EXTENDED REPORT

Influence of replacing tuberculin skin test with ex vivo interferon γ release assays on decision to administer prophylactic antituberculosis antibiotics before anti-TNF therapy

Xavier Mariette,¹ Gabriel Baron,² Florence Tubach,³ Frédéric Lioté,⁴ Bernard Combe,⁵ Corinne Miceli-Richard,¹ René-Marc Flipo,⁶ Philippe Goupille,⁷ Matthieu Allez,⁸ Dominique Salmon,⁹ Dominique Emilié,¹⁰ Guislaine Carcelain*,¹¹ Philippe Ravaud*²

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¹Rhumatologie, Hôpital Bicêtre, Assistance Publique-Hôpitaux de Paris (AP-HP), Université Paris-Sud 11, INSERM U1012, 78 rue du Général Leclerc, Le Kremlin-Bicêtre, France

²Centre d'épidémiologie clinique, Groupe Hospitalier Cochin-Hôtel Dieu, AP-HP, Université Paris Descartes, PRES Sorbonne Paris Cité, INSERM UMR-S 738, Paris, France

³Département d'Epidémiologie, Hôpital Bichat-Claude Bernard, Biostatistique et Recherche Clinique, Paris, France

⁴Rheumatology and INSERM UMR-S606, Paris Diderot University, Paris, France

⁵Rhumatologie, Hôpital Lapeyronie, Université Montpellier I, Montpellier, France

⁶Rhumatologie, Hôpital Roger Salengro, Université, Lille, France

⁷Rhumatologie, CHRU de Tours, Université François Rabelais, CIC INSERM-202, Tours, France

⁸Gastro-entérologie, Hôpital Saint-Louis, Paris, France

⁹Médecine interne et maladies infectieuses, Hôpital Cochin, Paris, France

¹⁰INSERM U996, Microbiologie-Immunologie Biologique, Hôpital Antoine Bécélère, AP-HP, Université Paris-Sud 11, 32 rue des Carnets, Clamart, France

¹¹Immunologie, Hôpital Pitié Salpêtrière, Paris, France

†Deceased. This paper is dedicated to his memory.

*GC and PR contributed equally to the study.

Correspondence to

Xavier Mariette, Service de Rhumatologie, Hôpital de Bicêtre, 78 rue du Général Leclerc, 94275 Le Kremlin-Bicêtre, France; xavier.mariette@bct.aphp.fr

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ABSTRACT

Background The recommendations for detecting latent tuberculosis infection (LTBI) before antitumour necrosis factor (anti-TNF) therapy are based on the tuberculin skin test (TST), which lacks both specificity and sensitivity and can lead to unnecessary treatment with antibiotics. A study was undertaken to investigate the effect of replacing TST with interferon γ (IFN γ) release assays (IGRA) in screening for LTBI and deciding to begin prophylactic antituberculosis (TB) antibiotics before anti-TNF therapy in immune-mediated inflammatory diseases.

Methods In 15 tertiary care hospitals, consecutive patients with rheumatoid arthritis, spondylarthropathies or Crohn's disease were screened for LTBI before anti-TNF therapy with TST, QuantiFERON TB Gold in tube (QFT-Gold IT) and T-SPOT.TB at the same time. The potential diagnosis of LTBI and the effect on the decision to begin antibiotic prophylaxis were assessed.

Results Among 429 patients, 392 had results for the three tests. The results for TST, T-SPOT.TB and QFT Gold IT were positive for 35.2%, 15.1% and 9.9% of patients, respectively ($p < 0.0001$). Antibiotics were required for 177 patients (45.2%) if positive TST results were included in the LTBI definition, 107 patients (27.3%) if TST results were replaced with results from one of the IGRA tests and 84 patients (21.4%) if TST results were replaced with QFT-Gold IT results ($p < 0.0001$). The decision on the use of antibiotic prophylaxis was changed for 113 patients (28.8%, 95% CI 24.4% to 33.6%) if TST results were replaced with QFT-Gold IT results.

Conclusions Replacing TST with IGRA for determining LTBI allowed the proportion of patients with immune-mediated inflammatory diseases needing prophylactic anti-TB antibiotics before beginning anti-TNF agents to be reduced by half.

