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ORIGINAL RESEARCH ARTICLE

Treatment of Psoriasis Patients with Latent Tuberculosis Using IL-17 and IL-23 Inhibitors: A Retrospective, Multinational, Multicentre Study

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Abstract

Background Tuberculosis has a major global impact. Immunocompetent hosts usually control this disease, resulting in an asymptomatic latent tuberculosis infection (LTBI). Because TNF inhibitors increase the risk of tuberculosis reactivation, current guidelines recommend tuberculosis screening before starting any biologic drug, and chemoprophylaxis if LTBI is diagnosed. Available evidence from clinical trials and real-world studies suggests that IL-17 and IL-23 inhibitors do not increase the risk of tuberculosis reactivation.

Objective To evaluate psoriasis patients with treated or untreated newly diagnosed LTBI who received IL-17 and IL-23 inhibitors and the tolerability/safety of tuberculosis chemoprophylaxis.

Methods This is a retrospective, observational, multinational study from a series of 14 dermatology centres based in Portugal, Spain, Italy, Greece and Brazil, which included adult patients with moderate-to-severe chronic plaque psoriasis and newly diagnosed LTBI who were treated with IL-23 or IL-17 inhibitors between January 2015 and March 2022. LTBI was diagnosed in the case of tuberculin skin test and/or interferon gamma release assay positivity, according to local guideline, prior to initiating IL-23 or IL-17 inhibitor. Patients with prior diagnosis of LTBI (treated or untreated) or treated active infection were excluded.

Results A total of 405 patients were included; complete/incomplete/no chemoprophylaxis was administered in 62.2, 10.1 and 27.7% of patients, respectively. The main reason for not receiving or interrupting chemoprophylaxis was perceived heightened risk of liver toxicity and hepatotoxicity, respectively. The mean duration of biological treatment was 32.87 ± 20.95 months, and only one case of active tuberculosis infection (ATBI) was observed, after 14 months of treatment with ixekizumab. The proportion of ATBI associated with ixekizumab was 1.64% [95% confidence interval (CI): 0–5.43%] and 0% for all other agents and 0.46% (95% CI 0–1.06%) and 0% for IL-17 and IL-23 inhibitors, respectively (not statistically significant).

Conclusions The risk of tuberculosis reactivation in patients with psoriasis and LTBI does not seem to increase with IL-17 or IL-23 inhibitors. IL-17 or IL-23 inhibitors should be preferred over TNF antagonists when concerns regarding tuberculosis reactivation exists. In patients with LTBI considered at high risk for developing complications related to chemoprophylaxis, this preventive strategy may be waived before initiating treatment with IL-17 inhibitors and especially IL-23 inhibitors.

Extended author information available on the last page of the article

Key Points

Because TNF inhibitors increase the risk of tuberculosis reactivation, current guidelines recommend tuberculosis screening before starting any biologic drug, and chemoprophylaxis if a latent infection (LTBI) is diagnosed.

The risk of tuberculosis reactivation in patients with psoriasis and LTBI does not seem to increase with IL-17 or IL-23 inhibitors.

IL-17 or IL-23 inhibitors should be preferred over TNF antagonists in patients with LTBI considered at high risk for developing complications related to chemoprophylaxis, avoiding this preventive strategy.

1 Introduction

Tuberculosis is an infectious disease, caused by *Mycobacterium tuberculosis,* that has a significant global impact and ranks among the top 10 causes of mortality worldwide. It stands as the leading cause of death attributed to a single infectious agent [1]. In immunocompetent hosts, this infection is initially controlled by their immune mechanisms, resulting in an asymptomatic condition known as latent tuberculosis infection (LTBI). It is estimated that around one-quarter of the world's population has LTBI, but only 5–10% of individuals with LTBI will develop active tuberculosis infection (ATBI) if left untreated [1, 2]. However, the presence of some medical conditions or therapies that suppress or modulate the immune system may increase the risk of reactivation [2].

Psoriasis is an inflammatory, immune-mediated, chronic disease significantly affecting patients' quality of life [3, 4]. Due to the increasing understanding of its pathogenesis over the last decades, psoriasis treatment has significantly changed with the development of highly effective biologic agents targeting specific cytokines of the immune system [5, 6]. However, blockade of crucial regulators in both the innate and adaptive immune systems has raised concerns about potential safety issues, such as an increased risk of opportunistic infections.

