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In routine UK hospital practice T-SPOT.TB™ is useful in some patients with a modest pre-test probability of active tuberculosis||

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Abstract

Objective—to assess the usefulness of the T-SPOT.TB™ interferon-gamma release assay (IGRA), as used in a regional hospital infectious diseases unit in Northwest England, for the diagnosis of active tuberculosis.

Design—Retrospective case series.

Results—T-SPOT.TB™ test was applied to a group of 64 patients, 20 of whom had tuberculosis (mostly extrapulmonary tuberculosis). The T-SPOT.TB™ test had a sensitivity of 83.3% and a specificity of 75% for the diagnosis of active tuberculosis, compared with culture. A positive IGRA approximately doubled the pre-test probability of disease from 0.23 to 0.5. This doubling of probability was true regardless of HIV status, though for HIV+ patients the sensitivity was lower (sensitivity 66.7%, post test probability 0.4 for a positive IGRA result). When extrapolated to the local population the test was most useful for exclusion of disease; post test probability 0.006 (or 1 in 167) for a negative IGRA result.

Conclusion—Although it can add weight to a clinical diagnosis, T-SPOT.TB™ assay is not reliable for the diagnosis of active tuberculosis in a real world setting where the test is often used in patients with smear negative or extra-pulmonary disease. The test is useful for ruling out disease in HIV negative patients.

Keywords

Tuberculosis; Sensitivity and specificity; ELISpot; Interferon-gamma release assay

1. Introduction

In the United Kingdom 9040 tuberculosis (TB) cases were reported in 2009, an increase in incidence of 4.8% compared with 2008 (14.6 per 100,000 of the population) [1]. Of these almost 500 will die.

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Conflict of interest statement

The authors have no conflict of interest to declare.

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The diagnosis of TB remains problematic, adversely affecting morbidity, mortality and efforts to prevent spread. Microscopy using acid fast staining has a sensitivity of approximately 70% [2-4] under ideal conditions, although this is often less due differences in facilities and operator variability [5]. Obtaining a positive culture for *Mycobacterium tuberculosis* (MTB) remains the 'gold standard.' However, there can be a delay of up to two weeks, even using the most advanced automated culture systems [6]. In addition, some cases of TB remain culture negative and in extra-pulmonary TB (particularly CNS TB) microbiological specimens may be difficult to obtain.

Immunological methods for diagnosis rely upon the detection of a specific host response to infection. An adaptive immune signature such as specific antibody or a T cell response is used to indirectly infer the presence of infection. The TB field has given rise to the oldest immune based test in use: the tuberculin skin test (TST). TST detects cellular immunity and is much faster than culture but suffers from both poor sensitivity and poor specificity. In recent years two techniques for the *ex vivo* detection of T cell responses have been applied to TB diagnostics. The T-SPOT.TB™ test uses separated peripheral blood mononuclear cells in an Enzyme Linked ImmunoSpot (ELISpot) IFN γ assay against synthetic peptides of MTB antigens; the Quantiferon™ test uses a whole blood peptide stimulation followed by ELISA for secreted IFN γ . The detection of a pathogen specific immune response does not equate with disease, and this test has been used mainly to infer the presence of latent MTB infection [7,8]. Since the introduction of T cell based assays for MTB infection, several studies [9-21] have investigated their performance for the diagnosis of TB disease in various locations around the world; sensitivities of between 70% and 90% were generally reported (Table 1). These studies have included both patients with and without HIV, usually finding a lower sensitivity in HIV+ patients.

The Liverpool Tropical and Infectious Disease Unit (TIDU) is a significant provider of tuberculosis treatment services within Northwest England, with on average 52 cases of TB each year in the Liverpool local authority area [1,6]. The cohort of tuberculosis patients is mixed and steadily increasing. It now includes a significant sub-Saharan African population as Liverpool was designated an asylum dispersal centre. Furthermore, an ever-increasing HIV positive population cohort has resulted in an inevitable rise in patients with HIV/TB co-infection.

As part of an on-going operational programme assessing TB diagnostics we examined our use of, and the usefulness of, TB ELISpot (T-SPOT.TB™) in our unit (predominantly within the in-patient population) for the diagnosis of TB.

2. Study population and methods

We retrospectively examined the use of the IFN γ release assay (IGRA) for the diagnosis of active tuberculosis in our unit. The T-SPOT.TB™ assay (Oxford Immunotec) was made available in January 2008 and was conducted according to the manufacturer's instructions. The Royal Liverpool and Broadgreen University Hospitals NHS Trust clinical governance committee approved the study. Because this work was undertaken as clinical governance and did not involve any intervention or alteration in care, ethical approval and informed consent were not sought.

