Tuberculosis screening in patients with psoriasis before antitumour necrosis factor therapy: comparison of an interferon-γ release assay vs. tuberculin skin test

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Summary

Background Antitumour necrosis factor (anti-TNF) treatments may reactivate latent tuberculosis infection (LTBI). For detecting LTBI, the tuberculin skin test (TST) has low sensitivity and specificity. Interferon-γ release assays (IGRA) have been shown to be more sensitive and specific than TST.

Objective To compare the TST and the T-SPOT.*TB* IGRA for identifying LTBI in patients with psoriasis before anti-TNF treatment.

Methods A retrospective study was carried out over a 4-year period on patients with psoriasis requiring anti-TNF treatment. All were subjected to the TST, T-SPOT.*TB* and chest X-ray. Risk factors for LTBI and history of bacillus Calmette–Guérin (BCG) vaccination were recorded. The association of T-SPOT.*TB* and TST results with risk factors for LTBI was tested through univariate logistic regression models. Agreement between tests was quantified using kappa statistics. Treatment for LTBI was started 1 month before anti-TNF therapy when indicated.

Results Fifty patients were included; 90% had prior BCG vaccination. A positive T-SPOT.*TB* was strongly associated with a presumptive diagnosis of LTBI (odds ratio 7·43; 95% confidence interval 1·38–39·9), which was not the case for the TST. Agreement between the T-SPOT.*TB* and TST was poor, $\kappa = 0{\cdot}33$ (SD 0·13). LTBI was detected and treated in 20% of the patients. In 20% of the cases, LTBI was not retained in spite of a positive TST but a negative T-SPOT.*TB*. All patients received an anti-TNF agent for a median of 56 weeks (range 20–188); among patients with a positive TST/negative T-SPOT.*TB*, no tuberculosis was detected with a median follow-up of 64 weeks (44–188). One case of disseminated tuberculosis occurred after 28 weeks of adalimumab treatment in a patient with LTBI in spite of treatment with rifampicin.

Conclusion This study is the first to underline the frequency of LTBI in patients with psoriasis (20%), and to support the use of IGRA instead of the TST for its detection. Nevertheless, there is still a risk of tuberculosis under anti-TNF therapy, even if LTBI is correctly diagnosed and treated.

Antitumour necrosis factor (anti-TNF)-α agents are approved for the treatment of psoriasis or other inflammatory diseases. However, they may reactivate latent tuberculosis infection (LTBI).[1,2] Thus, screening for LTBI is mandatory and preventive treatment should be given to all patients with evidence of LTBI before starting any anti-TNF-α therapy,[3] even if it does not offer complete protection.[4] Screening for LTBI is traditionally based on history, chest X-ray and the tuberculin skin test (TST).[5–7] However, the TST has disadvantages: a low specificity with false-positive results in bacillus Calmette–Guérin (BCG)-vaccinated subjects. This leads to unnecessary treatments for LTBI with a significant risk of drug toxicity, and lower sensitivity in immunosuppressed patients compared with healthy subjects resulting in false-negative results and a subsequent risk of tuberculosis reactivation with anti-TNF therapy. Finally, the limit above which the TST is considered positive (i.e. indicative of latent infection) differs according to countries and guidelines (5–10 mm).

Since the early 2000s, *in vitro* blood tests measuring production of interferon (IFN)-γ by T cells exposed to antigens highly specific for *Mycobacterium tuberculosis* have been developed. These tests (T-SPOT.*TB*; Oxford Immunotec, Oxford, U.K. and QuantiFERON®-TB Gold; Cellestis, Carnegie, Australia), collectively referred to as IFN-γ release assays (IGRAs), are not affected by prior BCG vaccination, thus offering increased specificity compared with the TST.[8] Their sensitivity, extrapolated from studies in patients with active tuberculosis, is probably at least as good as that of the TST in the detection of LTBI. Recent guidelines have integrated the use of IGRAs in screening strategies for subjects exposed to tuberculosis. The U.S. Centers for Disease Control and Prevention guidelines[9] state that the QuantiFERON-TB Gold test can be used in all circumstances in which the TST is used and can be used in place of the TST. The U.K. National Institute for Health and Clinical Excellence 2006 guidelines[10] and the 2007 Swiss national guidelines[11] both recommend, for immunocompetent adults, a two-step procedure, i.e. confirmation of positive TST results using an IGRA.