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INTRODUCTION

Antitumour necrosis factor (anti-TNF) agents are approved for the treatment of several immune-mediated inflammatory diseases including rheumatoid arthritis (RA), spondylarthropathies (SpA), Crohn's disease (CD), psoriasis and juvenile idiopathic arthritis and provide marked clinical benefit. However, one of the most problematic severe

adverse effects of these drugs is the possible reactivation of latent tuberculosis (TB) infection (LTBI) in patients previously exposed to TB bacilli.^{1,2} The presence of quiescent mycobacteria defines LTBI.³ Thus, screening for LTBI has been recommended before initiating treatment with TNF blockers.⁴ This screening has resulted in a decrease in the incidence of TB, but TB still remains a problem in patients receiving anti-TNF therapy with an incidence of 0.1–0.5/100 patient-years in western Europe where TB is not endemic.^{6–8}

TB is more frequent in patients receiving monoclonal antibodies than the soluble receptor,^{7,8} and remains the most frequent opportunistic infection in these patients receiving anti-TNF therapy.⁹

The recommendations for detecting LTBI differ worldwide,^{4,5,10,11} but are based mainly on the tuberculin skin test (TST) which has numerous drawbacks. The TST requires a return visit for reading the test result and it has poor specificity because previous vaccination with bacillus of Calmette and Guérin (BCG) and environmental mycobacterial exposure can result in false-positive results.^{10,12,13} This poor specificity can lead to unnecessary treatment with antibiotics with the possible risk of drug toxicity.^{14–16} However, TST results for patients with immune-mediated inflammatory diseases (IMID) are in general lower because of the disease or immunosuppressive drug use.^{17,18} This poor sensitivity can lead to false-negative results, with a subsequent risk of TB reactivation with anti-TNF therapy. Indeed, two-thirds (30/45) of patients with IMID and TB in the French RATIO registry had a TST result < 5 mm, a negative result.⁸

Identification of genes in the TB genome that are absent in BCG and most environmental mycobacteria offers an opportunity to develop more specific tests to investigate TB infection, particularly LTBI.¹⁹ Ex vivo interferon γ (IFN γ) release assays (IGRAs) investigating IFN γ release by T cells in the presence of these specific mycobacterial antigens, QuantiFERON TB Gold in tube (QFT-Gold IT) (Cellestis, Carnegie, Australia) and T-SPOT.TB (Oxford Immunotec, Abingdon, UK), seem to be more accurate than the TST for diagnosing active TB, recent primary infection or LTBI in the general population.¹³

Table 1 Characteristics of patients

	RA (N=123)	SpA (N=178)	CD (N=91)	Total (N=392)
Age, median (IQR)	56 (45–53)	42 (33–51)	36 (27–46)	45 (34–56)
Sex, M/F	26/97	94/83	42/47	162/227
Birth in endemic zone of TB	18 (14.6)	24 (13.6)	16 (17.6)	58 (14.8)
Corticosteroids or immunosuppressants	114 (92.7)	64 (36.0)	56 (61.5)	234 (59.7)
Corticosteroids	86 (69.9)	24 (13.5)	30 (33.0)	140 (35.7)
Immunosuppressants	103 (83.7)	55 (30.9)	40 (44.0)	198 (50.5)
BCG vaccination				
No	9 (7.3)	5 (2.8)	2 (2.2)	16 (4.1)
Yes	65 (52.8)	132 (74.6)	60 (65.9)	257 (65.7)
Unknown	49 (39.8)	40 (22.6)	29 (31.9)	118 (30.2)
LTBI defined by questioning	23 (18.7)	23 (12.9)	7 (7.7)	53 (13.5)
LTBI defined by x-ray	3 (2.5)	3 (1.7)	0 (0.0)	6 (1.6)
LTBI defined by questioning or x-ray	24 (19.5)	26 (14.6)	7 (7.7)	57 (14.5)

Data are number (%) unless indicated otherwise.

BCG, bacillus of Calmette and Guérin; CD, Crohn's disease; LTBI, latent tuberculosis infection; RA, rheumatoid arthritis; SpA, spondylarthropathies, TB, tuberculosis.

