysed with the addition of IGRA to determine if this had altered management. An independent physician subsequently reviewed the cases.

Results: Of 204 patients studied, 68 were immunocompromised. 120 patients had positive TSTs. Of these, 36 (30%) had a positive QFT and 84 (70%) had a negative QFT. Practice changed in 78 (65%) cases with positive TST, all avoiding TB chemoprophylaxis due to QFT. Of the immunocompromised patients, 17 (25%) underwent change of practice. No cases of active TB have developed.

Conclusions: This study demonstrates a significant change of clinical practice due to IGRA use. Our findings support the NICE 2011 recommendations.

Introduction

Latent tuberculosis infection (LTBI) is the presence of mycobacterium tuberculosis (TB) without any symptoms of active TB. Detection of LTBI is important in clinical practice and public health medicine due to its associated risk of progression to active TB. An immunocompetent individual with LTBI has a lifetime risk of progression of approximately 5–10%.1 The greatest chance of progressing to active disease is within the first 2 years after infection, and this risk of progression is greater in the immunocompromised population.2

Crucially, LTBI can be potentially eradicated with TB chemoprophylaxis. The National Institute of Clinical Excellence UK guidelines (NICE 2011) recommend a course of 6 months isoniazid or 3 months rifampicin + isoniazid in combination for management of LTBI.3 International healthcare authorities advocate similar regimens.4 Such prolonged therapy presents significant burden for patients, costs for health services and risk of complications, e.g. approximately 5% of patients may develop drug-induced hepatotoxicity.3–7

Suspected LTBI is a common reason for referral to specialist TB clinics. This is becoming increasingly frequent since the introduction of newer immunomodulatory drugs, such as Anti-TNFα agents. Traditional practice in management of possible
LTBI, in keeping with previous NICE guidelines, has been risk assessment through clinical history (country of origin/contacts/occupation/exposure/immune status/prior Bacille Calmette-Guerin (BCG) vaccination, chest X-ray (CXR) and Mantoux tuberculin skin test (TST). TST has well-recognized limitations including a significant false-positive rate and poor sensitivity in immunocompromised individuals whereby TST response can become inhibited.8–10 In light of emerging evidence, NICE recently updated their recommendations regarding the role of interferon-gamma release assay (IGRA) testing in the diagnosis of LTBI.5 The 2011 guidelines recommend offering IGRA testing to those with positive TST or in whom TST may be less reliable, for example, BCG-vaccinated people, immunocompromised patients and new entrants from high incidence countries. A similar statement had been made in the NICE 2006 guidelines (now superseded by the 2011 version).

IGRAs have been demonstrated to have comparable sensitivity to TST for LTBI, but their strength appears to be in their superior specificity, particularly in BCG-vaccinated populations.11,12 IGRAs have also been shown to correlate better with known TB risk factors, than TST.13 Recent modelling studies have investigated cost-effectiveness of screening for LTBI with IGRAs instead of or in combination with TST. Economic model studies have suggested that the combination of TST + IGRA may be more cost-effective than TST alone.14,15

The aim of this study is to determine whether an IGRA changes clinical practice in the management of cases referred to a TB specialist clinic for possible LTBI.

Design and methods

A prospective study was performed in adult patients referred to a TB respiratory specialist clinic for possible LTBI over a 29-month period (July 2008–November 2010) since the introduction of IGRA. The IGRA used by the local laboratory service was Quantiferon-TB Gold In- Tube® (QFT; Cellestis, Australia). The study design was originally based on the NICE 2006 guideline, suggesting consideration of IGRA in testing for LTBI. As the tertiary regional respiratory TB centre, all suspected regional TB cases, close contacts and patients with positive TST are referred to the service from other sources. These sources include primary care, occupational health, BCG vaccination clinics, travel clinics and other medical specialties (it should be noted that not all patients presenting to occupational health, BCG vaccination clinics etc. attended the respiratory TB specialist clinic; this clinic is restricted to those who were TST positive or had other suggestive clinical features/risk factors). The remaining patients were referred from medical specialties, mainly rheumatology, dermatology and gastroenterology, using disease modifying drugs.