2.1. Patients

All patients of the TIDU who had an IGRA performed between January 2008 and October 2009 were included in the study. The selection of patients for this study is shown in Fig. 1. Tests were performed as part of the clinical workup of outpatients or inpatients suspected of having TB, and we did not include patients having IGRA tests to screen for latent or past

MTB infection. The total population of patients with suspected TB in our institution was estimated as all patients who had either a sample processed for mycobacterial culture during the same time period, or an IGRA. Medical records were examined at least six months after the IGRA. Data collected were: IGRA result, age, sex, ethnicity, country of birth, medical history, HIV status, mycobacterial culture results, final diagnosis, outcome and details of anti-tuberculosis treatment. IGRA were conducted and interpreted as per the manufacturer's instructions.

2.2. Diagnosis

The diagnosis of tuberculosis was made if:

1. *M. tuberculosis* was recovered from clinical specimens in the correct clinical context (culture diagnosis).
2. The supervising clinician was sufficiently concerned that the diagnosis was TB to prescribe a full course of anti-tuberculous therapy which resulted in resolution of the clinical illness after at least 6 months of follow up (clinical diagnosis).

Decontaminated non-sterile samples and all sterile samples were cultured in MBBacT bottles in an automated system for 6–10 weeks. All tests were conducted routinely by personnel who were not aware of the study at the time due to its retrospective nature. Microbiological diagnoses were supplemented by molecular methods for early determination of mycobacterial species and rifampicin sensitivity, as previously described [6].

2.3. Analysis

IGRA results were compared with the culture and clinical diagnosis. Sensitivity, specificity, 95% confidence intervals (CI) and likelihood ratios were calculated for all patients and by HIV status using the function `epitests` in package `epiR` in R version 2.9.2 [22]. Post-test probabilities were computed using the odds form of Bayes rule:

$$O(A|B) = O(A) \cdot \Lambda(A|B)$$

where $O(A|B)$ is the post-test odds of disease, $O(A)$ is the pre-test odds and $\Lambda(A|B)$ is the likelihood ratio of the test being positive or negative.

3. Results

3.1. Descriptive analysis

Between January 2008 and October 2009 1171 patients in our institution were suspected of having TB (Fig. 1). Seventy-two patients seen within the TIDU had IGRA performed in this period. Eight patients had equivocal IGRA results rendering the assays inconclusive. (An equivocal result is one of: assay failure (all wells negative including the positive control), high background (negative control well > 10 spots) or a result very close to the assay cut-off.) One patient had a positive result on repeat testing. The remaining seven patients, and one patient for whom TB treatment data were missing, were excluded from the analysis.

Demographic details of the 64 patients in the analysis are described in Table 2. The median age was 36 and 34 (53%) were male. Twenty of 64 patients (31% overall) were HIV positive. The median CD4 cell count in HIV+ patients was 178 cells/ $\times 10^6$ /L (inter-quartile range 87–237). Twenty patients (31%) had a final diagnosis of TB, of whom 11 were culture positive for MTB and nine were clinical diagnoses. Three had pulmonary TB, three had abdominal TB, four had lymph node TB, one had pericardial TB, two had TB meningitis, six

had TB at >1 site (including the lung in three cases) and in one case the site was unknown. Two more patients were treated for TB but did not respond; both were culture negative, showed no evidence of drug resistant MTB, and were considered not to have TB at the end of the study. One further patient was culture positive for MTB (on one specimen) but was not treated because of extensive medical comorbidity and absence of symptoms of TB. Fourteen (70%) of the patients with positive IGRA received TB treatment; nine were culture positive for MTB. Seven patients with TB were IGRA negative; three were culture positive for MTB. Median follow-up (time from IGRA to data collection) was 405 days; no patient on TB treatment or with a diagnosis of TB died.

3.2. Performance of IGRA testing

Mycobacterial culture data were available for 52 out of 64 patients. The sensitivity of IGRA testing for a positive culture of MTB was 83.3% (95% CI 57.9–96.8%) and the specificity was 75% (95% CI 60.5–86.4%). When compared with the clinical diagnosis (for all 64 patients), the sensitivity was 70% (95% CI 49.1–86.4%) and the specificity was 86.4% (95% CI 74.4–94.3%). When compared with the overall clinical diagnosis, therefore, IGRA was less sensitive but more specific (Table 3). In HIV+ patients the sensitivity of IGRA was reduced (Table 3). The sensitivity was 66.7% compared with culture and 42.9% compared with clinical diagnosis. The respective sensitivities for HIV– patients were 80% (culture) and 84.6% (clinical diagnosis). The specificity in HIV+ patients, however, remained comparable with that in HIV– patients (Table 3).

