Screening for latent tuberculosis infection in patients with inflammatory bowel disease: Can interferon-gamma release assays replace the tuberculin skin test?

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ABSTRACT

Background/Aims: *Screening for latent tuberculosis infection is mandatory before starting anti-tumor necrosis factor therapy. New assays based on interferon-γ (IFN-γ) release have recently become available and may be more accurate. The aim of this study was to compare QuantiFERON-TB and tuberculin skin test in screening for latent infection in patients with inflammatory bowel disease.*

Materials and Methods: *We prospectively screened 138 patients with inflammatory bowel disease for latent tuberculosis infection with chest X-ray, tuberculin skin test, and a third-generation QuantiFERON-TB test. The association of the results in both tests with immunosuppression or inflammatory activity was determined by logistic regression.*

Results: *The tuberculin skin test and QuantiFERON-TB were positive in 21.7% and 24.6% of the patients, respectively. Overall, 71% patients were receiving immunosuppressants. Concordance between the two tests was moderate (κ=0.59; 95% confidence interval (CI), 0.43-0.75) and was higher in immunosuppressant-naïve patients (κ=0.75; 95% CI, 0.52-0.97) than in immunosuppressed patients (κ=0.51; 95% CI, 0.30-0.72). In both the tests, disease activity and receiving immunosuppression were not associated with the test results. Nevertheless, QuantiFERON-TB was negatively influenced with two or more immunosuppressive drugs.*

Conclusion: *Concordance between the two tests was moderate, and it appears lower with immunosuppression. QuantiFERON-TB alone may be appropriate in immunosuppressant-naïve patients. Both tests should be considered in immunosuppressed patients.*

Keywords: *Inflammatory bowel disease, tuberculosis, immunosuppression, interferon-γ release assay, tuberculin skin test*

INTRODUCTION

Mycobacterium tuberculosis (MT) is the microorganism responsible for causing tuberculosis (TB). The clinical phenotype resulting from infection is dependent on the axis formed by interleukin-12, interferon-γ (IFN-γ), and tumor necrosis factor (TNF). Entry of the bacilli into the host triggers an inflammatory response whereby macrophages engulf the bacilli, leading to release of cytokines that attract neutrophils, macrophages, and T cells. The T cells secrete TNF and IFN-γ, resulting in the clinical manifestations of TB infection. The bacilli can remain latent in macrophages without producing any symptoms, in what is termed as latent TB infection (LTBI), or progress to a disease state. It is estimated that 10% of individuals with LTBI develop active TB during their lifetime (1). This proportion may increase in certain circumstances such as immunosuppression.

Identification of patients with LTBI is a challenge because there is no gold standard. Until a few years ago, the only test available was the tuberculin skin test (TST), which comprises inoculation with a mixture of 200 antigens [purified protein derivatives (PPD)]. The main problem with this technique is that the proteins are not specific for MT but are shared by non-tuberculous mycobacteria (NTM). This decreases the specificity of the test and increases the number of false-positives in samples from patients with infections with atypical mycobacteria or from those who received the Bacillus Calmette-Guérin (BCG) vaccine. The sensitivity is also low, with false-negatives, particularly in immunosuppressed patients or those receiving immunosuppressive therapy. In inflammatory bowel disease (IBD), a high incidence of anergy is reported even in the absence of immunosuppressive therapy (2). New tests known as IFN-γ release assays (IGRAs) have been

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developed. T-SPOT.TB and QuantiFERON-TB offer improved sensitivity and specificity, at least in some populations, compared with the TST for detection of LTBI (3,4). Some countries have already incorporated these tests into their recommendations and diagnostic algorithms for LTBI (5,6). QuantiFERON-TB Gold In-Tube (QFT-GIT) (Cellestis, Carnegie, Australia) measures in vitro simulation of IFN production by MT-specific antigens such as early secretory antigen target (ESAT-6), culture filtrate protein 10 (CFP-10), and TB 7.7 (p4), which are absent from almost all BCG vaccine strains and from most of the NTM (4,6).

In the case of IBD, the need to identify patients with LTBI has arisen with the arrival of immunosuppressive drugs and, in particular, anti-TNF monoclonal antibodies. Patients receiving these agents have up to five-fold greater risk of LTBI reactivation in the first 52 weeks after starting treatment than the general population (7,8). Therefore, the guidelines of different scientific societies have established recommendations for screening for LTBI before starting these treatments, resulting in a clear decrease in infection (9-11). The primary objective of the present study was to compare the TST with the QFT-GIT in a prospective cohort of patients with IBD to assess whether this new assay could replace the TST. The secondary objective was to analyze the prevalence of LTBI in this cohort.