Every patient older than 16 years who had all three interventions (CXR+TST+QFT) during this period was included in the study. The TST was interpreted according to UK Department of Health ‘Immunisation against infectious disease - The Green Book’ 2010, whereby TST is considered positive with an induration diameter ≥6 mm in the absence of prior BCG vaccination and an induration diameter ≥15 mm if previously vaccinated with BCG.16 For further characterization, an additional class of ‘strongly positive TST’ was added at ≥30 mm induration diameter. Upon presentation to TB clinic, all patients underwent HIV testing, as per standard regional protocol.

The original decision of whether to treat patients with TB chemoprophylaxis had been made at the time of presentation by consensus decision within the TB team (consultant TB physician + respiratory specialty registrar + specialist TB nurse), based on clinical history and TST alone. Each case was then analysed with the addition of QFT. A change of practice was defined as ‘the patient avoiding or receiving TB chemoprophylaxis on the basis of QFT’ (Figure 1). In an attempt to enhance the objectivity of the decisions regarding change of practice, an independent, consultant infectious diseases physician (blinded to the previous TB team decision) reviewed the cases, following the same protocol. The cases were then discussed between the two independent teams to determine whether any discrepancies in decisions regarding change of practice occurred. All known active cases of TB in the region attend the clinic in which the study was performed. The computerized hospital microbiological and radiological network allowed the clinical research team access to all regional case results sent from both primary and secondary care. In this manner, the team would be made aware of any patients developing active TB.

For analysis purposes, the cases were divided into two separate cohorts: (i) immunocompetent (i.e. no known reason to be immunocompromised, e.g. no immunomodulatory medications and no HIV co-infection) and (ii) immunocompromised (i.e. known to have been prescribed immunomodulatory drugs within the preceding 6 weeks, HIV co-infection, etc.). The proportion of each cohort that underwent a change of practice (as defined earlier) was determined.
As a further exercise, each case was analysed on the presumption of QFT result being a ‘gold standard’, i.e. that a patient with a positive QFT result should be given chemoprophylaxis and a patient with a negative QFT result should avoid chemoprophylaxis. These outcomes were compared with the original clinician-based approach.

Results
A total of 204 patients were included in the study (mean age: 42.3 ± 16.1 years). Patient characteristics and distribution according to referral source are presented in Table 1. Of 204 patients, 136 were considered immunocompetent and 68 patients considered immunocompromised. None of the immunocompromised group tested positive for HIV co-infection at the time of presentation. Each of the 68 immunocompromised patients had been prescribed immunomodulatory medications (including methotrexate, prednisolone, ciclosporin and azathioprine), with 13 patients on a combination of agents.

One hundred and twenty patients had a positive TST, with 84 negative TSTs (or TST within normal limits). This high frequency of positive TSTs (59%) likely represents the pattern of referrals to TB clinic from sources outwith the hospital medical specialties (e.g. TST-negative occupational health patients with no other suggestive history do not attend our clinic).

Of the TST-positive group, 36 had a positive QFT and 84 had a negative QFT. Change of practice due to QFT occurred in 78 (65%) of the 120 TST-positive cases (immunocompetent + immunocompromised). All 78 patients avoided chemoprophylaxis due to a negative QFT. Change of practice occurred in 8 (9.5%) of the 84 TST-negative (or within normal limits) cases. These changes of practice were split between avoidance and receipt of chemoprophylaxis: five and three cases, respectively.
In the immunocompetent group (Figure 2), change of practice due to QFT occurred in 69 (51%) of 136 patients. The majority (67) of these patients avoided chemoprophylaxis due to QFT, but two patients received chemoprophylaxis. Discussion of these cases is shown in Figure 3.

In the immunocompromised group (Figure 4), change of practice due to QFT occurred in 17 (25%) of the 68 patients. Fourteen of these patients avoided chemoprophylaxis and three received chemoprophylaxis due to QFT (Figure 3).

One immunocompromised patient’s QFT result was indeterminate initially. A repeat QFT was negative. No change of practice occurred for this patient. No other cases in the study group had an indeterminate result. No other QFTs were repeated in the study.

