REVIEW ARTICLE

Safety of Interleukin Inhibitors in Psoriatic Patients with Latent Tuberculosis Infection Without Chemoprophylaxis: A Systematic Review

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Current guidelines recommend psoriatic patients with latent tuberculosis infection undergo chemoprophylaxis prior to initiating any biologic. However, clinical studies indicate that interleukin (IL) inhibitors may not increase the risk of tuberculosis reactivation. This review evaluates the safety in psoriatic patients with latent tuberculosis infection using IL inhibitors without chemoprophylaxis. PubMed and EMBASE were searched up to 1 November 2024 in accordance with PRISMA. Fifteen studies, including one safety analysis of a clinical trial, 2 case series, and 12 retrospective studies were analysed. The included studies reported a total of 837 cases: 179 patients were treated with secukinumab, 69 with ixekizumab, 8 with brodalumab, 539 with risankizumab, 22 with guselkumab, and 20 with tildrakizumab. Psoriatic patients with latent tuberculosis infection using an IL-12/23 inhibitor without chemoprophylaxis were not found in this review. Three of the 837 cases exhibited reactivation of tuberculosis. The reactivation rate is 0.78% among psoriatic patients with latent tuberculosis infection using IL-17 inhibitors, and 0.17% among those using IL-23 inhibitors. Our analysis shows that IL-17 and IL-23 inhibitors do not increase the risk of tuberculosis activation in psoriatic patients with latent tuberculosis infection. The impact of IL-12/23 inhibitors on tuberculosis reactivation among psoriatic patients with latent tuberculosis infection remains uncertain and requires further investigation.

Key words: psoriasis; biologics; latent tuberculosis; infection; safety.

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SIGNIFICANCE

Based on systematic retrieval, our analysis shows that the risk of tuberculosis reactivation is not increased in psoriatic patients using interleukin-17 or interleukin-23 inhibitors without chemoprophylaxis whereas use of the interleukin-12/23 inhibitor remains unclear. These results indicate that it is relatively safe for psoriatic patients to use interleukin-17 or interleukin-23 inhibitors with latent tuberculosis infection if chemoprophylaxis cannot be well tolerated.

Psoriasis is a chronic, inflammatory, systemic condition affecting approximately 0.5% to 11.3% of adults and 0% to 1.37% of children (1). Immune dysregulation is a key factor in the pathogenesis of psoriasis. As understanding of the mechanisms underlying psoriasis advanced, biologic agents targeting inflammatory cytokines have been developed, significantly enhancing the efficacy of psoriasis treatment. Tumour necrosis factor (TNF) inhibitors were the first biologics to be used in psoriasis, paving the way for subsequent biologic therapies. Following the introduction of TNF inhibitors, agents targeting interleukins (ILs) have been developed.

IL-17 inhibitors include secukinumab, ixekizumab, brodalumab, and bimekizumab. Secukinumab and ixekizumab specifically target IL-17A, while brodalumab antagonizes the IL-17A receptor. Bimekizumab, in contrast, acts on both IL-17A and IL-17F. Risankizumab, tildrakizumab, and guselkumab act on IL-23 by binding to the p19 subunit. Ustekinumab is a dual-target antibody that targets both IL-12 and IL-23. Clinical studies have demonstrated that biologics act quickly and provide substantial improvement in skin lesions, leading to their widespread use.

Latent tuberculosis infection (LTBI) is a clinical condition characterized by the presence of *Mycobacterium tuberculosis* (MTB) within the host without the manifestation of active tuberculosis (TB) disease. Due to the low bacterial load, both microbiological and radiological examinations are unable to detect it. Despite the absence of symptoms, LTBI poses a risk of progressing to active TB and serving as a source of new infection. Currently, the primary diagnostic methods for LTBI are the tuberculin skin test (TST) and interferon gamma release assays (IGRA). A positive result from either test necessitates further evaluation to rule out active TB.

By blocking mediators of innate or adaptive immunity, biologics therapy might theoretically increase the risk of infectious diseases. TNF inhibitors, the first biologics used for treating psoriasis, have been shown in multiple studies to elevate the risk of LTBI reactivation or new TB (2, 3). In contrast, research has found that IL-17 inhibitors and IL-23 inhibitors do not significantly increase the risk of TB activation in individuals with LTBI (4, 5).

Currently, it is recommended to perform TB screening before initiating any biologic therapy. If LTBI is detected, chemoprophylaxis should be started prior to commencing biologic treatment. However, anti-TB drugs have potential side effects, and some patients may not tolerate them well. Therefore, it is necessary to reassess the benefits of chemoprophylaxis in psoriatic patients with LTBI who are being treated with ILs inhibitors.

METHODS

This review was not registered. It was performed in accordance with PRISMA guidelines.