The prevalence of TB in the 64 patients analysed in this study was high, 31% by clinical diagnosis and 23% by culture diagnosis. In all patients at our institution suspected of having TB in the same time period (1157 patients for whom culture data were available, which includes many of the patients who had IGRA performed), 3.6% were MTB culture positive. When those patients who had IGRA performed were excluded, the culture positive prevalence in the remaining 1099 patients fell to 2.7% (indicating significant overlap between the culture positive patients and the patients who had IGRA performed). Because of this difference in prevalence, likelihood ratios, pre-test odds and post-test odds were calculated in place of positive and negative predictive values (Tables 3 and 4). Compared with culture, a positive IGRA result increased the likelihood of a diagnosis of TB around three-fold (positive likelihood ratio 3.33), whereas a negative test decreased the likelihood of a diagnosis of TB by a similar factor (Tables 3 and 4). IGRA was slightly better when compared with clinical diagnosis, particularly in HIV– patients. The post-test probability of disease for all patients (compared with culture result) increased from 0.21 to 0.47 for a positive IGRA result (HIV– from 0.24 to 0.50; HIV+ from 0.17 to 0.4 – Table 4A). Thus, in both HIV+ and HIV– TB suspects a positive test approximately doubled the probability of disease. A negative test led to post-test probabilities of 0.05 in HIV– and 0.08 in HIV+ suspects (Table 4A).

The post-test probabilities of disease would achieve greatest utility if they could be generalised for the whole population suspected of having TB, not just this selected cohort with a high TB prevalence. Therefore we extrapolated the pre and post-test probabilities to the whole population suspected of having TB in our institution (1099 patients, defined above), excluding those in the IGRA cohort, based on the calculated sensitivity, specificity (Table 3) and the prevalence of culture positivity in this group (2.7%). We find point estimates of the post-test probabilities (assuming most of the population to be HIV negative) to be 0.083 for a positive IGRA and 0.006 for a negative IGRA (Table 4B).

4. Discussion

In this study we describe the usefulness of IGRA (T-SPOT.TB™) as it was used in our unit for the first 21 months after introduction. Although we provide some evidence that a positive IGRA can contribute to diagnosis if the pre-test probability is high, it is not diagnostically decisive even in this scenario. The test is particularly insensitive in HIV+ patients; on average 1 out of every 12 HIV+ patients with a negative IGRA still has active TB.

In this study IGRA was used in the assessment of active disease, whereas it is approved and marketed for assessment of latent infection. This study was retrospective and did not include pre-defined inclusion criteria, so the patient group in whom IGRA testing was used in this study will not be directly comparable with that in clinical trials and there will inevitably be a degree of bias. In routine clinical practice, however, this test is often used in patients where the diagnosis is not immediately obvious (such as smear negative). For example most patients in this study had extra-pulmonary TB, suggesting that there is selection bias for patients in whom the diagnosis was difficult. Moreover, fewer than half of all the patients with TB in the study time period had IGRA performed. Despite this, we find a similar performance of IGRA to that previously described in other studies. In both HIV+ and HIV- patients IGRA testing is insensitive, particularly in HIV+ patients. We would predict the exclusion of patients with “clinically obvious” TB from this study has the effect of reducing sensitivity whilst preserving specificity, i.e. the number of false negatives is reduced. This biases this study towards a lower sensitivity but is helpful for the exclusion of disease as the post-test probability conditional on a negative IGRA is therefore a minimum estimate.

In our unit the T-SPOT.TB™ test is used in preference over the Quantiferon™ test. In the research context whole blood assays for T cell function are generally quicker and require a smaller blood sample than those that require mononuclear cell separation. However, Quantiferon™ takes no account of the lymphocyte count and therefore gives issues with setting the cut-off for a positive test. The mononuclear cell method overcomes this because a standard number of cells are used in the assay. Both methods suffer from indeterminate results. Such results are not diagnostically helpful and are best regarded as if the test had not been done. In our study eight patients had equivocal tests one of which was positive upon repeat; an assay failure rate of around 10%, a significant limitation of the test.