Tumour necrosis factor (TNF) inhibitors were the first biologic agents approved for the treatment of psoriatic disease. It has been widely reported from both clinical trials and real-world data that patients treated with TNF inhibitors have an increased risk of LTBI reactivation or developing new onset tuberculosis infection, particularly in the first months of treatment [7–10].

New biologic agents, selectively targeting the interleukin (IL)-23/IL-17 axis, were later developed for the treatment of psoriatic disease. Available evidence from clinical trials and real-world studies suggests that the impairment of IL-17 and IL-23 does not affect the progression of primary infection by *M. tuberculosis*, nor does it lead to its reactivation [11–13]. This suggests that there is no heightened risk of tuberculosis reactivation, even in patients who do not receive tuberculosis (TB) chemoprophylaxis [14]. Nevertheless, this evidence is still very limited, particularly in patients with untreated LTBI.

Current guidelines and the prescribing information of approved biologic agents do not differentiate the approach to LTBI on the basis of the specific biologic therapy used. Currently, it is recommended to conduct tuberculosis screening prior to initiating biologic therapy, regardless of the chosen agents. If latent LTBI is detected, tuberculosis chemoprophylaxis should be initiated before starting the biologic therapy [15, 16].

However, anti-tuberculosis treatments can have significant side effects, and there are several contraindications to their use. Thus, the risk–benefit of starting anti-tuberculous treatment should be carefully weighed.

Therefore, we conducted a retrospective, multinational, multicentre, real-world study with the aim of evaluating patients with moderate-to-severe chronic plaque psoriasis with newly diagnosed LTBI who received IL-17 and IL-23 inhibitors regarding chemoprophylaxis, LTBI evolution (reactivation) and comorbidities; as a secondary endpoint, we evaluated the tolerability and safety of TB chemoprophylaxis.

2 Material and Methods

2.1 Study Population

This is an international retrospective observational study from a series of 14 dermatology centres based in Portugal, Spain, Italy, Greece and Brazil which included adult patients with moderate-to-severe chronic plaque psoriasis and newly diagnosed LTBI who were treated with IL-23 or IL-17 inhibitors (i.e. guselkumab, risankizumab, tildrakizumab, secukinumab, ixekizumab and brodalumab) between January 2015 and March 2022. LTBI was diagnosed in the case of tuberculin skin test (TST) and/or interferon gamma release assay (IGRA) positivity, according to local guidelines, prior to initiating IL-23 or IL-17 inhibitor. Patients with prior diagnosis of LTBI (treated or untreated) or treated ATBI were excluded. Patients receiving at least one drug administration were included in the study, regardless being treated with concomitant anti-psoriatic drugs (i.e. methotrexate) and regardless biological treatment duration.

2.2 Data Collection

The type of chemoprophylaxis regimen chosen (type and duration of therapy), eventual discontinuation and reason for discontinuation (i.e. drug tolerability and/or safety issues) were collected. The choice to administer chemoprophylaxis or avoid it was based on the dermatologist's judgement according to the patient contraindication to chemoprophylaxis, local recommendations/guidelines and consultation with the infectious disease specialist. Patients were stratified into three groups on the basis of whether they received complete, incomplete (did not complete standard chemoprophylaxis dose regimen: isonizid for 6 months, rifampicin for 4 months and isoniazid plus rifampicin for 3 months) [17] or no chemoprophylaxis at all. Demographic and clinical data were recorded, including age, gender, diagnosis of psoriatic arthritis, and comorbidities, including type 2 diabetes mellitus, cardiovascular diseases, dyslipidemia, fatty liver disease, cyrrhosis, human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, epilepsy, depression/anxiety or other relevant comorbidities. History of previous conventional and biological anti-psoriatic treatments including TNF inhibitors was also collected.

2.3 Statistical Analysis

Absolute and relative frequencies were used to describe qualitative variables; mean and standard deviation (SD) or median and interquartile range (IQR) were used to describe quantitative variables. Groups were compared using chi-square test for qualitative variables and independent sample *t*-test or analysis of variance (ANOVA) for quantitative variables with symmetric distribution. Multiple comparisons were performed based on the Dunnett test. The Mann–Whitney test or Kruskal–Wallis test were used for quantitative variables with skewed distribution. A level of 0.05 was considered significant. Statistical analyses were performed using IBM SPSS version 28 (Armonk, NY: IBM Corp).