*1 missing data for Anti-TB antibiotic prophylaxis

** questioning reveals previous TB without adequate treatment or primary TB infection without adequate treatment or previous confirmed close contact with a patient having pulmonary TB or chest X-ray shows residual nodular tuberculous lesions > 1 cm in the absence of previous adequate TB treatment

Figure 1 Flow chart of patients effectively receiving antibiotic prophylaxis depending on (A) what was planned in the protocol and (B) what was expected from the results of interferon γ (IFN γ) release assays (IGRA). TST, tuberculin skin test.

Table 2 Comparison of interferon γ (IFN γ) release assay and TST, with a threshold for TST of 5 mm or 10 mm

		Positive QTF-Gold IT or T-SPOT.TB result		
		No	Yes	Total
TST ≥ 5 mm	No	229	25	254
	Yes	97	41	138 (35.2%)
	Total	326	66 (16.8%)	392
Observed agreement		$\kappa=0.23$ (95% CI 0.13 to 0.32)		
69% (95% CI 64% to 73%)				
		Positive QTF-Gold IT result		
		No	Yes	Total
TST ≥ 5 mm	No	239	15	254
	Yes	114	24	138 (35.2%)
	Total	353	39 (9.9%)	392
Observed agreement		$\kappa=0.14$ (95% CI 0.06 to 0.22)		
67% (95% CI 62% to 72%)				
		Positive T-SPOT.TB result		
		No	Yes	Total
TST ≥ 5 mm	No	234	20	254
	Yes	99	34	138 (35.2%)
	Total	333	59 (15.1%)	392
Observed agreement		$\kappa=0.23$ (95% CI 0.14 to 0.33)		
70% (95% CI 65% to 74%)				
		Positive QTF-Gold IT or T-SPOT.TB result		
		No	Yes	Total
TST ≥ 10 mm	No	276	41	317
	Yes	50	25	75 (19.1%)
	Total	326	66 (16.8%)	392
Observed agreement		$\kappa=0.21$ (95% CI 0.10 to 0.33)		
77% (95% CI 72% to 81%)				
		Positive QTF-Gold IT result		
		No	Yes	Total
TST ≥ 10 mm	No	294	23	317
	Yes	59	16	75 (19.1%)
	Total	353	39 (9.9%)	392
Observed agreement		$\kappa=0.17$ (95% CI 0.06 to 0.29)		
79% (95% CI 75% to 83%)				
		Positive T-SPOT.TB result		
		No	Yes	Total
TST ≥ 10 mm	No	282	35	317
	Yes	51	24	75 (19.1%)
	Total	333	59 (15.1%)	392
Observed agreement		$\kappa=0.23$ (95% CI 0.11 to 0.35)		
78% (95% CI 74% to 82%)				

QTF-Gold IT, QuantiFERON TB Gold in tube; TST, tuberculin skin test.

In this large prospective study we aimed to investigate the potential influence in clinical practice of replacing the TST with the QFT-Gold IT and/or T-SPOT.TB for diagnosis of LTBI in deciding on prophylactic anti-TB antibiotic therapy before anti-TNF therapy in patients with IMID.

METHODS

Study design

A prospective pragmatic multicentre study was conducted to assess the effect of replacing the TST with IGRAs on the diagnosis of LTBI and on the physician's decision on treatment for patients with IMID (ie, the percentage of patients for whom the decision for antibiotic prophylaxis changed).

Patients and follow-up

Consecutive patients with RA, SpA or CD with an indication for initial biological treatment with anti-TNF agents in 14 rheumatology departments and five gastroenterology departments from 15

tertiary care hospitals were included in the study. In accordance with the French recommendations for screening for LTBI,²⁰ all patients underwent a clinical examination focused on questioning about previous contact with TB and a chest x-ray.

Patients were followed for 1 year. Antibiotic treatment, side effects of antibiotics and eventual occurrence of TB were recorded. All patients gave their informed consent to participate in the study.

Tests studied

Before anti-TNF therapy was started, patients underwent the TST and a blood sample was taken for QFT-Gold IT and T-SPOT.TB within 3 days.

The TST involved intradermal injection of five tuberculin units corresponding to 0.1 ml of purified protein derivative (Tubertest, Sanofi Pasteur, France) according to the intradermal Mantoux method. The main diameter of skin induration was recorded in millimeters by an experienced clinician 72 h after

the inoculation and the result was considered positive if skin induration was ≥ 5 mm.

