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Latent tuberculosis infection in patients with psoriasis using biologic therapies

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Abstract

Some studies have demonstrated a high prevalence of latent tuberculosis infection (LTBI) in patients with psoriasis and a higher risk of active tuberculosis (TB) in patients with severe psoriasis. The objective of this study is to identify the prevalence of LTBI before starting treatment with different biologicals and to identify the prevalence of LTBI and active TB while using these medications. We conducted a cross-sectional study with retrospective data collection in the outpatient department of dermatology at a general, tertiary care, university-affiliated hospital. The electronic medical records of all adult patients (18 years old) with psoriasis undergoing treatment with biologics were reviewed, and information about psoriasis, the type of biological therapy used, and the tuberculin skin test (TST) results were collected. The patients included had an indication for the TST test according to the Ministry of Health. In total, 126 patients were included in the study. The median duration of disease was 20 years. A total of 31 patients (24.6%) had LTBI diagnosed at screening before the use of biologicals, and an additional 17 (17.9%) patients had a diagnosis of LTBI during biological therapy. There were no cases of active TB during treatment with biologicals. There was no difference in the prevalence of LTBI during treatment with tumor necrosis factor inhibitors, interleukin (IL)-17 inhibitors, IL-23 inhibitors, and IL-12/23 inhibitors (p=0.228). In conclusion, we found that 24.6% of patients with psoriasis in an endemic TB region had LTBI. Additionally, 16.8% had a diagnosis of LTBI during biological therapy. Our data corroborate the recommendation that patients who live in high TB incidence settings should be tested annually for LTBI.

Key words: tuberculosis, psoriasis, latent tuberculosis infection, *Mycobacterium tuberculosis*, biologic therapy.

Introduction

Psoriasis is an immune-mediated, inflammatory disease with a genetic basis, but its etiopathogenesis is not yet fully understood [1-3]. Approximately 2% to 3% of the world's population is affected by psoriasis [2]. In Brazil, patients with severe cutaneous psoriasis who do not respond adequately to conventional therapies, or who are intolerant or cannot use these treatments, biologic therapies are recommended. In the last decade, with the increased understanding of the immunopathogenesis of psoriasis, several biological agents have been introduced to the market in order to treat patients with severe psoriasis. However, the inhibition of crucial mediators of the innate and adaptive immune system generated by these drugs has also increased the risk of developing opportunistic infections, such as tuberculosis (TB) [3,4].
Some studies have demonstrated a high prevalence of latent TB infection (LTBI) in patients with psoriasis and a higher risk of active TB in patients with psoriasis classified as severe [5,6]. Due to the high prevalence of TB in our setting, in addition to the increased risk of severe forms of TB in patients using biologicals, TB/LTBI screening should be performed before starting these medications. Many cases of LTBI reactivation during treatment with TNF-alpha inhibitors and some isolated cases with IL-12/23 inhibitors (ustekinumab) have been reported. However, the risk of LTBI reactivation in patients with psoriasis using IL-17 and IL-23 blockers seems remote [4,7-9].
The objective of this study is to identify the prevalence of LTBI before starting treatment with different biologicals and to identify the prevalence of LTBI and active TB while using these medications, in a city of a developing country with intermediate-to-high TB endemicity.

Materials and Methods

Study design and location

We conducted a cross-sectional study with retrospective data collection in the outpatient department of Dermatology at a general, tertiary care, university-affiliated hospital (Hospital de Clínicas de Porto Alegre [HCPA]). This hospital is located in the city of Porto Alegre, in southern Brazil, with a TB incidence of 64.8 cases/100,000 population [10]. The study was approved by the Ethics Committee at HCPA (number 20210431).

Patients and data collection

The electronic medical records of all adult patients (18 years old) with psoriasis, undergoing treatment with biologics were reviewed. A standardized form was completed for each patient, with the following information: demographic data, comorbidities, duration of psoriasis, subtype and severity (PASI [Psoriasis Area Severity Index], BSA [Body Surface Area]), type of biological therapy used, and the tuberculin skin test (TST) results.

In Brazil, according to the Ministry of Health, it is recommended screening to identify LTBI in all patients being considered for therapy with biological agents. TST is the suggested test and is performed by intradermal injection on the flexor aspect of forearm of 0.1 mL (2 IU) of standard preparation of PPD RT-23 (Statens Serum Institut - Copenhagen, Denmark) (Mantoux method). Induration was measured 72 h after the injection. If positive ($\geqslant$ 5 mm) in the absence of active TB, treatment of LTBI is indicated [11,12]. Since 2019, according to the Clinical Protocol and Therapeutic Guidelines for Psoriasis adopted in Brazil, the recommendation is that in cases of negative TST, adalimumab should be used [13].

Statistical analysis

Data analysis was performed using IBM SPSS Statistics for Windows, version 22.0 (Armonk, NY, IBM Corp). Data were presented as number of cases, mean ± standard deviation (SD), or median with interquartile range (IQR). Categorical comparisons were performed by chi-square test using Yates's correction if indicated or by Fisher's exact test. Continuous variables were compared using the *t*-test or Wilcoxon test. A two-sided p value < 0.05 was considered significant for all analyses. Sample size calculation was based on the prevalence of LTBI in patients with psoriasis using biologic therapies found in a previous study: 20% [13]. Thus, considering a confidence interval width of 0.10 and a confidence level of 95%, it will be necessary to include at least 126 patients in the study.