There was no discrepancy between the decisions of the original TB team and those of the independent infectious diseases physician, although both followed the decision-making algorithm (Figure 1).

Comparison of a presumed gold-standard QFT versus clinician-based approach revealed 12 (6%) discrepant cases, i.e. QFT negative in each case but patient received chemoprophylaxis on the basis of clinician opinion.

There were no QFT-positive cases that did not receive chemoprophylaxis. No local cases of active TB have developed in the study population to date, with a maximum follow-up period of 36 months (16.9 ± 6.9 months).

**Conclusions**

This study was designed to assess whether an IGRA (QFT) changes practice in the management

![Figure 2](image_url) **Figure 2.** Outcomes of immunocomponent patients. Total number of immunocomponent cases with change of practice: 69 of 136 (51%). Key: For * please refer to Figure 3. Strongly positive = TST ≥ 30 mm.

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of cases referred to a TB specialist clinic for possible LTBI.

In the study population, IGRA testing changes practice in the majority of cases who are TST positive. This is demonstrated in both the immunocompetent and immunocompromised cohorts, although more so in the former, whereby change of practice occurred in 67% of patients. All these patients avoided potential anti-TB chemoprophylaxis, with its recognized adverse effects and associated financial and personal costs. This supports the NICE (2011) recommendation to consider

Figure 3. Notable cases—discussion.

Figure 4. Outcomes of immunocompromised patients. Total number of immunocompetent cases with change of practice: 17 of 68 (25%). Key: For ** and *** please refer to Figure 3. Strongly positive = TST ≥ 30 mm.
IGRA testing in people whose TST shows positive results. More than half of the immunocompetent patients in this study underwent change of practice due to IGRA. Interestingly, two immunocompetent + TST-positive patients did not have a change of practice, despite a negative IGRA. Both of these patients were of UK origin, referred from other medical specialties before commencement on biological agents and had chest radiology suggestive of previous tuberculous disease. In both cases, the investigating team elected to offer chemoprophylaxis due to radiological appearances and the assumption of false-negative IGRA tests.

One quarter of the immunocompromised study patients underwent change of practice due to IGRA. Six (13%) TST-negative-immunocompromised patients underwent change of practice. In this group, the change of practice was split evenly between avoidance and receipt of chemoprophylaxis (Figure 4). We note that three TST-negative + QFT-negative patients avoided chemoprophylaxis. Here, the clinicians initially presumed false-negative TST results due to immunocompromised state; however, the addition of negative QFT provided more clinical confidence to avoid chemoprophylaxis and hence changed practice.

The remaining 11 immunocompromised patients with changes of practice were TST positive + QFT negative. All were of British origin, referred from other medical specialties and taking immunomodulatory medications at the time of presentation, with a view to commencement on more aggressive drugs. All 11 cases avoided chemoprophylaxis due to negative QFT results. Here, the authors note the unexpected cohort of four immunocompromised patients with strongly positive (≥ 30 mm) TSTs who tested QFT negative. On closer review, three of these patients were referred from dermatology, whereby the excessive skin test result may be more representative of their skin disorders than indicative of tuberculous disease. The one remaining patient in this group was referred from rheumatology, already on methotrexate, with a history of TB contact and normal radiology. Given the strongly positive TST, the clinical team offered this patient chemoprophylaxis, again on the presumption of a false-negative QFT. In light of this study’s overall results, it may be now argued that this patient could avoid chemoprophylaxis, but, at the time, there was felt to be insufficient evidence to support exclusion of LTBI.

Those receiving chemoprophylaxis on the basis of a positive QFT may be doing so unnecessarily, but this was thought to be safest clinical practice by the investigating team. Although there must always be an acceptance that a small number of patients may receive inappropriate chemoprophylaxis due to positive IGRA, this is thought to represent a significant reduction from the number who may have potentially received unnecessary chemoprophylaxis due to falsely positive TSTs.