IGRAs were performed following training of staff in 15 hospital laboratories and interpreted by local immunologists according to the manufacturers' instructions who were blind to the TST results. The cut-off value for a positive T-SPOT.TB result was >7 spots. Indeterminate results were defined as an IFN γ level ≥ 2.0 IU/ml in the negative control well or <0.5 IU/ml in the positive control well for QFT-Gold IT and >10 spot-forming cells (SFCs) in the negative control well or <20 SFCs in the positive control well for T-SPOT.TB.

Assessment of diagnosis and influence on physician's therapeutic decision

According to French recommendations,²⁰ patients with LTBI require prophylactic antibiotic treatment under at least one of the following three conditions: (1) questioning reveals previous TB without adequate treatment, primary TB infection without adequate treatment, or previous confirmed close contact with a patient having pulmonary TB; (2) the chest x-ray shows residual nodular tuberculous lesions ≥ 1 cm in the absence of previous adequate TB treatment; or (3) wheals ≥ 5 mm in diameter on TST. In this study, for a diagnosis of LTBI followed by a decision to give antibiotic prophylaxis treatment, we used conditions 1 and 2 but replaced TST positivity with IGRA positivity (at least one positive result for QFT-Gold IT or T-SPOT.TB), except if TST yielded a blister on skin. In the case of one indeterminate blood test result, the other test result was used. If both blood test results were indeterminate, the TST result was used.

Sample size

The main objective of this study was to estimate the proportion of patients in whom the decision to administer antibiotic prophylaxis would change. We hypothesised that this change might occur in 20% of patients. To estimate this proportion with a two-sided 95% exact CI (based on a binomial distribution) and a precision of 4%, 385 patients were required.

Statistical analysis

The influence on the physician's decision was assessed by the McNemar test, which was used to compare paired proportions of patients needing antibiotics according to the definition of LTBI (defined by tests (TST, IGRA) and/or questioning or chest x-ray).

The influence on the decision whether or not to administer antibiotic prophylaxis was also computed by determining the proportion of patients with a change in decision for antibiotic prophylaxis (with an exact 95% binomial CI for proportions).

Table 3 Comparison of interferon γ (IFN γ) release assay and TST in the 57 patients with LTBI defined by questioning or x-ray

Test	N	Sensitivity	95% CI	N	Specificity*	95% CI
TST	57	0.32	0.20 to 0.45	335	0.54	0.69 to 0.70
QFT-Gold IT	57	0.21	0.11 to 0.34	335	0.92	0.89 to 0.95
T-SPOT.TB	57	0.25	0.14 to 0.38	335	0.87	0.82 to 0.90
QFT-Gold IT or T-SPOT.TB	57	0.28	0.17 to 0.42	335	0.85	0.81 to 0.89

*Indeterminate and negative results were pooled.

LTBI, latent tuberculosis infection; QFT-Gold IT, QuantiFERON TB Gold in tube; TST, tuberculin skin test

To identify factors associated with positive TST or IGRA results, we performed bivariate analysis (χ^2 tests). The following factors were tested: age, pathology, birth in an endemic TB zone, treatment with corticosteroids or immunosuppressive drugs or corticosteroids alone, BCG vaccination, LTBI defined by questioning alone or chest x-ray. Multiple logistic regression analysis was then performed and variables with $p \leq 0.2$ on bivariate analysis were included in the model. Variables retained in the final multivariate model were selected by a backward procedure. ORs and 95% CI were computed. The same methodology was used to find factors associated with an indeterminate IGRA result (QFT-Gold IT or T-SPOT.TB).

All analyses were performed using SAS 9.1 (SAS Institute, Cary, North Carolina, USA) and a $p < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics

We included 429 patients (table 1) from 15 hospitals (14 rheumatology centres and five gastroenterology centres) who had not previously received biological agents. IGRA findings were analysed in the local immunology laboratories. Results for the three tests (TST and both IGRAs) were available for 392 patients (91.4%).

Overall, 57 patients (14.5%) had a diagnosis of LTBI made independently of the TST or IGRA results (based on previous TB contact without adequate treatment on questioning or abnormal chest x-ray results).