To interpret the sensitivity and specificity of a test, the disease prevalence, or the pre-test probability, should be known. Because of the selection of patients who have an IGRA performed in our unit, the probability of disease is already ten-fold greater than the background. Extrapolating point estimates of the post-test probabilities of IGRA testing to all patients in our institution suspected of having TB shows the greatest clinical utility of IGRA is for excluding disease where the pre-test probability is low. Applying the test systematically in this context would reduce the odds of disease conditional on a negative IGRA from 1 in 36 to 1 in 167 whilst generating 25 false positive results for each hundred patients tested. Although this is surprisingly high, an independent audit undertaken in the rheumatology department of our institution showed that 17% of the patient population (predominantly of low epidemiological risk for TB) had a positive IGRA (Dr B Chikura, unpublished data [23]).

5. Learning points

- With modest pre-test probability of TB a positive IGRA will increase the chance of disease to approximately 50% and will contribute if clinical suspicion is high and microbiological samples difficult to obtain.

- In HIV+ patients a negative IGRA halves the probability of disease; but still leaves an unacceptably high 8% chance of active TB.
- In a low prevalence cohort a high rate of false positives can be expected with only 1 in 25 with a positive IGRA having disease. The chance of disease in those with a negative test, however, is reduced to 0.6%.

IGRA should not be routinely used for the diagnosis of disease, but should be reserved for situations where clinical suspicion is high but microbiological samples are difficult to obtain. Further prospective studies using clinical cure as an outcome in addition to culture would be of value in informing the use of this test. This study provides “real world” data and again confirms that TB diagnostics capable of supporting clinicians in the diagnosis of active disease remain inadequate.

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Fig. 1.

Selection of patients for this study. The flow chart shows the number of patients seen for suspected TB during the period January 2008–October 2009. Any patient who had either IGRA or TB culture performed was considered to have suspected TB. *NTM=non tuberculous *Mycobacteria*.

Table 1
Sensitivity of Interferon Gamma Release Assays for TB disease. Studies published between 2008 and 2010.

Study	No. of Patients	No. of HIV+ patients	Setting	Gold standard	Test	Sensitivity
Aabye et al. 2010 ¹⁰	161	68	Tanzania	Culture	QFT-IT	Overall HIV +ve 86% HIV -ve 83% 88%
Cattamanchi et al. 2010 ¹¹	126	126	Kampala, Uganda	Culture	T-SPOT.TB™	73%
Kabeer et al. 2010 ¹²	177	0	Chennai, India	Culture/Clinical/ Smear Microscopy	QFT-IT	91%
Kabeer et al. 2009 ¹³	105	105	Chennai, India	Culture/Smear Microscopy/ Xray	QFT-G	74%
Kim et al. 2009 ¹⁴	75	4* (24 immuno-compromised)	Seoul, Korea	Culture/PCR/Histology/ Radiological	ELISpot	93%
Metcalfe et al. 2009 ¹⁵	65	0	San Francisco	Culture	QFT-G	72%
Winqvist et al. 2009 ¹⁶	70	Not clear** (19 immuno-compromised)	Southern Sweden	Culture/PCR/ Clinical	QFT-G	63%
Chee et al. 2008 ¹⁷	270	7	Singapore	Culture	T-SPOT.TB™ QFT-IT	94% 83%
Dosanjh et al. 2008 ¹⁸	194	20	Birmingham and London, UK	Culture/Clinical	ELISpot PLUS ELISpot	89% 85%
Harada et al. 2008 ¹⁹	100	1	Japan	Culture/ PCR	QFT-GIT QFT-G	93% 81%
Kobashi et al. 2008 ²⁰	130	0	Japan	Culture	QFT-2 G	95%
Raby et al. 2008 ²¹	112	59	Zambia / South Africa	Smear microscopy	QFT-GIT	Overall HIV -ve: 86% HIV +ve: 97% 76%
Soysal et al. 2008 ²²	100	0	Istanbul, Turkey	Culture	T-SPOT.TB™ QFT-G	83.5% 78%

Indeterminate results have been excluded from the table.

QFT = Quantiferon™, QFT-G = Quantiferon™ Gold, QFT-IT = Quantiferon™ In Tube, QFT-GIT = Quantiferon™ Gold In Tube.

* 24 immunocompromised patients: HIV(4), transplant recipients(3), malignancy(9), renal failure(5), rheumatologic disease(1), diabetes(5).

** 19 immunocompromised patients (details unavailable): HIV, immunosuppression, drug / alcohol use, diabetes, cancer.

Table 2

Characteristics of the 64 patients analysed in the study.