2.4 Ethical Statement

The present study was conducted in accordance with the Declaration of Helsinki (initially published in 1964) on Ethical Principles for Medical Research Involving Human Subjects. Ethical approval was waived in view of the retrospective nature of the study, and all the procedures being performed were part of the routine care.

3 Results

A total of 405 patients with moderate-to-severe psoriasis and a new diagnosis of LTBI and who started an IL-23 or IL-17 inhibitor were included (Portugal = 81; Spain = 29; Italy = 162; Greece = 91; Brazil = 42). Characteristics of the study population are summarized in Table 1. LBTI was diagnosed by positive IGRA in 205 (50.6%), positive IGRA and TST in 113 (27.9%) and positive TST in 87 (21.5%) patients. Chest X-ray was performed in 396 patients and revealed calcified nodules in 20 cases (5.1%). Of note, 14 of the 87 patients with positive TST (16.1%) had lung X-ray radiologic alterations. Complete chemoprophylaxis was administered in 252 (62.2%) patients, whereas incomplete prophylaxis was administered in 41 (10.1%) of patients. A total of 112 (27.7%) patients received no prophylaxis at all. Patients did not receive any chemoprophylaxis because of (1) the physician's decision due to perceived higher risk of liver toxicity [99 (88.4%)], (2) refusal of the patient to receive prophylaxis [11 (9.8%)] or (3) risk of drug interactions [2 (1.8%)]. Chemoprophylaxis was interrupted because of hepatotoxicity (i.e. increase of serum liver enzyme levels to > 3 times normal values) in 31 (75.6%) patients, cutaneous toxicity in 8 (16.2%), other toxicity (peripheral neuropathy) in 1 (2.4%) and non-compliance in 1 (2.4%). Isoniazid was the most common chemoprophylactic agent used (in 55.6% patients), followed by rifampicin in 15.6% and combination of isoniazid plus rifampicin in 5.4% (Table 2 and Supplementary Table 1). In those who did not complete chemoprophylaxis, the mean duration of chemoprophylaxis for the isoniazid regimen was 2.09 ± 1.53 months, for the rifampicin regimen 2.71 ± 1.16, and for the isoniazid plus rifampicin combination 1 ± 0 months. In the group comparison stratifying patients according to complete, incomplete or no chemoprophylaxis, the presence of hypertension, hepatitis C and fat liver disease were significantly more common in patients with no or incomplete chemoprophylaxis than in the complete treatment group [66 (43.1%) versus 81 (32.1%), $p = 0.026$; 10 (6.5%) versus 5 (2.0%), $p = 0.019$; and 53 (34.6%) versus 26 (10.3%), $p < 0.001$, respectively]. A higher body mass index (BMI) and a higher proportion of obese patients were found in the complete treatment group versus no or incomplete chemoprophylaxis (27.8 ± 4.6 versus 26.6 ± 4.9, $p = 0.020$ and 78 (31.0%) versus 32 (20.9%), $p = 0.028$, respectively; Supplementary Table 2). A significant proportion of patients had been previously treated with conventional systemic therapies (including methotrexate and cyclosporin) and other biologic agents (including TNF inhibitors), as shown in Table 1. Nine (2.2%) patients were concomitantly treated with another systemic therapy, of which seven (1.7%) received methotrexate.

Table 1 Characteristics of the study population, including comorbidities and previous and current psoriatic disease treatment