However, there are few data on LTBI detection and use of IGRAs in patients with psoriasis. The aim of this study was (i) to determine the frequency of LTBI in a population of patients with psoriasis before anti-TNF treatment, (ii) to compare the TST with T-SPOT.*TB* for detecting LTBI, and (iii) to evaluate the tolerance and effectiveness of treatment for LTBI under anti-TNF therapy in our patients.

Materials and methods

This retrospective study was conducted in two academic dermatological centres (University Hospital, Geneva and CHUV, Lausanne). All patients seen between November 2004 and March 2008 with moderate to severe psoriasis qualifying for anti-TNF-α therapy were screened for LTBI with a chest X-ray, a TST and a T-SPOT.*TB* IGRA. The TST was considered positive if the induration diameter was ≥ 5 mm. As there is no 'gold standard' test for the diagnosis of LTBI, we aimed to evaluate the risk factors for LTBI by recording the following data: age; country of origin and tuberculosis incidence in the country of origin according to World Health Organization data; history of tuberculosis exposure (family or work); history of prolonged stay in a high-incidence area; BCG vaccination; and prior immunosuppressive therapy (methotrexate, ciclosporin or efalizumab).

In the absence of a 'gold standard' for the diagnosis of LTBI, we analysed results of the T-SPOT.*TB* and the TST in relation to the risk factors for LTBI, BCG-vaccination status, and to a composite variable defining a probable diagnosis of LTBI ('probable LTBI') defined as having a history of definite exposure to a case of active tuberculosis and/or having a chest X-ray suggestive of prior tuberculosis infection (granulomas, calcified adenopathy) and/or originating from a high-incidence country (defined as > 40 cases in 100 000 per year).

The association of either T-SPOT.*TB* or TST results with risk factors for LTBI or BCG-vaccination status was tested through univariate logistic regression models. Agreement between tests was quantified using kappa statistics. All statistical analyses were performed with SPSS version 14.0, 2006 (Statistical Package for Social Sciences Inc., Chicago, IL, U.S.A.).

If LTBI was diagnosed, treatment with either rifampicin (10 mg kg^{-1}, max. 600 mg daily) for 4 months or isoniazid (5 mg kg^{-1}, max. 300 mg daily) for 9 months was started 1 month before introducing anti-TNF-α therapy, according to the Swiss guidelines.[11]

Results

Fifty patients were analysed (Table 1). Ten patients (20%) came from or had lived in a country with a high incidence of tuberculosis. Forty-five patients (90%) had prior BCG vaccination.

Comparative results of tuberculin skin test and T-SPOT.*TB*

In 28 patients (56%), the TST and T-SPOT.*TB* were both negative. In eight patients (16%) both the T-SPOT.*TB* and TST (≥ 5 mm) were positive. Two cases had a negative TST but a positive T-SPOT.*TB* with a chest X-ray suggestive of LTBI (granuloma). In 12 cases (24%) the TST was positive and the T-SPOT.*TB* was negative; all had prior BCG vaccination and a normal chest X-ray. Agreement between both tests was poor for TST ≥ 5 vs. T-SPOT.*TB*: 36/50 (72%), $\kappa = 0{\cdot}33$ (SD 0·13).

Probability of having a positive interferon-γ release assay or tuberculin skin test according to specific risk factors

Table 2 shows the association between the presence of risk factors for LTBI and results of an IGRA and TST based on univariate logistic regression analyses. Significant associations were found between having a positive T-SPOT.*TB* and probable LTBI, a chest X-ray suggestive of LTBI or a history of exposure to active tuberculosis. There was no association with age, previous immunosuppressive therapy or country of origin with a high incidence of tuberculosis. Conversely, none of the above-mentioned variables was associated with having a TST either ≥ 5 or 10. Association with BCG-vaccination status could not be tested, because of the high rate of patients vaccinated (90%). Results from the multivariable analysis (not shown) were not significant.