Results

In total, 126 patients with psoriasis were treated with biologic therapies and were included in the study. The characteristics of the study population are shown in Table 1. The mean age was 53.5 ± 15.3 years and 53.2% were females. The median duration of disease was 20 years (IQR:14 - 28 years). The median baseline PASI score was 11.2 (IQR: 6.5 - 17.2) and the median BSA was 16% (IQR: 9.1% - 28.3%). The most common types of psoriasis were: plaque (n=117; 92.9%), inverse (n=12; 9.5%), and erythrodermic (n=10; 7.9%). The biologic therapies used were: etanercept (n=1; 0.8%), adalimumab (n=28; 22.2%), secukinumab (n=35; 27.8%), ixekizumab (n=1; 0.9%), risankizumab (n=10; 15.1%), and ustekinumab (n=42; 33.3%).

Thirty one patients (24.6%) had LTBI diagnosed at screening before the use of biologicals, and an additional of 16 (16.8%) patients had diagnosis of LTBI during biological therapy. There were no cases of active TB during treatment with biologicals. Three patients had had active TB in the past and they had no relapse during the study period (2 used Ustekinumab and 1 used secukinumab). There was no difference in the prevalence of LTBI during treatment with TNF inhibitors, IL-17 inhibitors, IL-23 inhibitors, and IL-12/23 inhibitors (p=0.228) (Table 2).

Discussion and Conclusions

In this study, we found a prevalence of LTBI among patients with psoriasis of 24.6%. During treatment with biologicals there were no cases of active TB; however, an additional of 17 (17.9%) patients had diagnosis of LTBI. The prevalence of LTBI was not different among patients who were treated with TNF inhibitors, IL-17 inhibitors, IL-23 inhibitors, and IL-12/23 inhibitors.

According to the World Health Organization (WHO), approximately 2–3 billion people are infected with *Mycobacterium tuberculosis* in the world, and 5%–15% of these people will progress from LTBI to active TB disease during their lifetime. In this sense, diagnosis and treatment of LTBI is crucial, especially in high-risk groups, as reactivation of LTBI accounts for a large proportion of active TB incidence [14,15]. In this study, we evaluated the prevalence of LTBI in a group of patients with psoriasis, and the percentage found was similar to that of previous studies [13,16]. In a study conducted with data from Spanish registry for systemic biological and non-biological treatment in psoriasis (BIOBADADERM) [13], including 793 patients, the prevalence of LTBI before starting biological treatment was 20.5%. In the Latent study [16], that included 440 patients with moderate to severe plaque psoriasis, the prevalence of LTBI was 23%.

TB cases during treatment with biologicals are usually a consequence of new infection or reactivation of LTBI not diagnosed during screening (due to false-negative TST) [17]. In the present study, there were no cases of TB diagnosed during biologic therapy. This absence of TB cases may be due to the fact that there were only 29 patients using TNF-alpha inhibitors, which are the biologicals associated with the highest risk of LTBI reactivation [18]. On the other hand, this may be related to a high level of compliance with the recommendations for screening, and also to the fact that patients with indication for LTBI treatment underwent treatment appropriately. However, we did not collect data related to LTBI treatment to confirm this hypothesis.

The Skin Inflammation and Psoriasis International Network-Fondation René Touraine (SPIN-FRT) recommends that all patients starting biologic and non-biologic therapies should be screened for LTBI/TB disease according to local guidelines. However, due to the low number of TB reactivation cases with IL-17 and IL-23 inhibitors, they highlight the need of reconsideration of the indication for screening and preventive treatment in these cases [18]. In the present study, we were unable to assess whether there was a difference in the number of TB cases according to the biological treatment used, since we did not have any TB cases.

This study has some limitations that we have to take into account. First, we recruited patients from a single center. However, we believe the results may apply to other settings, especially

endemic TB areas. Second, this was a retrospective study, but the information we obtained retrospectively from chart review was as complete as if it was collected prospectively.

In conclusion, we found that 24.6% of patients with psoriasis in an endemic TB region had LTBI. Additionally, 17.9% had diagnosis of LTBI during biological therapy. Our data corroborates the recommendation that patients who live in high TB incidence settings should be tested annually for LTBI. Despite the high incidence of tuberculosis in our population, there are few studies on psoriasis patients undergoing biologic treatment in our country.

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Table 1. Characteristics of study patients.

Characteristics	n (%), mean ± SD or median (IQR)
Age, in years	53.5 ± 15.3
Female sex	67 (53.2)
Psoriasis disease duration, in years	20 (14-28)
Baseline PASI	11.2 (6.5-17.2)
Baseline BSA	16 (9.1-28.3)
Type of psoriasis	
Plaque	117 (92.9)
Guttate	4 (3.2)
Pustular	6 (4.8)
Inverse	12 (9.5)
Erythrodermic	10 (7.9)
Palmoplantar	5 (3.9)
Nail	9 (7.1)
Ostraceous	1 (0.8)
Psoriatic arthirtis	32 (25.4)
Active smoking	20 (15.9)
Abusive alcohol intake	2 (1.6)
HIV	1 (0.8)
Diabetes	43 (34.1)
Biologic therapy	
Etanercept	1 (0.8)
Adalimumab	28 (22.2)
Secukinumab	35 (27.8)
Ixekizumab	1 (0.8)
Risankizumab	19 (15.1)
Ustekinumab	42 (33.3)
LTBI prior to biological therapy	31 (24.6)
LTBI during biological therapy	17 (17.9)

SD, standard deviation; IQR, interquartile range; PASI, Psoriasis Area Severity Index; BSA, body surface area; HIV, human immunodeficiency virus; LTBI, latent tuberculosis infection.

Table 2. LTBI prevalence according to biologic therapy used.

LTBI	TNF inhibitors	IL-17 inhibitors	IL-23 inhibitors	IL-12/23 inhibitors	p-value
Yes	2 (12.5)	3 (18.8)	4 (25.0)	7 (43.8)	
No	26 (34.2)	18 (23.7)	10 (13.2)	22 (28.9)	0.228

LTBI, latent tuberculosis infection.