Characteristics of the population	Values
Number of patients	405
Age, mean (SD)	55.3 (13.9)
Gender (male), *n* (%)	275 (67.9)
Height (m), mean (SD)	1.72 (0.09)
Weight (kg), mean (SD)	80.6 (15.4)
BMI, mean (SD)	27.3 (4.76)
Psoriasis disease duration in years, median (SD)	17.9 (12.25)
Baseline PASI, mean (SD)	15.4 (7.6)
Psoriatic arthritis, *n* (%)	103 (25.4)
Obesity, *n* (%)	110 (27.2)
Hypertension, *n* (%)	147 (36.3)
Diabetes, *n* (%)	68 (16.8)
Dyslipidemia, *n* (%)	159 (39.3)
Alcohol intake, *n* (%)	
None	212 (52.3)
Mild	134 (33.1)
Moderate	50 (12.3)
Severe	9 (2.2)
Smoking, *n* (%)	148 (36.5)
Hepatitis B, *n* (%)	20 (4.9)
Hepatitis C, *n* (%)	15 (3.7)
Fatty liver disease, *n* (%)	79 (19.5)
Cirrhosis, *n* (%)	11 (2.7)
Depression/anxiety, *n* (%)	23 (5.7)
Cardiovascular diseases, *n* (%)	15 (3.7)
HIV infection, *n* (%)	3 (0.7)
Epilepsy, *n* (%)	3 (0.7)
Atopy, *n* (%)	7 (1.7)
Hypothyroidism, *n* (%)	10 (2.5)
Previous non-biologic systemic therapy, *N* (%)	
Retinoids	87 (21.5)
Methotrexate	216 (53.3)
Cyclosporine	127 (31.4)
Phototherapy	130 (32.1)
Apremilast	42 (10.4)
Fumarates	2 (0.5)
Bio-naive	213 (52.6)
Previous biologic therapy	192 (47.4)
Etanercept	47 (11.6)
Adalimumab	70 (17.3)
Infliximab	18 (4.4)
Ustekinumab	50 (12.3)
Secukinumab	47 (11.6)
Ixekizumab	21 (5.2)
Brodalumab	16 (4.0)
Guselkumab	10 (2.5)
Risankizumab	9 (2.2)
Tildrakizumab	1 (0.2)
Current biologic therapy, *n* (%)	
Guselkumab	58 (14.3)
Risankizumab	101 (24.9)
Tildrakizumab	30 (7.4)
Secukinumab	121 (29.9)
Ixekizumab	61 (15.1)
Brodalumab	34 (8.4)

BMI body mass index, *PASI* Psoriasis Area Severity Index

Table 2 Tuberculosis (TB) chemoprophylaxis status throughout this study of the psoriasis patients with newly diagnosed latent tuberculosis infection

	n	%
Chemoprophylaxis		
Complete chemoprophylaxis	252	62.2
Incomplete chemoprophylaxis	41	10.1
No chemoprophylaxis	112	27.7
Reason for incomplete chemoprophylaxis		
Hepatic toxicity to anti-TB	31	75.6
Other toxicity to anti-TB[a]	1	2.4
Skin adverse drug eruption[b]	8	19.6
Non-compliance of the patient	1	2.4
Reason for no chemoprophylaxis		
Physician decision	99	88.4
Drug interaction	2	1.8
Patient decision	11	9.8

[a]Peripheral neuropathy

[b]Maculopapular rash

The mean duration of biological treatment was 32.87 ± 20.95 months (range: 1.05–110.82 months). Only one case of latent tuberculosis reactivation was observed. This was a 32-year-old, bio-naive Italian patient with mild cognitive impairment and hearing loss, with no other concomitant medication, IGRA positivity and normal lung X-ray (did not perform TST test), who did not accept TB chemoprophylaxis (for fear of isoniazid hepatotoxicity) and was diagnosed with extrapulmonary TB (i.e. intestinal TB) after 14 months of therapy with ixekizumab. The patient was first diagnosed with appendicitis (acute abdomen pain). Laparoscopy revealed appendicitis, terminal ileitis and mesenteritis. Histological examination demonstrated a giant cell granulomatous infiltrate with non-necrotizing granulomas and evidence of *M. tuberculosis* DNA. In the chest X-ray, areas of apical thickening were observed with positive bronchoalveolar lavage for *M. tuberculosis*. Biologic therapy was discontinued, and the patient started the standard four-drug

regimen consisting of isoniazid, rifampicin, pyrazinamide and ethambutol for 9 months, without any side effects or clinical sequelae of TB.

Thus, the proportion of patients treated with ixekizumab who developed ATBI was 1.64% (95% CI 0–5.43%) and 0% for all other agents (not statistically significant). When we compare the proportions in IL-17 (0.46%; 95% CI 0–1.06%) and IL-23 (0%), the difference is also not statistically significant.