Search strategy

A literature search of PubMed and EMBASE using the keywords "secukinumab OR ixekizumab OR brodalumab OR bimekizumab OR guselkumab OR risankizumab OR tildrakizumab OR ustekinumab AND psoriasis OR psoriatic arthritis AND latent tuberculosis OR tuberculosis" from inception to 1 November 2024 was performed (shown in **Fig. 1**). The titles and abstracts of the retrieved articles were read by 2 independent researchers. For relevant articles, the full texts were read independently. In the case of inconsistent opinions, a third researcher was consulted for solution. Additional potentially relevant articles were sought by reviewing the references. There was no restriction on publication language. The complete search strategy is shown in Appendix S1.

Eligibility criteria

This article assesses the safety of using IL inhibitors in psoriatic patients with LTBI. Articles including the following populations were included: those who (1) were diagnosed with psoriasis or psoriatic arthritis; (2) tested IGRA or/and TST positive before the treatment of ILs inhibitors; (3) received IL-17 inhibitor or IL-23 inhibitor or IL-12/23 inhibitor; (4) have been followed up. Articles were excluded if patients had active TB or received chemoprophylaxis (including incomplete courses).

Data extraction

Information on the study design, first author, publication year, follow-up term, age, gender, LTBI criteria, ILs inhibitors used, and whether TB was activated in psoriatic patients with LTBI were extracted. If the original data were unclear, we contacted the corresponding author via email to request further details.

RESULTS

Our search yielded 117 articles from PubMed and 740 articles from EMBASE. After removing duplicates, 723 articles remained. Following an independent screening of 723 articles by 2 reviewers, 37 studies were assessed for eligibility. Twenty-two studies were excluded for different reasons: baseline TST/IGRA is unknown, borderline or negative ($n=5$), received chemoprophylaxis ($n=7$), unclear information ($n=9$), overlap in included population (1). Therefore, there are 15 studies included in total (shown in Fig. 1). Of these, 1 was a safety analysis of randomized controlled trial, 2 were case series, 12 were retrospective studies. The 15 included studies reported a total of 837 cases. Details of the 15 studies are listed in **Table I.**

Interleukin-17 inhibitors

A total of 256 psoriasis patients with LTBI who were treated with IL-17 inhibitors without receiving chemoprophylaxis were included in the analysis. Eleven studies