Furthermore, we note that four immunocompromised + TST-positive patients did not undergo change of practice (i.e. were still offered chemoprophylaxis) despite negative IGRA. All four patients had normal radiology and were referred from other specialties before commencement on biological agents. Two of these patients were from the dermatological group, discussed earlier, who developed strongly positive TSTs despite current immunomodulatory therapy. The remaining two had both previously demonstrated positive TSTs during childhood, one of whom was from an area of high incidence. These negative IGRA tests were surprising, therefore interpreted as potential false negatives and cautious practice with chemoprophylaxis prevailed.

One patient had an indeterminate initial QFT result. This patient was on a combination of immunosuppressant drugs at the time of presentation. The TST result in this case was 0 mm, and the patient’s CXR was entirely normal. A repeat QFT was negative, and the patient did not receive anti-TB chemoprophylaxis. It was felt that no change of practice occurred due to QFT in this case. This patient was included in the immunocompromised-TST-negative + QFT-negative cohort.

Analysis of the study population from the perspective of QFT as ‘gold standard’ vs. Clinician case review revealed 12 (6%) discrepant cases, i.e. QFT negative in each case, but patient received chemoprophylaxis on the basis of clinical opinion. A distinct pattern emerged here: (i) 8 of 12 cases received chemoprophylaxis on the basis of radiology suggestive of previous TB infection. These cases raise the question of whether too much clinical emphasis is placed on old radiological changes, which could be due to pathology other than TB or, indeed, do these represent false-negative QFT results? (ii) The remaining 4 of 12 cases were identified as the same four immunocompromised + TST-positive patients highlighted earlier, who did not undergo change of practice despite negative IGRA. It was felt that safest practice for each of these cases was to prescribe chemoprophylaxis, raising again the possibility of false-negative QFT results. We believe that this group of 12 discrepant cases highlight the value of real world clinician-based interpretation of IGRA testing in the context of all the other factors of a specific case. Simply relying on IGRA alone could potentially miss a small proportion of true LTBI cases.
The authors recognize that the strength of IGRA tests is predominantly their high specificity, which is superior to TST for LTBI. \textsuperscript{11–13} The nature of LTBI and its variable progression to microbiologically confirmed active TB make assessment of the true sensitivity of IGRA testing difficult. TST results are confounded by many other variables, including previous BCGG vaccination and other environmental mycobacteria. We acknowledge the argument that QFT testing in this study may provide additional, rather than better, information for each patient. However, the aim of the study was to determine whether IGRA changes clinical practice when added to standard protocols. Hence, even the provision of additional information of similar clinical value can enhance confidence in our clinical decision making and is potentially useful.

All known active cases of TB in the region attend the clinic in which the study was performed. All patients referred for assessment before commencement on immunomodulatory drugs have remained within the region. It is possible that some patients (e.g. TB contacts) may have left the area; hence, it is difficult to be completely certain that no cases have developed elsewhere. The computerized regional microbiological and radiological network allows the clinical research team access to all regional case results sent from both primary and secondary care. This facilitates a confident declaration of no cases of active TB developing in our region to date. With no local cases of active TB developing in the study population to date and a maximum follow-up period of 36 months, this appears to be safe practice.

This study is limited to a single centre. Excluding the single indeterminate result, none of the IGRA tests were repeated for confirmation of original results. At the time of writing, there is no gold standard test for LTBI, and, to an extent, the decisions regarding change of practice are subjective. In an attempt to mitigate this, three professionals were involved in the original consensual decision. We believe that the incorporation of an external, blinded reviewer was a reasonable means of improving the objectivity of these complex decisions. We all followed the algorithm described in Figure 1, and, after discussion of the cases, there was 100% correlation between the change of practice decisions of the original team and the external reviewer. This is reassuring.

This study demonstrates that an IGRA test has significantly changed practice in the management of possible LTBI in our clinic population. The outcomes of this study support the NICE 2011 recommendations with respect to TST-positive patients (irrespective of immune status) and immunocompromised patients. The majority of patients who underwent change of practice avoided anti-TB chemoprophylaxis.

There were a small number of discrepant cases between IGRA result and clinical practice, demonstrating the important role of clinician-based interpretation in this complex and controversial area. Further studies are needed.

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