Outcome and compliance with the planned intervention

Twenty-seven of the 392 patients (6.9%) were lost to follow-up at 1 year. None of the 365 patients who completed the 1-year follow-up had TB.

The decision whether or not to administer anti-TB antibiotic prophylaxis according to the protocol or only the IGRA test results was in compliance with the planned intervention in 83.4% and 91.8% of the patients, respectively (figure 1). All but four patients (94%) received the combination of isoniazid and rifampicin for 3 months.

Comparison between TST and IGRA results

The direct comparison of TB screening tests is shown in table 2. TST results were positive for 35.2% of patients (indicating LTBI) whereas the results for either IGRA were positive for 16.8% ($p < 0.0001$). The number of patients with discordant results was high: 122 (31.1%, 95% CI 26.6% to 36.0%) for all discordant results, 97 (80%) with positive TST and negative IGRA results and 25 (20%) with negative TST and positive IGRA results. If we considered only QFT-Gold IT, the difference from TST was greater: 9.9% with positive QFT-Gold IT results versus 35.2% with positive TST results ($p < 0.0001$; table 2).

The percentage of positive TST results with a threshold of TST of 10 mm and positive IGRA results was similar (19.1% vs 16.8%, $p = 0.35$) but the number of patients with discordant results remained high (91 (23.2%), 95% CI 19.1% to 27.7%, table 2).

Patients with each IMID showed differences in positivity between TST and IGRA results (see table 1 in online supplement).

The frequency of positive IGRA results was the same whether or not patients received corticosteroids or immunosuppressants (any disease-modifying antirheumatic drug or azathioprine) (18.6% and 17.1%, respectively). Conversely, TST results were less frequently positive for patients receiving corticosteroids

or immunosuppressants than for those receiving no treatment (31.2% vs 41.1%, $p=0.04$).

With regard to the 57 patients considered to have LTBI on questioning or x-ray independently from the tests, the sensitivity of TST and IGRA was equally low but the specificity of IGRA was higher (table 3).

The agreement rate between the two IGRA assays was 91% (95% CI 88% to 94%) with a κ coefficient of 0.61 (95% CI 0.49 to 0.73) (see table 2 in online supplement).

Diagnosis and influence on physician's decision to administer antibiotic prophylaxis in patients with LTBI defined by tests and questioning or chest x-ray

When a positive response to questioning or a positive chest x-ray was added to positive TST results with a threshold of 5 mm, 177 patients (45.2%) had LTBI. TST results were replaced by one or the other positive IGRA results and 107 patients (27.3%) were then considered to have LTBI (45.2% vs 27.3%, $p<0.0001$) and received antibiotic prophylaxis (table 4). The number of patients in whom there was a change in the decision on antibiotic prophylaxis was 106/392 (ie, the influence on the physician's therapeutic decision was 27.0%, 95% CI 22.7% to 31.7%). Among these 106 patients, 88 (83%) had positive TST and negative IGRA results and 18 (17%) had negative TST and positive IGRA results.

If TST results were replaced with only QFT-Gold IT results, 84 patients (21.4%) were considered to have LTBI (45.2% vs 21.4%, $p<0.0001$). The number of patients with a change in the decision on antibiotic prophylaxis was 113 (ie, the influence on the physician's therapeutic decision was 28.8%, 95% CI 24.4% to 33.6%).

Factors associated with positive TST or IGRA results

The factors associated with positive QFT-Gold IT, T-SPOT.TB and TST results on bivariate and multivariate analysis are shown in table 5. Importantly, QFT-Gold IT positivity was associated with LTBI defined by only questioning or x-ray, birth in an endemic TB zone, absence of or unknown BCG vaccination and age. Risk factors associated with T-SPOT.TB positivity and with TST positivity were having RA or SpA versus CD, birth in an endemic TB zone and age.

Even though previous BCG vaccination was not found to be a risk factor for TST positivity, the 97 patients with positive TST and negative IGRA results had received a previous BCG

vaccination more frequently than the other 295 patients (76.3% vs 62.0%, $p=0.02$). Moreover, the frequency of TST positivity was the same in patients with or without BCG vaccination (37.7% and 37.5%, respectively), whereas it was very different for IGRA (15.6% and 43.8%, respectively) (see table 3 in online supplement). Interestingly, in the small group of patients without BCG vaccination ($n=16$), the observed proportion of agreement between IGRA and TST was good (81.3%, 95% CI 54.4% to 81.2%), much better than in patients with previous BCG vaccination ($n=257$) (64.6%, 95% CI 58.4% to 70.4%).