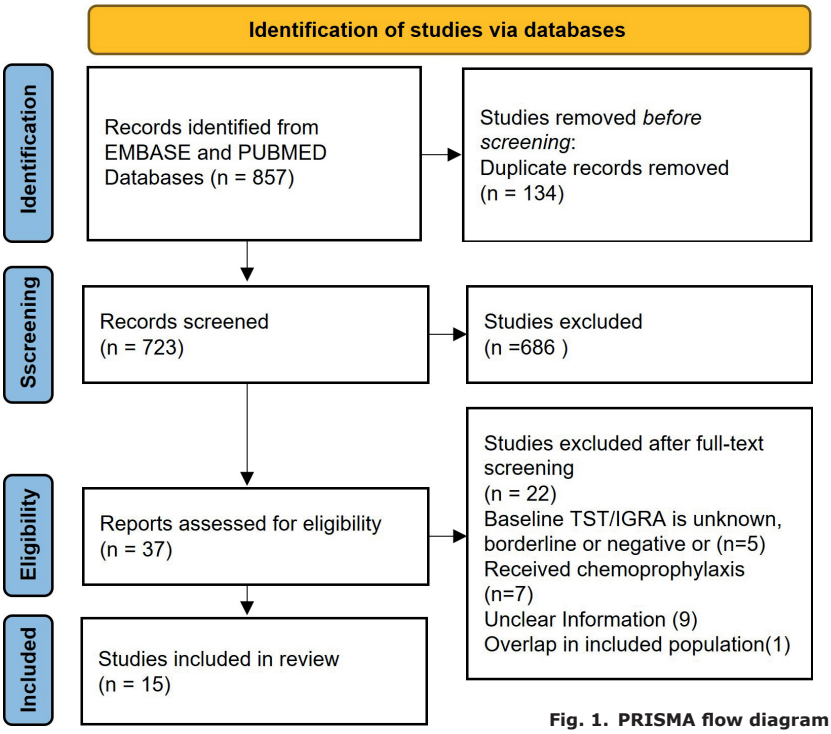

Fig. 1. PRISMA flow diagram of selection of publications included in this review

Table I. Studies included: general summary

Study (year)	Study type	Drug (patient number)	Reactivation (Patien No)	Age (SD)	Gender male%	LTBI criteria	Follow up term
Ribero (2019) (6)	Case series	Secukinumab (12)	N	55.9 (17.5)	75	TST	52w
Shu (2020) (7)	Retrospective analysis	Secukinumab (16)	N	38.8 (14.8)	68.8	IGRA	16–268 weeks (average 51.5 weeks)
Machado (2020) (8)	Case series	Secukinumab (2)	N	67.0 (11.0)	50.0	IGRA or TST	104 weeks
Megna (2022) (9)	Retrospective analysis	Secukinumab (10)	N	Unknown	Unknown	IGRA	Average 84 weeks
Mastorino (2022) (10)	Retrospective Analysis	Secukinumab (2), Brodalumab (1), Risankizumab (1)	N	58.5 (3.3)	100.0	IGRA	12–120 months (average 48.1 months)
Xiao (2023) (11)	Retrospective analysis	Secukinumab (14)	N	41.4 (7.5)	92.9	IGRA	24–72 weeks (average 23.37 weeks)
Yuan (2023) (12)	Retrospective analysis	Secukinumab (6), Ixekizumab (2), Guselkumab (1)	Secukinumab (1), Guselkumab (1)	Unknown	Unknown	IGRA	24 weeks
Manzanares (2024) (13)	Retrospective analysis	Secukinumab (1), Ixekizumab (2), Brodalumab (1), Risankizumab (21), Guselkumab (5), Tildrakizumab (5)	N	59.5 (16.7)	60.0	IGRA	at least 24 weeks
Torres (2024) (4)	Retrospective analysis	Secukinumab (24), Ixekizumab (22), Brodalumab (6), Risankizumab (30), Guselkumab (16), Tildrakizumab (14)	Ixekizumab (1)	Unknown	Unknown	IGRA or TST	Unknown
He (2024) (14)	Retrospective analysis	Secukinumab (90), Ixekizumab (19)	N	44 (13)	74.2	IGRA	2 years
Raimondo (2024) (15)	Retrospective analysis	Risankizumab (13)	N	Unknown	Unknown	IGRA	52 weeks
Ibba (2023) (16)	Retrospective analysis	Risankizumab (5) Tildrakizumab (1)	N	52.2 (13.4)	66.7	IGRA	18.8 months
Zhao (2024) (17)	Retrospective analysis	Ixekizumab (25)	N	Unknown	Unknown	IGRA	22.5 months
Galluzzo (2020) (18)	Retrospective analysis	Secukinumab (2)	N	Unknown	Unknown	IGRA	136 weeks
Gordon (2024) (19)	Safety analysis of clinical trial	Risankizumab (334 PSO, 135 PSA)	N	Unknown	Unknown	IGRA	PSO 6 years, PSA 2.2 years

LTBI: latent tuberculosis infection; IGRA: interferon gamma release assays; TST: tuberculin skin test; N: none; PSO: psoriasis; PSA: psoriatic arthritis.

reported on patients using secukinumab, totalling 179 patients, with 1 case of TB reactivation (details shown in Table II). Five studies covered patients using ixekizumab, with 69 patients in total, and 1 case of TB reactivation (details presented in **Table II**). Three studies involved patients using brodalumab, with 8 patients in total, and no cases of TB reactivation were observed. Data on patients using bimekizumab were not found in our search. The overall rate of psoriatic patients with LTBI who developed active TB while using IL-17 inhibitors is 0.78%. Of the 2 cases of TB reactivation, 1 patient developed intestinal TB after 14 months of treatment with ixekizumab (4). Information was missing for another case involving secukinumab, so the timing of TB reactivation could not be determined (15).

Interleukin-23 inhibitors

A total of 581 psoriatic patients with LTBI using IL-23 inhibitors without receiving chemoprophylaxis were included in the review. Three studies included patients using guselkumab, with 22 patients in total; 1 case of TB reactivation occurred during the 24-week follow-up (details presented in Table II). Six studies involved patients using risankizumab, with 539 patients in total. Three studies covered patients using tildrakizumab, with 20 patients in total. No cases of TB reactivation were reported among patients using risankizumab or tildrakizumab. In summary, among psoriatic patients with LTBI who did not receive chemoprophylaxis while using IL-23 inhibitors, the rate of TB reactivation was 0.17%.

Interleukin-12/23 inhibitors

We did not find any psoriasis patients with LTBI using IL-12/23 inhibitor who did not receive chemoprophylaxis.

DISCUSSION

LTBI is a global concern. Although LTBI itself is non-infectious, it carries a risk of reactivation. Statistics indicate that approximately one-quarter of the global population has been infected with MTB, with 5% to 10% progressing to active TB (20). The advent of biologic agents has revolutionized the treatment of psoriasis.