MATERIAL AND METHODS

Patients

We enrolled a prospective cohort of 138 consecutive patients with evaluable results in both tests and with IBD in follow-up in our clinics. In four patients with indeterminate result in the first QFT-GIT, an evaluable result was obtained after a second test. Overall, 112 patients (82%) were diagnosed with Crohn's disease and 26 patients with ulcerative colitis according to the usual Lennard-Jones criteria. In all cases, disease characteristics, presence of active inflammation according to the physician global assessment, and treatments at baseline were recorded (12). Immunosuppressive therapy was defined as treatment with corticosteroids at a prednisone or equivalent dose ≥15 mg/d for at least 1 month or stable treatment (≥3 months) with anti-TNF agents or immunomodulators (IMM), such as azathioprine, mercaptopurine, or methotrexate (13,14). All patients were screened for LTBI by assessing medical records for risk factors for LTBI (history of confirmed active TB, prolonged contact with a patient with active TB, residence in an epidemic area for more than 3 months, health workers, intravenous drug users, immunosuppressive conditions, and other significant comorbidities) as well as vaccination history with BCG if it was known, along with chest X-ray and TST and QFT-GIT results (15). The two tests were performed sequentially, with the TST being performed after obtaining the blood sample for the QFT-GIT. The incidence of TB at the start of the study in the areas of Spain where the data were obtained from was almost 20 cases per 100,000 inhabitants (16). The local ethics committee approved the study protocol. All patients gave their informed consent before being included in the study.

Procedures

The TST was performed according to the Mantoux methodology by health workers unaware of the result of the QFT-GIT. Two units of antituberculin PPD RT-23 (0.1 mL) were injected intradermally with a 27-gauge needle into the anterior surface of the forearm. The reading was noted 72 h after injection by measuring the transverse diameter of induration along the long axis of the forearm. As in previous studies in this field and according to local guidelines at the time of conducting the study, an induration greater than 5 mm was considered a positive result in patients receiving immunosuppressive therapy as defined earlier in those who had been in contact with bacilliferous patients and in those with findings suggestive of past TB infection in the chest X-ray (calcification shadows more than 5 mm, pleural thickening, or linear opacities) (17,18). An induration greater than 10 mm was considered a positive result in patients who were not receiving immunosuppressive therapy. Among patients who were receiving immunosuppressive therapy and with a negative TST result, the test was repeated after 7 d in the contralateral arm (booster effect).

The QFT-GIT was performed according to the manufacturer's instructions (Cellestis Ltd., Carnegie, Victoria, Australia) with a positive control (mitogen stimulation), a negative control (without mitogen), and two samples (stimulated with ESAT-6, CFP-10 or TB 7.7). The samples were incubated immediately after extraction for 18 h at 37°C under a humidified atmosphere. The IFN-γ reading in the negative control was taken as baseline and was subtracted from both the positive control with mitogens and from the antigen-stimulated samples. A result was considered positive if the IFN-γ levels in the antigen-stimulated samples were ≥0.35 IU/mL, regardless of the result of the positive control. The test was considered negative if the IFN-γ reading was <0.35 IU/mL and

the IFN-γ reading in the positive control was >0.5 IU/mL. The result was indeterminate if the levels of IFN-γ were <0.35 IU/mL in the antigen-stimulated samples and <0.5 IU/mL in the positive control or if levels of IFN-γ in the stimulated samples were more than half the value for the negative control and greater than 0.7 IU/mL in negative controls.

Statistical analysis

Statistical analysis was performed using the SPSS Statistics version 20 (IBM Corp.; Armonk, NY, USA). Continuous variables were presented as mean or median with the corresponding ranges; categorical variables were presented as absolute numbers and percentages. Differences between data for the categorical variables were analyzed with the χ^2 test or the Fischer exact test. The degree of concordance was assessed by determining the κ-index and classified according to the Landis and Koch classification (excellent concordance as a κ of 0.81-1.00, substantial concordance as a κ of 0.61-0.80, moderate concordance as a κ of 0.41-0.60, fair concordance as a κ of 0.21-0.40, slight concordance as a κ of 0.01-0.20, and poor concordance as a κ of 0).