Latent tuberculosis infection diagnosis and treatment

A diagnosis of LTBI was considered in the 10 cases (20%) with a positive T-SPOT.*TB*. In 28 patients with both a negative TST and T-SPOT.*TB*, LTBI was considered as reasonably excluded. In 12 cases (24%) with a TST ≥ 5 but a negative T-SPOT.*TB*, all with a prior BCG vaccination and a normal X-ray, a diagnosis of LTBI was not considered.

A total of 12 patients were treated for LTBI (nine with rifampicin and three with isoniazid): the 10 patients with LTBI,

Table 1 Characteristics of the 50 patients analysed

Characteristic	All (n = 50)	T-SPOT.TB		TST ≥ 5 mm		TST ≥ 10 mm	
		Pos (n = 10)	Neg (n = 40)	Pos (n = 20)	Neg (n = 30)	Pos (n = 18)	Neg (n = 32)
Age (years), mean (range)	48 (17–74)	54·3 (25–63)	46·4 (17–75)	47·5 (17–64)	48·3 (25–74)	49·2 (25–64)	47·3 (17–75)
Male, n (%)	35 (70)	6 (60)	29 (72)	12 (60)	23 (77)	11 (61)	24 (75)
Prior immunosuppressive therapy[a], n (%)	34 (68)	8 (80)	26 (65)	12 (60)	22 (73)	10 (55·5)	24 (75)
BCG vaccination, n (%)	45 (90)	9 (90)	36 (90)	19 (95)	26 (87)	17 (94)	28 (87·5)
Risk factors for LTBI, n (%)							
High TB incidence in country of origin	10 (20)	3 (30)	7 (17)	6 (30)	4 (13)	5 (27·8)	5 (15·6)
Contact with TB patient (family or work)	11 (22)	5 (50)	6 (15)	6 (30)	5 (17)	5 (27)	6 (18·75)
Chest X-ray suggestive of TB	4 (8)	4 (40)	0 (0)	2 (10)	2 (7)	2 (11·1)	2 (6·25)
Probable LTBI[b]	21 (42)	8 (80)	14 (35)	11 (55)	11 (37)	12 (66·6)	10 (31·2)

BCG, bacillus Calmette–Guérin; LTBI, latent tuberculosis infection; TST, tuberculin skin test; Pos, positive; Neg, negative. [a]Methotrexate, ciclosporin or efalizumab. [b]Probable LTBI was defined as having a history of definite exposure to a case of active TB and/or having a chest X-ray suggestive of prior TB infection (granulomas, calcified adenopathy) and/or originating from a country with a high incidence (defined as > 40 in 100 000 per year).

Table 2 Association of either T-SPOT.TB or the tuberculin skin test (TST) results with risk factors for latent tuberculosis infection (LTBI): univariate logistic regression models

Characteristics	T-SPOT.TB	TST ≥ 5 mm	TST ≥ 10 mm
	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)
Age	1·05 (0·99–1·11)	0·99 (0·95–1·0)	1·01 (0·99–1·11)
Prior immunosuppressive therapy[a]	1·71 (0·31–9·3)	0·85 (0·24–2·97)	0·66 (0·18–2·36)
Risk factor for LTBI			
High TB incidence in country of origin	2·02 (0·42–9·8)	2·78 (0·67–11·7)	2·07 (0·51–8·47)
Contact with TB patient (family or work)	**5·67 (1·25–25·7)**	2·14 (0·55–8·3)	1·67 (0·43–6·5)
Chest X-ray suggestive of TB	**25·3 (2·41–267)**	2·6 (0·39–17·4)	3·21(0·48–21·4)
Probable LTBI[b]	**7·43 (1·38–39·9)**	3 (0·93–9·7)	2·08 (0·64–6·73)

