CLINICAL REPORT

Patients with Psoriasis are More Likely to be Treated for Latent Tuberculosis Infection Prior to Biologics than Patients with Inflammatory Bowel Disease

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Screening for latent tuberculosis infection (LTBI) is recommended before treatment with biologics is initiated in patients with psoriasis or inflammatory bowel disease (IBD). Our objective was to evaluate the effect of underlying disease (psoriasis or IBD) on the risk of LTBI diagnosis prior to anti-tumor necrosis factor-alpha (TNF-α) therapy. During a two-year period LTBI diagnosis rate was compared in consecutive patients with psoriasis or IBD (Crohn's disease or ulcerative colitis). IBD patients ($n = 33$) had significantly smaller tuberculin skin testing compared to psoriasis patients ($n = 30$) ($p = 0.007$). Applying LTBI diagnosis guidelines resulted in more psoriasis (50%) than IBD patients (24.2%) receiving treatment for LTBI prior to onset of anti-TNF-α treatment ($p = 0.04$). In conclusion, current recommendations for LTBI diagnosis must be re-evaluated to account for the unique tuberculin hyperactive state of the skin of patients with psoriasis. *Key words: psoriasis; inflammatory bowel disease; tuberculosis; tuberculin skin test; biologics.*

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Screening for latent *Mycobacterium tuberculosis* infection (LTBI) before initiating therapy with immunomodulating medications, including tumour necrosis factor-alpha blocking (anti-TNF-α) agents, is part of current therapeutic strategies for the management of common inflammatory disorders, such as psoriasis and inflammatory bowel diseases (IBD). Despite recent advances in *ex vivo* diagnostic techniques, tuberculin skin testing (TST)-based algorithms are still in use worldwide for diagnosis of LTBI (1–3). This has minimized the risk of tuberculosis reactivation in patients under immunosuppressive regimens (3, 4). Recent data suggest that the clinical activity of psoriasis substantially affects the outcome of TST (5); however, the impact of this finding on the likelihood of LTBI diagnosis in patients with moderate-to-severe plaque psoriasis is still obscure. In order to examine the influence of the deviate TST reactivity of patients with psoriasis on the probability of positive LTBI diagnosis we compared the rate of LTBI diagnosis of patients with psoriasis or IBD evaluated for commencement of anti-TNF-α treatment.

MATERIALS AND METHODS

Following approval from the ethics committee of the University Hospital of Ioannina we retrospectively reviewed the files of 30 patients with moderate-to-severe plaque psoriasis (Psoriasis Area and Severity Index (PASI) scores: 9.5–37; median PASI: 15.5) and 33 patients with IBD (Crohn's disease or ulcerative colitis) who had been evaluated in the Departments of Dermatology and Internal Medicine of this hospital for LTBI in the period 1 January 2006 to 31 December 2007. The patients had been screened for LTBI according to the Centers for Disease Control and Prevention – American Thoracic Society (CDC-ATS) guidelines for the diagnosis of tuberculosis, with a cut-off level of TST ≥ 5 mm (1, 2). TST, using the one-step method according to the Mantoux technique, was uniformly provided to all patients in the Department of Hygiene and Vaccinations of this Hospital using a commercial purified protein derivative (PPD) solution (PPD RT 23 SSI, Statens Serum Inst, Copenhagen, Denmark; testing details in (5)). A TST cut-off level ≥ 5 mm is generally recommended for admission to LTBI treatment for patients with psoriasis (2) and IBD (3) treated with anti-TNF-α agents, irrespective of their immunovigilance status, and has been proved effective in preventing tuberculosis reactivation after therapy with anti-TNF-α agents in Spain (4), an area with tuberculosis risk characteristics comparable to those of Greece (6). Patients under immunosuppressive treatment at the time of testing with TST values < 5 mm were further evaluated as recommended (1, 2) to determine their *M. tuberculosis* infection status. One-way analysis of variance (ANOVA), Fisher's exact and the Mann–Whitney *U* tests were calculated with the SPSS software version 17.0 (Chicago, IL, USA). Two-sided *p*-values < 0.05 were applied to indicate statistical significance.