4 Discussion

Tuberculosis remains a significant global health concern [1]. Although immunocompetent hosts can generally control *M. tuberculosis* infection and develop an asymptomatic form of the disease, the potential for reactivation should not be disregarded. It is estimated that 5–10% of LTBI will eventually advance to active infection [1, 2]. While all patients have a baseline risk, individuals with immunosuppressive conditions, including those treated with TNF inhibitors, are at a heightened risk [1, 2, 7–9]. Randomized clinical trials on infliximab first reported a four-fold increase in the risk of TB infection, and subsequent studies indicated a greater risk of TB in patients treated with TNF antagonists compared with those in the placebo group, with a relative risk ranging from 1.6 to 25.1 [18].

T helper (Th) 1 cells play an important role in the control of *M. tuberculosis* infection via Th1 cytokines such as interferon (IFN)-y, interleukin (IL)-12 and TNF, which are crucial in granuloma formation and maintenance. Granulomas consist of aggregates of macrophages and B and T lymphocytes, organized to control a pathogen that cannot be eliminated. This mechanism is crucial for controlling *M. tuberculosis* infection, as supported by reports of individuals with mutations in the IL-12/IFN-y axis who have developed disseminated infections following vaccination with the Bacillus Calmette–Guerin [19]. The central role of this pathway in the control of tuberculosis infection is impaired by blocking TNF, thus explaining the higher reactivation risk [20]. Ustekinumab, a monoclonal antibody targeting the shared p40 subunit of IL-12 and IL-23 cytokines, may also potentially increase the risk of TB reactivation due to impairment of the Th1 pathway through IL-12 inhibition. A safety analysis across five clinical studies indicated that ustekinumab, when given concurrently with antituberculosis prophylaxis, did not appear to increase the risk of tuberculosis reactivation [21]. However, a few real-world cases of tuberculosis infection and reactivation have been reported in patients receiving this drug, with and without chemoprophylaxis [22–25].

The IL-23/IL-17 axis is also theoretically involved in defence against tuberculosis infection, but in a different way. The IL-23 produced by antigen-presenting cells (APC) induces the differentiation of Th17 cells. These cells will then produce IL-17A, IL-17F and IL-22. The first two act through recruitment of neutrophils to the infected site, modulation of granulopoiesis and development of a local inflammatory response mediating tissue damage. IL-22 induces the production of several anti-bacterial peptides and activation of macrophages to better control mycobacterial infections [26]. In mice, IL-23-dependent expansion of Type 3 innate lymphoid cells (ILC3s) and production of IL-17 and IL-22 were found to be critical inducers of lung CXC motif chemokine ligand 13 (CXCL13), early innate immunity and the formation of protective lymphoid follicles within granulomas [27]. However, Th1 and Th17 cross-regulation is essential for an optimized response against *M. tuberculosis*. When Th17 cell responses become pathogenic rather than protective, Th1 cells are induced to stop these harmful effects through IFN-y [28, 29].

The relationship between IL-23/IL-17 and host defence against *M. tuberculosis* has been under debate, as preclinical studies in animal models suggest that the absence of IL-23 and shortage of IL-17 do not change the progression of disease in primary infection by *M. tuberculosis*, as long as the Th1 response is not compromised [11, 30–32]. An in vitro human microgranuloma model study also advocated that IL-17A inhibition had little effect on *M. tuberculosis* reactivation, in contrast with TNF inhibition [13].

Still, current guidelines dictate that all patients get screened for tuberculosis before initiating biologic therapy and receive chemoprophylaxis if an LTBI is diagnosed, irrespective of the chosen agents [15, 16]. Additionally, the labels of all biologic agents state the same. But it is already known that selective IL-23 inhibitors, by blocking the p19 subunit, maintain the integrity of the IL-12/Th1 axis, enabling it to stimulate both innate and adaptive immune mechanisms, and the same applies to IL-17 inhibitors [30]. Currently available data on the safety of IL-17 and IL-23 inhibitors regarding tuberculosis infection risks are quite reassuring. No cases of tuberculosis reactivation have been reported thus far, both in clinical trials and real-world studies, among patients with treated and non-treated LTBI who were exposed to IL-17 and IL-23 inhibitors [14]. In the phase 3 clinical trial IMMhance, 31 patients who had LTBI at screening received no chemoprophylaxis for LTBI and were treated with risankizumab, a IL-23p19 inhibitor. None developed tuberculosis reactivation for a follow-up period of 55 weeks [33]. Additionally, in two real-world studies, no cases of reactivation were reported in 12 and 10 patients with non-treated LTBI treated with secukinumab, an IL-17A inhibitor, for a period of 52 and 84 weeks, respectively [34, 35]. In another analysis from several clinical trials of ixekizumab, another IL-17A inhibitor, it was highlighted that, in 11 patients who developed treatment-emergent LTBI and