Variables that could be associated with TST and QFT-GIT results were as follows: sex, age, presence of epidemiological risk factors for LTBI, X-ray findings indicative of LTBI, immunosuppressive therapy, and inflammatory disease activity at the time of performing the test were included in the exact logistic regression analysis, including variables with p<0.10 in the univariate analysis.

RESULTS

The clinical characteristics of the 138 patients included in the study are presented in Table 1. Of the 138 patients, 18 reported a prior contact of risk, five had a history of TB, and two showed active pulmonary TB during screening, and appropriate treatment administered.

The prevalence of LTBI in this cohort as determined by the presence of at least one positive test and/or suggestive findings on chest X-ray was 30.4%. The TST was positive in 30 (21.7%) patients and the QFT-GIT in 34 (24.6%) patients, with an overall agreement rate of 85%. The overall concordance was moderate (κ= 0.59; 95% CI, 0.43-0.75).

At the time of testing, 98 (71%) patients were receiving immunosuppressive therapy and 24 (17%) patients were receiving two or more drugs with immunosuppressive effects (corticosteroids and IMM or IMM and anti-TNF agents). Two patients were receiving a combination of three drugs; 11 patients were on anti-TNF treatment, which started after a negative screening for LTBI with TST. As reflected in Table 2, the degree of concordance was moderate in patients receiving immunosuppressive therapy (κ= 0.51; 95% CI, 0.30-0.72) but substantial in patients not receiving immunosuppressants, that is, immunosuppressant-naïve patients (κ=0.75; 95% CI, 0.52-0.97). There were no statistically significant differences in the positivity rate with both tests according to the presence or absence of immunosuppressive therapy when all the drugs were assessed together (Table 3).

Table 1. Baseline characteristics of the patients

Number of Patients, n	138
Sex, male n (%)	77 (56%)
Age, y [median (IQR)]	39.5 (30.5-49.5)
Type IBD; Crohn n (%)	112 (82.4%)
Follow-up, months [median (IQR)]	15.5 (8.5-18.5)
Inflammatory activity present at the time of the tests, n (%)	67 (48.6%)
Baseline immunosuppressive therapy, n (%)	98 (71%)
CS alone	32 (23%)
IMM alone	41 (30%)
Anti-TNF alone	1 (0.7%)
≥2 immunosuppresive therapies: CS+IMM; IMM+anti-TNF; CS+IMM+anti-TNF	24 (17.3%)
Signs of LTBI in X-ray, n (%)	19 (13.8%)

Anti-TNF: anti-tumor necrosis factor agents; CS: corticosteroids; IBD: inflammatory bowel disease; IMM: immunomodulators; IQR: interquartile range; LTBI: latent tuberculosis infection

Table 2. Concordance of results between QuantiFERON-TB Gold In-Tube Test and tuberculin skin test

		QFT-GIT (+)	QFT-GIT (-)	κ
Overall n=138	TST(+)	22	8	0.59; 95% CI 0.43-0.75
	TST(-)	12	96	
No IMS n=40	TST(+)	9	0	0.75, 95% CI 0.52-0.97
	TST(-)	4	27	
IMS n=98	TST(+)	13	8	0.51, 95% CI 0.30-0.72
	TST(-)	8	69	

QFT-GIT: QuantiFERON-TB Gold In-Tube Test; TST: tuberculin skin test; IMS: immunosuppressant; CI: confidence interval

Table 3. Univariate and multivariate analyses of factors associated with results of tuberculin skin test (TST) and/or QuantiFERON-TB Gold In-Tube Test (QFT-GIT)