RESULTS

In this cohort psoriasis and IBD patients did not differ in their core demographic characteristics. None of the 63 patients was diagnosed with overt tuberculosis at the time of evaluation and none developed tuberculosis after a follow-up period of 2–4 years (events up to 31 December 2009 were taken into consideration). The results of tuberculin testing prior to onset of therapy are shown in Fig. 1 and Table I. Patients with psoriasis showed significantly larger TST reactions (median TST = 4.5 mm) compared
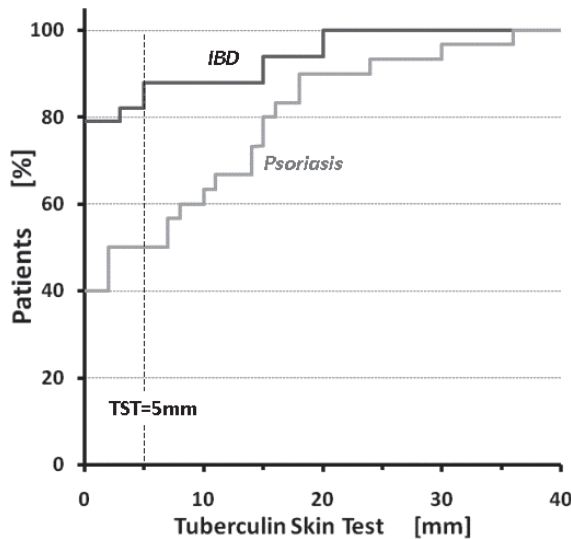
Fig. 1. Cumulative frequency distributions of patients with either psoriasis or inflammatory bowel disease (IBD) according to tuberculin skin testing (TST) results prior to onset of therapy with anti-tumour necrosis factor-α biologics. Note the significantly larger TST outcomes in patients with psoriasis ($p=0.007$; Mann–Whitney U test). The perpendicular dashed line corresponds to the cut-off value of TST = 5 mm, which indicates a treatment-needy *M. tuberculosis* latent infection in patients prior to onset of anti-TNFα biologics.

with patients with IBD (median TST = 0 mm; $p=0.007$, Mann–Whitney U test). Furthermore, significantly more patients with psoriasis received LTBI treatment prior to onset of biologics ($p=0.040$, Fisher's exact test), 50% of patients with psoriasis (15 patients with TST ≥ 5 mm) compared with only 24% of patients with an IBD (6 patients with TST ≥ 5 mm and 2 patients with TST <5 mm who were diagnosed with LTBI according to demographic and/or radiological criteria (1, 2)).

DISCUSSION

The present data indicate that patients with moderate-to-severe plaque psoriasis, when evaluated according to TST-based guidelines for tuberculosis prior to the onset of biologics (1, 2), are more likely to be treated for LTBI than corresponding IBD patients sharing the same demographic background. A stronger degree of immunosuppression was present in patients with IBD (all receiving corticosteroids plus either azathioprine or methotrexate) compared with patients with psoriasis (non receiveing systemic treatment during the last month prior to TST) at the time of LTBI evaluation. However, this difference cannot account for the observed discrepancy in LTBI treatment rates, since the immuno-vigilance state of the patients is adequately considered in all current diagnosis and treatment guidelines (1, 2). This conclusion is further supported by the absence of differences in hepatitis viruses A, B and C serology status of patients with IBD and psoriasis in the present cohort (data not shown). Additionally, the following evidence is in line with the suggestion that patients with psoriasis

Table I. *Comparison of the results of tuberculin skin test (TST) screening for latent Mycobacterium tuberculosis infection (LTBI) prior to onset of treatment with anti-TNF-α biologicals in patients with either psoriasis or inflammatory bowel diseases (IBD)*