CI, confidence interval. [a]Prior immunosuppressive therapy: methotrexate, ciclosporin or efalizumab. [b]Probable LTBI defined as having a history of definite exposure to a case of active TB and/or having a chest X-ray suggestive of prior TB infection (granulomas, calcified adenopathy) and/or originating from a country with a high incidence (defined as > 40 in 100 000 per year). Bold text: significant association ($P < 0·01$)

and two patients with a positive TST (≥ 5 mm) and a negative T-SPOT.TB but included in a clinical trial which did not accept the validity of T-SPOT.TB. There were no serious adverse effects with the LTBI treatment; two patients had an elevation of transaminase less than five times the normal limit, which did not required the interruption of therapy.

Antitumour necrosis factor therapy

Patients received anti-TNF-α therapy (etanercept, infliximab or adalimumab) for a median of 56 weeks (range 20–188). No case of tuberculosis occurred in the 10 patients with a positive TST/negative T-SPOT.TB who were not treated for LTBI, after a median duration of 64 weeks of anti-TNF therapy (range 44–188). A disseminated tuberculosis occurred after 28 weeks of adalimumab in a patient with LTBI treated with rifampicin for 4 months.

Discussion

The present study is to our knowledge the first to show that, in a population of patients treated for psoriasis, a positive T-SPOT.TB IGRA is strongly associated with the presence of risk factors for LTBI. This association was not found for the TST, and agreement between the T-SPOT.TB and TST was poor, probably because of a high rate of BCG-vaccinated patients (90%) acting as a confounding factor. As there is no gold standard for the diagnosis of LTBI, it was impossible to estimate the true sensitivity and specificity of either test in this setting.

There are very few data concerning LTBI and the use of IGRAs in patients with psoriasis. In a recent report of 11 patients, Desai *et al.*[12] studied the utility of another IGRA (QuantiFERON) in screening for LTBI before anti-TNF therapy. They suggest that QuantiFERON should replace the TST for LTBI screening because its validity is well documented in rheumatological disorders, but there was no evaluation of risk factors for LTBI in the patients assessed.

We chose to base our diagnosis of LTBI on the results of the T-SPOT.TB rather than on the TST. Several points suggest that patients with LTBI were correctly identified: patients with a positive T-SPOT.TB had a significant association with risk factors for LTBI; and in 10 of 12 patients with a positive TST and a negative T-SPOT.TB, no treatment was given and no tuberculosis occurred under anti-TNF therapy with a mean follow-up of 76 weeks. According to the literature, most cases of tuberculosis in patients receiving anti-TNF therapy are detected within 12 months of the beginning of anti-TNF treatment.[13] Treatment for LTBI was administered in 12 cases, and was avoided in 10 patients, whereas it would have been given to 22 patients if we have followed the guidelines based on the TST alone. Treatment for LTBI was relatively well tolerated, with a slight elevation of transaminases in two patients.

Twenty per cent of our patients had a probable LTBI which we consider to be a high rate; however, we were unable to compare our results with those from other studies, as published data only report the frequency of tuberculosis in patients under an anti-TNF agent for moderate to severe plaque psoriasis.[6] In these studies, the patients were screened for LTBI and treated if necessary before the anti-TNF treatment, but the actual number diagnosed with LTBI, and the tolerance of its therapy are not reported.

An important message from our observations is that the risk of active tuberculosis under anti-TNF therapy persists even if LTBI is diagnosed and treated. Indeed, a case of disseminated tuberculosis occurred in a patient adequately treated for LTBI. Even if screening of LTBI reduces the occurrence of active tuberculosis under anti-TNF therapy,[14] a residual risk remains, with atypical and disseminated presentations that dermatologists should be aware of.

Our study had a few limitations. It was retrospective in design, but as all patients seen in both institutions were analysed, the risk of selection bias was limited. Also, we included a relatively low number of patients, which may have limited the feasibility of certain statistical computations (i.e. multivariate logistic regression). However, the data presented are the first to show in this population highly significant univariate results between risk factors for LTBI and the T-SPOT.TB, and support the use of IGRAs instead of the TST.

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