Factors associated with indeterminate test results

The percentage of indeterminate test results was lower with QFT-Gold IT than with T-SPOT.TB (2.8% vs 6.4%, $p=0.01$). Among the 11 indeterminate test results with QFT-Gold IT, 10 were due to a low IFN γ response in the positive control mitogen tube and eight had a negative T-SPOT.TB result. Among the 25 indeterminate test results with T-SPOT.TB, 16 were due to a high background IFN γ level in the negative control nil tube and most were negative QFT-Gold IT results (14/16). Only four indeterminate test results with T-SPOT.TB were due to a low mitogen response and there were five difficulties in interpretation.

No factor was associated with an indeterminate IGRA result (indeterminate QFT-Gold IT or T-SPOT.TB result) and, in particular, neither steroid nor immunosuppressant use.

DISCUSSION

In this study of 392 patients with IMID in whom two IGRAs and TST were evaluated before beginning anti-TNF therapy, we have shown that replacing TST with IGRA in screening for LTBI allowed the proportion of patients requiring antibiotic prophylaxis to be reduced by half. Taking into account the number of diseases with an indication for anti-TNF therapy and the possible inconvenience of antibiotic prophylaxis (cost, possible side effects, delay in anti-TNF treatment), the conclusions of this study have important practical consequences.

IGRAs have been validated for detecting LTBI in unselected and HIV-positive populations¹³ but, despite its widely recognised limitations, the TST remains the most generally used method for screening for LTBI before anti-TNF therapy. The difficulty in evaluating IGRAs for this indication is the lack of a gold standard for defining LTBI and the fact that the outcome we aim to prevent by screening for LTBI represents a significant concern but occurs too infrequently to design studies for comparison of the

Table 4 Comparison of patients with and without LTBI including either IGRA or TST (threshold 5 mm) in the algorithm

		LTBI defined by questioning or x-ray or a positive result with one of the IGRAs		
LTBI defined by questioning or x-ray or TST result ≥ 5 mm	No LTBI	No LTBI	LTBI	Total
	LTBI	197	18	215
	Total	88	89	177 (45.2%)
		285	107 (27.3%)	392
		LTBI defined by questioning or x-ray or positive QFT-Gold IT result		
LTBI defined by questioning or x-ray or TST result ≥ 5 mm	No LTBI	No LTBI	LTBI	Total
	LTBI	205	10	215
	Total	103	74	177 (45.2%)
		308	84 (21.4%)	392
		LTBI defined by questioning or x-ray or positive T-SPOT.TB result		
LTBI defined by questioning or x-ray or TST result ≥ 5 mm	No LTBI	No LTBI	LTBI	Total
	LTBI	200	15	215
	Total	90	87	177 (45.2%)
		290	102 (26.0%)	392

IGRA, IFN γ release assay; LTBI, latent tuberculosis infection; QFT-Gold IT, QuantiFERON TB Gold in tube; TST, tuberculin skin test.

different screening methods. The ideal study design would be to compare the incidence of reactivation of TB in patients receiving prophylactic antibiotics according to standard recommendations including TST and those including IGRA. Taking into account the incidence of reactivation of TB in patients screened using standard recommendations (about 1/1000 patients starting anti-TNF therapy in the BSRBR⁷ and the RATIO registry),⁸ this study would need 5000–10 000 patients in each group, which is unrealistic. Thus, the only way to assess the usefulness of these new tests is to compare both tests and TST with classic risk factors of LTBI in a sufficiently large sample of homogeneous patients with IMID with no previous biotherapy and to include the IGRA in the decision on whether or not to prescribe TB antibiotic prophylaxis. To date, some reports of the use of IGRA in IMID have been published, but most have included few patients, are heterogeneous concerning the time of the tests (before or during anti-TNF treatment) or did not perform the two IGRAs and the TST at the same time.^{21–27} However, some of these studies gave indications concordant with our results,

with a decrease in patients requiring antibiotic prophylaxis and a better association with classic risk factors for LTBI with IGRA than with the TST.^{23–26}

There is no gold standard for defining LTBI and thus we cannot calculate the sensitivity and specificity of the tests. We can approach these data by focusing on the 57 patients considered to have LTBI on questioning or x-ray independently from the tests. However, we have to keep in mind that the diagnosis of putative LTBI in these patients is based mainly on questioning and not on objective features. In these patients, the sensitivity of TST and IGRA was equally low but the specificity of IGRA was higher (table 3).