were not treated, no cases of reactivation were identified [36]. Recently, no cases of TB reactivation were observed in a retrospective multicentre trial from Spain, which included 35 psoriasis patients with untreated LTBI treated with biologic therapy [risankizumab (21 patients), guselkumab (5), tildrakizumab (5), ixekizumab (2), secukinumab (1) and brodalumab (1)] for a median duration of biologic therapy of 24 months [37]. To our knowledge, there are seven cases of "de novo" active tuberculosis in patients receiving IL-23 and IL-17 inhibitors: five patients with secukinumab [38], one with ixekizumab [39], and one receiving tildrakizumab [40].

The present study analyses over 400 psoriasis patients from 5 different countries (Brazil, Greece, Italy, Portugal and Spain) with newly diagnosed LTBI who were treated with IL-17 or IL-23 inhibitors, of which 37.8% received incomplete or no chemoprophylaxis. For a mean follow-up time of 32.87 ± 20.95 months, there was only one reactivation reported, a case of intestinal tuberculosis after 14 months of treatment with ixekizumab. Currently available literature suggests that the reactivation of tuberculosis associated with TNF inhibitors is commonly observed within the initial 6 months of treatment [41, 42]. Given the prolonged time frame until reactivation, and considering that every LTBI patient carries an inherent risk of conversion to ATBI, it may be debateable whether reactivation was truly linked to the use of the IL-17 inhibition. Furthermore, it is estimated that 5–10% of patients with latent tuberculosis will develop active tuberculosis, which places this case within the expected rate for reactivation. Moreover, although unusual, extra-pulmonary tuberculosis is not necessarily a consequence of a state of immunosuppression [43]. Nevertheless, we cannot exclude this possibility. So, although a case of ATBI has been observed with an IL-17 inhibitor in our series, the risk appears to be very low and not statistically different from that associated with IL-23 antagonists. This study supports and reinforces the existing evidence indicating that the risk of reactivation of tuberculosis in patients with psoriasis does not seem to be increased with the administration of IL-17 and IL-23 inhibitors.

This debate is particularly important for some complex patients. There are many possible therapeutic schemes regarding LTBI treatment, comprising short, rifampicin-based regimens, including 4 months of daily rifampicin and 3 months of daily isoniazid plus rifampicin, or longer regimens such as 6 or 9 months of daily isoniazid [16].

In our study, 40 out of 293 patients (13.7%) had to discontinue chemoprophylaxis due to toxicity (mostly hepatotoxicity). Both isoniazid and rifampicin are associated with several side effects, some of them extremely severe. Isoniazid is mainly linked to dermatological manifestations, gastrointestinal symptoms, hepatotoxicity and neuropsychiatric adverse effects, which include cognitive impairment, lethargy and peripheral neuropathy [44]. In most cases, liver injury is asymptomatic and is only detected by measuring markers of hepatocyte injury such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST), especially in mild toxicities, which occur in up to 20% of patients treated with this drug [45]. However, several reports of fulminant hepatitis requiring liver transplantation have been reported, even culminating in the death of the patients [46–49]. Rifampicin also has the potential to induce significant adverse effects, namely "flu-like" symptoms, immune-mediated thrombocytopenia and hepatotoxicity [50], in addition to many drug interactions that may have management implications for patients with psoriatic disease, who are often multimorbid and receive concomitant medications.