	TST			QFT-GIT		
Variables	Univariate OR (95% CI)	p	Multivariate OR (95% CI)	Univariate OR (95% CI)	p	Multivariate OR (95% CI)
Age	1.085 (1.04-1.12)	<0.001	1.037 (1.029-1.119)	1.06 (1.03-1.10)	0.001	1.046 (1.005-1.089) p=0.026
Male sex	2.17 (0.91-5.16)	0.081	1.476 (0.529-4.12) p=0.457	2.78 (1.18-6.52)	0.019	2.4075 (0.965-6.009)
Inflammatory activity	0.765 (0.34-1.73)	0.519		0.674 (0.31-1.48)	0.323	
Immunosuppression	0.939 (0.39-2.28)	0.890		0.567 (0.25-1.29)	0.174	
Use of ≥2 immunosuppressive therapies	3.581 (0,79-16.2)	0.098	5.773 (0.652-51.16) p=0.115	1164 (0-infinite)	0.0001	17.595 (3.502-infinite)
Personal history of TB	5.89 (0.94-37.02)	0.059	2.166 (0.179-26.23) p=0.544	4.94 (0.79-30.88)	0.088	1.12 (0.085-14.781) p=0.932
Contacts of risk	2.68 (0.94-7.67)	0.066	1.515 (0.427-5.38) p=0.521	2.89 (1.04-8.01)	0.043	1.978 (0.562-6.97) p=0.288
Signs of LTBI in chest X-ray	3.207 (1.15-8.91)	0.025	2.171 (0.567-8.312) p=0.258	4.40 (1.61-12.02)	0.004	5.739 (1.747-18851)

NS: non-statistically significant

In patients with inflammatory disease activity, the rate of positive results both in the TST and QFT-GIT was not significantly different between patients who had inflammatory activity at the time of the test and those without activity: 19% vs 24 % for TST (p=0.5181) and 21% vs 28% for QFT-GIT (p=0.3217).

Table 3 shows the univariate and multivariate analyses for factors associated with the results of the tests. Neither inflammatory activity nor immunosuppression at the time of the test was associated with positive results, either for the TST or for the QFT-GIT; however, the results of QFT-GIT were influenced in those patients receiving two or more immunosuppressive drugs. In the multivariate analysis for a positive result in the TST, only age remained significant [odds ratio (OR), 1.037; 95% CI, 1.029-1.119]. In the case of positive results in the QFT-GIT, the absence of two or more immunosuppressive therapies (OR, 17.595; 95% CI, 3.502-infinity), presence of X-ray findings indicative of LTBI (OR, 5.739; 95% CI, 1.747-18.851), and male sex (OR, 2.408; 95% CI, 0.965-6.009) remained in the model.

We also studied those cases with disagreements between the two tests. There were eight patients with QFT-GIT(-) but TST(+), of whom seven were receiving immunosuppressive therapy. Of them, five patients had a history of previous contact or chest X-ray with residual changes. Three patients received chemoprophylaxis with isoniazid and one subsequently received anti-TNF treatment. Active TB was not detected in any patient during follow-up. There were 12 patients with QFT-GIT(+) but TST(-), of whom eight were receiving immunosuppressive therapy (nine of them received chemoprophylaxis with isoniazid and none received anti-TNF therapy). Overall, 30 patients started chemoprophylaxis with isoniazid and 18 continued or initiated treatment with anti-TNF agents. After a median follow-up of 15 months (interquartile range (IQR),

8.5-18.5 months), no patients developed active TB in the overall series.

DISCUSSION

Screening for LTBI is routine in patients with IBD who are candidates for IMM and/or anti-TNF therapies to avoid the risk of developing active TB (119. Historically, screening consists of the TST and chest X-ray. However, new techniques based on IGRA have been developed to address substantial limitations with the TST. For example, the TST has limited specificity because prior contact with other NTM or BCG vaccination can influence the results (19,20). Likewise, immunosuppression, an incorrect administration, or reading of the test can affect the sensitivity, and administration by an experienced nurse is recommended to avoid variability in the interpretation of the test (21). The test also requires at least two visits to the clinic (four if a booster test is administered). Measurement of QFT-GIT in a single routine blood draw could help overcome some of the drawbacks if the diagnostic precision of the two tests was similar or better. Indeed, IGRAs are now included in some clinical practice guidelines. However, data on their role in patients with IBD are limited (6,8,18,22). Theoretical advantages of IGRAs include the objectivity of the test, rapidly available results, ease of use and reproducibility in the laboratory, possibility of repetition without causing immunostimulation, greater specificity given that antigens absent in most NTMs are used, and use of a positive mitogen control to enable interpretation of apparently negative results according to the immune status of the patient (19).