The better specificity of IGRAs was confirmed by the fact that, with the classic method of screening for LTBI (ie, including TST), 45.2% of the patients with IMID should receive antibiotic prophylaxis. If TST is replaced with one of the IGRAs, this percentage falls to 27.3%, and to 21.4% if only QTF-Gold IT results are considered. The percentage of patients with at least one positive IGRA result is twice as low as that of patients with

Table 5 Factors associated with positive QTF-Gold IT, positive T-Spot.TB and positive TST results in bivariate and multivariate analysis

	Bivariate analysis			Multivariate analysis		
	Positive QTF-Gold IT result (n=39)	Negative or indeterminate QTF-Gold IT result (n=353)	p Value	OR	95% CI	p Value
Age, median (IQR)/(OR per 10 years)	53 (43–64)	44 (33–44)	0.0006	1.42	1.09 to 1.85	0.0081
RA and SpA (vs CD)	32 (82.1)	269 (76.2)	0.4118			
Birth in endemic TB zone	12 (30.8)	46 (13.1)	0.0032	2.97	1.33 to 6.66	0.0081
Corticosteroids or immunosuppressors	26 (66.7)	2 (58.9)	0.3495			
Corticosteroids alone	19 (48.7)	121 (34.3)	0.0741			
BCG vaccination			0.0005			0.0357
No	6 (15.4)	10 (2.8)		1		
Yes	20 (51.3)	237 (67.1)		0.23	0.07 to 0.73	
Unknown	13 (33.3)	106 (30.0)		0.23	0.07 to 0.77	
LTBI defined by questioning alone* or chest x-ray†	12 (30.8)	45 (12.7)	0.0024	2.30	1.04 to 5.11	0.0407
	Positive T-SPOT.TB result (n=59)	Negative or indeterminate T-SPOT.TB result (n=333)	p Value	OR	95% CI	p Value
Age, median (IQR)/(OR per 10 years)	51 (39–60)	44 (33–54)	0.0025	1.27	1.03 to 1.57	0.0232
RA and SpA (vs CD)	53 (89.8)	248 (74.5)	0.0100	2.69	1.08 to 6.71	0.0342
Birth in endemic TB zone	17 (28.8)	41 (12.3)	0.0010	3.11	1.59 to 6.10	0.0009
Corticosteroids or immunosuppressors	36 (61.0)	198 (59.5)	0.8221			
Corticosteroids alone	23 (39.0)	117 (35.1)	0.5697			
BCG vaccination			0.1805			
No	5 (8.5)	11 (3.3)				
Yes	37 (62.7)	220 (66.1)				
Unknown	17 (28.8)	102 (30.6)				
LTBI defined by questioning alone* or chest x-ray†	14 (23.7)	43 (12.9)	0.0298			
	Positive TST result (n=138)	Negative TST result (n=254)	p Value	OR	95% CI	p Value
Age, median (IQR)/(OR per 10 years)	44 (36–51)	45 (33–58)	0.1619	0.80	0.68 to 0.94	0.0059
RA and SpA (vs CD)	120 (87.0)	181 (46.2)	0.0004	3.76	2.04 to 6.91	<0.0001
Birth in endemic TB zone	28 (20.3)	30 (11.9)	0.0250	2.15	1.19 to 3.88	0.0108
Corticosteroids or immunosuppressors	73 (52.9)	161 (63.4)	0.0432			
Corticosteroids alone	41 (29.7)	99 (39.0)	0.0674			
BCG vaccination			0.2846			
No	6 (4.3)	10 (3.9)				
Yes	97 (70.3)	160 (63.0)				
Unknown	35 (25.4)	84 (33.1)				
LTBI defined by questioning alone* or chest x-ray†	18 (13.0)	39 (15.4)	0.5353			

Data are number (%) unless otherwise specified.