Considering that antituberculosis therapy is associated with several side effects, the risks and benefits of treating LTBI should be balanced before making any clinical decision. Currently available data are reassuring regarding the use of IL-17 and especially IL-23 antagonists in patients with LTBI or at risk of new-onset tuberculosis, with no evidence of increasing the risk of reactivation to ATBI. Even though screening can still be performed to assess patient's global health, the diagnosis of LTBI should not dictate its treatment, especially in patients with identified predisposition to drug toxicity, since the potential risks may outweigh the benefits of treatment.

Current literature suggests that the risk for antituberculosis drugs side effects is increased by some factors, including advanced age (above 40–60 years old), pre-existent liver disease (hepatitis B and C) or other liver disease risk factors (alcoholism, diabetes, overweight/obesity, concomitant hepatotoxic drugs or liver metabolized drugs), low body mass index/malnutrition, anaemia, HIV infection, chronic renal disease (which increases the risk of isoniazid-induced peripheral neuropathy), thrombocytopenia (which may be aggravated by rifampicin), pregnancy and genetic predisposition [45, 51, 52]. In addition, rifampicin is frequently associated with drugs interactions that need to be considered in comorbid patients [53]. In fact, our findings align with the existing literature, as the presence of hepatitis C and fat liver disease were more common in patients without or with incomplete treatment. Patients with these comorbidities were more likely to discontinue LTBI treatment due to hepatotoxicity or were unable to initiate chemoprophylaxis due to the clinician's prediction of an increased risk of hepatotoxicity. In the presence of one or more of these contraindicating factors, it is important to start questioning whether the benefits of treating LTBI outweigh the risks when IL-17 and IL-23 inhibitors are available.

This study has certain limitations, particularly its retrospective nature, depending on the quality of the available recorded data and its relatively short follow-up period. But there are also some strengths that can be highlighted: its multicentre and multinational approach, which improves

the generalization of the results and the sample size, clearly larger than that of the small case series available [35, 54–57].

5 Conclusion

With the current evidence, it would be worth reviewing the current guidelines for the management of latent tuberculosis in patients with an indication for biologic therapy, regarding screening and treatment, and probably also to review the label of IL-23 and IL-17 inhibitors.

Thus, when concerns regarding tuberculosis reactivation exist, IL-17 or IL-23 inhibitors should be preferred over TNF antagonists for treatment of psoriatic disease. Additionally, in patients with LTBI considered at high risk for developing complications related to chemoprophylaxis, this preventive strategy may be waived before initiating treatment with IL-17 inhibitors and especially IL-23 inhibitors.