Diagnosis	Patients admitted to TST (*n*)	Female[a] *n* (%)	Age, years Median [range][b]	TST, mm Median [range][c]	TST, mm Mean (SD)	Patients with TST=0 mm[d] *n* (%)	Patients with TST reactivity according to screening guidelines for tuberculosis cut-off values[e]			Patients admitted to LTBI treatment[g] *n* (%)
							TST <5 mm[f] *n* (%)	TST 5–15 mm *n* (%)	TST >15 mm *n* (%)	
Psoriasis	30	9 (30)	43.0 [18–66]	4.5 [0–36]	8.30 (9.91)	12 (40)	15 (50)	7 (23)	8 (27)	15 (50)
IBD	33	11 (33)	41.5 [16–68]	0 [0–20]	2.52 (5.86)	26 (79)	27 (82)	2 (6)	4 (12)	8 (24)
Crohn's disease	22	7 (32)	38.5 [16–68]	0 [0–20]	3.09 (6.45)	16 (73)	17 (77)	2 (9)	3 (14)	6 (27)
Ulcerative colitis	11	4 (36)	52.0 [27–64]	0 [0–15]	1.36 (4.53)	10 (90)	10 (90)	0 (0)	1 (10)	2 (18)

[a]No difference in gender distribution between patients with psoriasis and IBD ($p=0.767$; Fisher's exact test).
[b]No difference in age between patients with psoriasis and IBD ($p=0.98$; Mann–Whitney test).
[c]Patients with psoriasis show statistically significant larger TST results than patients with IBD ($p=0.007$; Mann–Whitney test).
[d]Statistically significant more patients with an IBD present with TST=0 ($p=0.002$; Fisher's exact test).
[e]TST results differ between patients with psoriasis and with IBD (TST categories according to cut-off values proposed in guidelines for screening for tuberculosis infection prior to immunosuppressive/immunomodulating treatment ($p=0.02$; one-way analysis of variance (ANOVA)).
[f]Statistically significant more patients with an IBD present with "negative" TST results <5 mm ($p=0.015$; Fisher's exact test).
[g]Statistically significant more patients with psoriasis receive treatment for LTBI ($p=0.04$; Fisher's exact test).

are overtreated for LTBI prior to onset of biologics: (*i*) no case of tuberculosis reactivation occurred in the present cohort of IBD patients during adequate follow-up period under immunosuppressive treatment; and (*ii*) a similar rate of LTBI treatments of IBD patients prior to onset of biologics (approximately 25%) has been reported from a comparable population (7).

Considering the reason for the presently observed excess LTBI treatment rates of patients with psoriasis, previous observations suggest that patients with psoriasis show increased TST reactivity (5), probably resulting from a priming of their clinically healthy skin to over-react to a broad spectrum of antigenic triggers (8), including *M. tuberculosis*-derived antigens (9). Psoriasis is currently conceptualized as a T-lymphocyte-mediated disease, with TH-1 cytokines having a key role in eliciting and maintaining skin lesions (10). Similarly in TST, in the presence of intradermal mycobacterial antigens neutrophilic granulocytes are initially recruited to the site of tuberculin injection and in turn stimulate local dendritic cells to produce TH-1 cytokines (11). Increased numbers of activated plasmacytoid pre-dendritic cells are found in non-lesional psoriasis skin (12) and are probably the main source of interferon alpha (IFN-α), the core cytokine mediating the development of both the psoriatic plaque and TST induration. Additionally, β-defensin 2 (hBD2), which currently emerges as a central player in the orchestration of genetic and environmental effects on disease activity in psoriasis, is globally overexpressed in the skin of patients with psoriasis (13). On the other hand, hBD2 induction by *M. tuberculosis* is essential for the pathogenesis of tuberculosis in humans (14). It seems therefore reasonable to propose that injection of tuberculin antigens into the unaffected skin of patients with overt plaque psoriasis triggers augmented inflammatory reactions resulting in stronger TST. Future studies designed to compare TST reactivity in patients with psoriasis as a function of disease activity and TST-independent measurements of tuberculosis immunity should challenge this prediction.

In conclusion, the evidence presented here suggests that adherence to the widely accepted TST-based recommendations for the diagnosis of tuberculosis leads to overdiagnosis of LTBI in patients with plaque psoriasis. TST-independent laboratory methods to diagnose LTBI are a promising approach to overcome this problem, yet their predictive values have to be evaluated in patients with psoriasis (15). Finally, the present observation calls for re-application of the official LTBI diagnosis algorithms and adaptation to the particular situation of patients with psoriasis.

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