In our study, the rate of positive results for the TST and the QFT-GIT test was 21.7% and 24.6%, respectively. The rate of LTBI for patients with IBD is reportedly between 12% and 34%, although these rates can vary according to factors such as prevalence of LTBI in each geographic region and concomitant corticosteroid and immunosuppressive therapy (14,17,23). In our study, 71% of the patients were receiving immunosuppressive therapy, a percentage similar to those reported by other authors (17). In a Spanish study in the region of Asturias, Arias et al. (24) investigated the performance of two IGRAs (QFT-IT and T-SPOT.TB). They found a lower rate of positivity in the QFT-GIT (7.8%) and the T-SPOT.TB (12.6%) than in the TST (26.8%). In this cohort, the global rate of LTBI was almost 35%. The difference in the rate of positive test for QFT-GIT compared with our study is difficult to explain. We hypothesize that some factors as the high prevalence rate of TB in our area, the percentage of patients under immunosuppressive therapy (in particular with ≥2 immunosuppressive drugs), or a potential variability in laboratory procedures could have influenced our results. In other areas with a high prevalence of TB infection, a 22% positive QFT-IT have been found (25).

Patients with IBD can present some degree of anergy secondary to multiple immunosuppressive drugs and/or concomitant malnutrition associated with the disease that can lead to false-negative results in TST (2). With regard to the influence of immunosuppressive therapy on the results, the evidence is contradictory. Similar to the results in our case, Papay et al. (17) did not find any relevant difference in the rate of positive results for TST according to immunosuppressive therapy. In contrast, Schoepfer et al. (14) reported a negative influence of immunosuppressive therapy on the TST but not the QFT-GIT in their series wherein 81% of patients were receiving immunosuppressive therapy. The sample size, degree of inflammatory activity at the time of performing the test, the different criteria for interpreting the results of the test, and the heterogeneity in the study populations (geographic area, percentage of vaccinated patients, and in immunosuppressive therapy) may explain these differences (14,17,25-27). Recent data indicate in particular how treatment with corticosteroids alone or in association with IMM may lead to a higher rate of indeterminate or negative results in QFT-GIT (28). In view of the above, to avoid the potential influence of immunosuppression on these tests, it is recommended to screen for LTBI before starting immunosuppressive therapy (25,27,29).

The QFT-GIT(+)/TST(-) discordances have been attributed in the literature to a theoretically larger influence of immunosuppressive therapy on TST, although this effect has not been confirmed by all authors (14,17,30). Cases of TST(+)/QFT-GIT(-) discordance have been attributed to lower TST specificity in patients with a history of contact or prior BCG vaccination. However, the influence of BCG vaccination seems to be of little relevance 10-15 years after immunization and in children and adults older than 30 years, regardless of the age of vaccination (11,31). The median age of patients in our cohort was 40 years. In Spain, the rates of childhood vaccination with BCG have varied over time and by geographic location. Moreover, at the time of conducting the study and according to local guidelines, BCG vaccination should not influence the evaluation of patients with IBD (18). In view of this, we believe that BCG vaccination may have limited or no impact on TST results in our study. The discordances may also be related to the fact that the tests measure different immune responses and that the IGRA tests detect more recent infections, which theoret-

ically are those with greatest risk of progression to active TB (32). One study did not identify any cases of active TB in TST(+)/QFT-GIT(-) contacts in which chemoprophylaxis was not administered, but no data are available in patients with IBD (33).

Concordance between tests varies according to the study. The meta-analysis in the study conducted by Shahidi et al. (27) showed an 85% agreement, and this appears to be higher in the absence of immunosuppressive therapy. In immunosuppressant-naive patients in our study, no positive results for the TST were reported that were not also detected with the QFT-GIT test. In the case of immunosuppressive therapy, several observations point to the need to perform the TST and IGRA jointly and in sequence, and in some cases, the evidence suggests that T-SPOT.TB is less influenced by immunosuppressive therapy than QFT-GIT (17,20,24,34).

Our study has certain limitations. The main one is the small sample size that limits the power of the subanalysis to assess the influence of immunosuppressive therapy and its types and the degree of inflammatory activity on the results in both tests. The current guidelines in our country recommend using only the TST in immunocompetent subjects (35). On the other hand, in some countries in Europe, it has been suggested to use the new IGRA instead of TST (36).

In summary, despite its limitations, our results suggest that although in those patients who are receiving immunosuppressants it may be indicated to use both test simultaneously according to the IDSA Guidelines, the use of QFT-GIT test to screen for LTBI may be sufficient in patients with IBD who have not started immunosuppressive therapy, particularly if TST has not been performed in optimal conditions (22). Nevertheless, our data should be confirmed in multicentric collaborative studies including a higher number of patients and with different immunosuppressive regimens.

Ethics Committee Approval: Ethics committee approval was received from the Local Ethics Committee.

Informed Consent: Informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

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