*TB primary infection, close contact with TB patient, TB with no treatment, anti-TB treatment initiated before 1970 or less than 2 months with the combination rifampicin-pyrazinamide treatment.

†Nodules >1 cm.

BCG, bacillus of Calmette and Guérin; LTBI, latent tuberculosis infection; QTF-Gold IT, QuantiFERON TB Gold in tube; RA, rheumatoid arthritis; SpA, spondylarthropathies; TB, tuberculosis; TST, tuberculin skin test.

positive TST results (16.8% vs 35.2%). This 16.8% rate of history of contact with TB bacillus is high, but is in accordance with previous studies in this type of population of the same age.^{23–25} The sensitivity of IGRA is also probably better than that of TST because, in 20% of the discordant results, the TST result was negative whereas the IGRA results were positive. This finding is probably due to the fact that the frequency of positive IGRA results, but not of TST results, was the same whether patients received corticosteroids or immunosuppressants.

Finally, an important argument in favour of the validity of the IGRA is the association with classic risk factors for LTBI. Both IGRA and TST results are associated with birth in endemic areas of TB, whereas QFT-Gold IT results alone are associated with LTBI defined only by questioning or by x-ray and with an absence of BCG vaccination. Our data therefore suggest that BCG vaccination can protect from positive IGRA and, even though not found as an independent risk factor of TST positivity, can favour a non-specific positive TST result. Interestingly, among the six patients with blister on TST, five of six had a positive IGRA result and the one patient with a negative IGRA test had previous BCG vaccination.

If we consider the two IGRAs independently as in the study by Kleinert *et al*,²⁶ QFT-Gold IT but not T-SPOT.TB results were

associated with classic risk factors for LTBI, probably because of the better specificity of QFT-Gold IT.²⁸ Supporting this assertion, among the 27 patients with positive T-SPOT.TB and negative QFT-Gold IT TB results, the frequency of LTBI defined by questioning alone or x-ray was the same as in the whole population (14.8% vs 14.5%). However, as found in recent meta-analyses^{29 30} on the effect of these tests in diagnosing active TB, T-SPOT.TB had better sensitivity than QFT-Gold IT in our study (15.1% vs 9.9%). As no gold standard exists, it is not possible to say if the better sensitivity of T-SPOT.TB corresponds to false positives. In fact, most of the discordant results (positive T-SPOT.TB and negative QFT-Gold IT) were in patients with SpA, with less immunosuppressant treatment suggesting that the number of positive spots for defining the threshold of positivity of T-SPOT.TB could be too low in patients without immunosuppressant treatment.

Finally, indeterminate results were less frequent with QFT-Gold IT than with T-SPOT.TB (2.8% vs 6.4%), which is similar to that reported for the general adult population²⁸ and also in a small series of patients with IMiD.³¹ Interestingly, the high number of indeterminate results for T-SPOT.TB was mainly due to a high background IFN γ level in the negative control well for patients with negative QFT-Gold IT results.

Figure 2 Proposed algorithm for screening for latent tuberculosis (TB) infection before anti-tumour necrosis factor treatment. TST, tuberculin skin test.

Together these results support the fact that using IGRAs (instead of TST) results in fewer patients with IMIDs with an indication for anti-TNF therapy being diagnosed and treated for LTBI. Our data support recent expert recommendations³² suggesting, without evidence, that IGRAs are superior to the TST in identifying individuals with a prior history of BCG vaccination at risk of developing TB with anti-TNF therapy. x-Rays do not appear to be informative for this purpose, but baseline reference x-rays are useful before starting anti-TNF therapy and we therefore propose that they should be left in the algorithm. The question of performing one or both IGRAs remains debatable. For economic, practical (compared with T-SPOT.TB, QFT-Gold IT does not require Ficoll separation and thus can be fully automatic) and scientific reasons stated previously, we propose the following algorithm: questioning, chest x-ray and QFT-Gold IT testing. T-SPOT.TB should be performed in cases with indeterminate QFT-Gold IT results and TST in cases with indeterminate results for both IGRAs (figure 2). With this algorithm, the proportion of patients requiring anti-TB antibiotic prophylaxis would decrease from 45.2% to 21.4%. This strategy needs to be evaluated from a medico-economic point of view and validated in other cohorts.

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