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Declarations

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Conflict of interest Tiago Torres declares the following conflicts of interest: AbbVie, Almirall, Amgen, Arena Pharmaceuticals, Biocad, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Fresenius Kabi, Janssen, LEO Pharma, Eli Lilly, MSD, Mylan, Novartis, Pfizer, Samsung-Bioepis, Sanofi-Genzyme, Sandoz and UCB. Andrea Chiricozzi has served as advisory board member and consultant and has received fees and speaker's honoraria or has participated in clinical trials for AbbVie, Almirall, Bristol Myers Squibb, Leo Pharma, Lilly, Janssen, Novartis, Pfizer and Sanofi Genzyme. Luís Puig has received consultancy and/or speaker's honoraria from and/or participated in clinical trials sponsored from AbbVie, Almirall, Amgen, Baxalta, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Fresenius-Kabi, Janssen, JS BIOCAD, LEO Pharma, Lilly, Mylan, Novartis, Pfizer, Regeneron, Roche, Sandoz, Samsung-Bioepis, Sanofi and UCB. Ana Maria Lé has no conflicts of interest. Angelo Valerio Marzano reports consultancy/advisory board disease-relevant honoraria from AbbVie, Boehringer Ingelheim, Novartis, Pfizer, Sanofi and UCB. Paolo Dapavo has no conflicts of interest. Esteban Dauden has the following conflicts of interest: advisory board member, consultant, grants, research support, participation in clinical trials, honorarium for speaking, and research support, in connection with the following pharmaceutical companies: Abbvie/Abbott, Almirall, Amgen-Celgene, Janssen-Cilag, Leo-Pharma, Novartis, Pfizer, MSD-Schering-Plough, Lilly, UCB, Brystol-Myers and Boehringer Ingelheim. José-Manuel Carrascosa acted as a consultant and/or speaker for and/or participated in clinical trials sponsored by Janssen Pharmaceuticals Inc., Eli-Lilly, AbbVie, Novartis, Amgen, Leo-Pharma, UCB, Boehringer Ingelheim, Almirall, Sandoz and Bristol Myers Squibb. Elizabeth Lazaridou has the following conflicts of interest: speaker's honoraria from and participation in clinical studies and advisory boards with Abbvie, Leo, Novartis, Pfizer, UCB, Sanofi, Janssen, Lilly-Galderma, Pierre Fabre, L'Oreala and Galenica. Gleison Duarte is/has served as a scientific consultant, speaker or clinical trial investigator for Abbvie, Bayer, Janssen, Leo-Pharma, Galderma, Sanofi, Boehringer, Novartis, Pfizer and UCB. André V. E. de Carvalho: Dr Carvalho acted as a consultant and/or speaker for and/or participated in clinical trials sponsored by companies that manufacture drugs used for the treatment of psoriasis, including Janssen Pharmaceuticals Inc., Eli-Lilly, AbbVie, Novartis, Amgen, Leo-Pharma, UCB and Boehringer Ingelheim. Ricardo Romiti has received consulting fees from AbbVie, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Galderma, Janssen, LEO Pharma, Novartis, Pfizer, Sanofi, and UCB Pharma; his institution has received research grants from AbbVie; and he has served as a paid speaker for AbbVie, Boehringer Ingelheim, Eli Lilly, Janssen, LEO Pharma, Novartis, Pfizer, Sanofi and UCB Pharma. Natalia Rompoti has received honoraria for lectures from Janssen, AbbVie, Genesis Pharma, Leo, Lilly Pharmaserve, Novartis and UCB, and support for scientific congress attendance from AbbVie, Janssen, Leo, Lilly Pharmaserve, Novartis and UCB. Laetitia Teixeira has no conflicts of interest to declare. Miguel Abreu has no conflicts of interest to declare. Elena Ippoliti has no conflicts of interest to declare. Carlo Alberto Maronese has no conflicts of interest to declare. Mar Llamas-Velasco has the following conflicts of interest: advisory board member, consultant, grants, research support, participation in clinical trials, honorarium for speaking, research support, in connection with the following pharmaceutical companies: Abbvie, Almirall, Amgen, Biogen, Celgene, Janssen-Cilag, Leo Pharma, Lilly, MSD, Novartis, Pfizer, UCB, Kyowa Kirin, Brystol-Myers and Boehringer Ingelheim. Eva Vilarrasa has received honoraria for acting as a consultant and/or speaker for AbbVie, Almirall, Boehringer, Celgene, Janssen, Leo Pharma, Eli Lilly, MSD, Novartis, Pfizer and UCB. Elena del Alcázar has participated as an Secondary investigator and/or invited speaker for AbbVie, Janssen, Novartis, Lilly, Leo Pharma, Almirall, Amgen, UCB and Sanofi. Athina-Ioanna Daponte has no conflicts to declare. Marina Papoutsaki has received honoraria for advisory boards and lectures from Janssen, Leo Pharma, MSD, Genesis Pharma, Pfizer, Novartis, AbbVie and UCB, and support as an investigator in clinical studies from AbbVie, Novartis, Leo Pharma and Janssen. Andrea Carugno has no conflicts of interest. Francesco Bellinato has no conflicts of interest. Paolo Gisondi has received honoraria for acting as a consultant and/or speaker for AbbVie, Almirall, Amgen, Biogen, Bristol Myers Squibb, Celgene, Janssen, LEO Pharma, Eli Lilly, MSD, Novartis, Pierre Fabre, Sanofi and UCB.

Ethics approval The present study was conducted in accordance with the Declaration of Helsinki (initially published in 1964) on Ethical Principles for Medical Research Involving Human Subjects. Ethical approval was waived in view of the retrospective nature of the study, and all the procedures being performed were part of the routine care.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and materials Data are available within the article or its supplementary materials.

Code availability Not applicable.

Author contributions TT and PG contributed to the study conception, design and statistical analyses; TT, AML, FB and PG contributed to manuscript writing. All authors contributed to data collection and interpretation of the data, provided critical feedback on the manuscript, approved the final manuscript for submission, and were accountable for the accuracy and integrity of the article.

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