Median age (range)	36 (17–78)
Male (%)	34 (53%)
Ethnicity (%)	
Black	21 (33%)
Asian	16 (25%)
White	23 (36%)
Mixed	0
Other/unknown	4 (6%)
HIV+ (%)	20 (31%)
Median CD4 (range)	178 (3–491)
Region of origin (%)	
Europe	27 (42%)
Middle East	1 (2%)
Africa	20 (31%)
Indian subcontinent	8 (13%)
Asia other	3 (5%)
Unknown	5 (8%)
Final diagnoses	
TB	20 (31%)
Other infection, respiratory tract	7 (11%)
Other infection, non-respiratory tract	7 (11%)
Other mycobacteria	2 (3%)
Lymphadenopathy other than TB	5 (8%)
Malignancy	4 (6%)
Inflammatory/rheumatic	7 (11%)
Other	8 (13%)
No specific diagnosis made	2 (3%)
Unknown/Missing data	2 (3%)

Data shown are numbers (%). All diagnoses were reviewed at least six months after the test was performed. Other infections, respiratory tract were predominantly pneumonia. Non-respiratory infections included endocarditis, osteomyelitis, orchitis, syphilis and toxoplasmosis. Other *Mycobacteria* were *M. avium* and *M. gordonae*. Inflammatory/rheumatic conditions included Behçet's disease, sarcoidosis, pericarditis and systemic lupus erythematosus. Other diagnoses included haemoptysis, drug reaction, postural hypotension and iron deficiency anaemia.

* IQR=inter-quartile range.

Table 3Performance of the T-SPOT.TB™ interferon- γ release assay.

Gold standard comparator: culture of <i>M. tuberculosis</i>			
	<i>All patients</i> (n =52)	<i>HIV- patients</i> (n =34)	<i>HIV+ patients</i> (n = 18)
Sensitivity (95% CI)	83.3% (57.9–96.8)	88.9% (60.2–99.3)	66.7% (22.8–95.6)
Specificity (95% CI)	75% (60.5–86.4)	72.0% (53.3–86.6)	80% (56.9–94.3)
Positive LR (95% CI)	3.33 (1.84–6.03)	3.17 (1.62–6.20)	3.33 (0.92–12.1)
Negative LR (95% CI)	0.22 (0.06–0.80)	0.15 (0.02–1.00)	0.42 (0.08–2.11)
Gold standard comparator: clinical diagnosis			
	<i>All patients</i> (n=64)	<i>HIV- patients</i> (n=44)	<i>HIV+ patients</i> (n=20)
Sensitivity (95% CI)	70.0% (49.1–86.4)	84.6% (60.5–97.1)	42.9% (14.9–74.6)
Specificity (95% CI)	86.4% (74.4–94.3)	87.1% (77.7–95.7)	84.6% (60.5–97.1)
Positive LR (95% CI)	5.13 (2.31–11.4)	6.56 (2.55–16.9)	2.78 (0.60–12.9)
Negative LR (95% CI)	0.35 (0.17–0.69)	0.18 (0.05–0.64)	0.67 (0.34–1.34)

Performance of the T-SPOT.TB™ interferon- γ release assay (IGRA) for *M. tuberculosis* in all patients in this study and broken down by HIV status is shown. The gold standard against which the IGRA was compared was either isolation of *M. tuberculosis* in culture or a clinical diagnosis of tuberculosis, defined as receipt of TB therapy with resolution of clinical disease at six months of follow up. Data are percentages for sensitivity and specificity; and numbers for likelihood ratios. 95% confidence intervals are indicated.

LR: likelihood ratio. CI: confidence interval.

Table 4

Probabilities, odds and likelihood ratios of IGRA.

A	IGRA result	Pre-test probability	Pre-test odds	Likelihood ratio	Post-test odds	Post-test probability
All patients (n = 52)	Positive	0.21	0.27	3.33	0.89	0.47
	Negative	0.21	0.27	0.22	0.06	0.06
HIV – Patients (n=34)	Positive	0.24	0.32	3.17	1.00	0.50
	Negative	0.24	0.32	0.15	0.05	0.05
HIV+ Patients (n=18)	Positive	0.17	0.20	3.33	0.67	0.40
	Negative	0.17	0.20	0.42	0.08	0.08
B	Extrapolated IGRA result	Pre-test probability	Pre-test odds	Likelihood ratio	Post-test odds	Post-test probability
All MTB culture (n=1099)	Positive	0.027	0.028	3.33	0.093	0.083
	Negative	0.027	0.028	0.22	0.006	0.006

^AComparison with culture results for the patients having IGRA in this study.

^BThe values shown are extrapolated from applying the sensitivity and specificity of IGRA to the total population who were screened for TB (any patient having mycobacterial culture) based on the prevalence in that population.