Table II. Cases of TB reactivation among psoriasis patients with LTBI using IL inhibitors having not received chemoprophylaxis

Case no.	Biologic used before diagnosis of TB reactivation	Interval between first injection to TB reactivation	Active TB type	Concomitant treatment for psoriasis	Biologic discontinuation	TB treatment regimen
1	Ixekizumab	14 months	Intestinal TB	No	Yes	INH, RFP, PZA, EB
2	Secukinumab	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned
3	Guselkumab	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned

TB: tuberculosis; LTBI: latent tuberculosis infection; INH: Isoniazid; RFP: rifampicin; PZA: pyrazinamide; EB: ethambutol.

While these agents are generally safer and have fewer side effects compared with traditional disease-modifying antirheumatic drugs (DMARDs), they might pose an increased risk of infections due to their impact on immune system inflammatory mediators. Nonetheless, this risk appears to be closely related to the specific biologic agent used. The World Health Organization (WHO) has provided guidelines on the management of LTBI, recommending treatment for patients receiving TNF inhibitors with a strong recommendation level (21). However, IL inhibitors are not listed among high-risk groups. In the past 20 years, there has been a surge in IL inhibitors for the treatment of psoriasis, showing dramatic efficacy. However, some patients exhibit inadequate responses to multiple IL inhibitors, necessitating a switch between different biologic therapies (22, 23). Many patients receiving IL inhibitors may have been previously treated with TNF inhibitors and received preventive treatment when LTBI status was identified. In such cases, further testing or treatment for LTBI is typically unnecessary. Screening for LTBI remains essential before initiating biologic treatment for psoriatic disease in biologic-naive or systemic treatment-naive patients, but the decision as to which biologic to start may depend on individual factors that might increase the potential toxicity of preventive treatment. We believe that a better understanding of psoriatic patients with concurrent LTBI who are treated with different biologics can provide more effective guidance for clinical practice. Furthermore, it is important to consider the possibility of *de novo* TB infection in patients receiving IL inhibitors or TNF inhibitors, regardless of their prior LTBI status or even preventive treatment. This underscores the critical need for epidemiologic surveillance, particularly in regions with a high prevalence of TB or among patients with an elevated risk of exposure due to occupational or environmental factors. Such measures are essential to ensure early detection and management of TB in vulnerable populations.

Th1 cells play a crucial role in controlling TB infection through the secretion of Th1 cytokines, such as IFN-γ, IL-12, and TNF. TNFα is particularly important for the formation and maintenance of granulomas, which explains the increased risk of TB associated with TNF inhibitors. The role of IL-17 and IL-23 in controlling TB infection is more contentious compared with TNF. Research indicates that IL-17A may exacerbate chronic TB infection by amplifying pathological harm and bacterial burden (24). Conversely, another study found IL-17A is essential for early granuloma formation during MTB infection (25). A human microgranuloma model-based *in vitro* study revealed that inhibiting IL-17A exerts minimal impact on MTB reactivation, in comparison with the potent effects observed with TNF inhibition (26). In terms of clinical implications, aggregated data from clinical trials of secukinumab and ixekizumab reported no cases of TB reactivation among psoriasis patients with LTBI who received chemoprophylaxis (27, 28). This observation provides reassurance regarding the safety of IL-17-targeted therapies in such populations. Turning to IL-23, its role in orchestrating the production of IL-17 and IL-22 is a pivotal mechanism for upregulating CXCL13, a key factor in the early immune response to TB (29). However, a mouse model study challenges this narrative by demonstrating that the absence of IL-23 does not affect the progression of primary MTB infection as long as Th1 cytokines are present (30). Furthermore, pooled analyses of risankizumab, guselkumab, and tildrakizumab, all directed against IL-23, also identified no cases of TB activation in psoriasis patients with LTBI (31–33). These findings collectively enhance the growing body of evidence supporting the safe administration of IL-23 targeted therapies in individuals at risk of TB reactivation.

Ustekinumab, as a dual-target inhibitor of IL-12 and IL-23, may potentially increase the risk of TB infection, given that IL-12 is crucial for Th1 development and subsequent IFN-γ production (30). Notably, individuals with congenital immunodeficiencies tied to disruptions in the IL-12/23-IFN-γ axis have been observed to have a higher risk of TB infection (34). A safety analysis of ustekinumab showed no cases of TB reactivation among patients who started INH chemoprophylaxis either with or before the first dose of the study agent (35). However, cases of TB reactivation among psoriasis patients with LTBI who used ustekinumab have been reported irrespective of their chemoprophylaxis status (36–39). These findings highlight the need for careful monitoring of psoriatic patients with LTBI who are receiving ustekinumab.

Most international guidelines continue to recommend chemoprophylaxis for all patients with LTBI, regardless of the biologic agent used, although current evidence indicates that IL-17 and IL-23 inhibitors pose a low risk of TB reactivation. However, a recently published expert consensus suggests that these concepts need to be updated (40). Consequently, the benefits and risks of treating LTBI require re-evaluation. The most commonly used preventive medications are isoniazid and rifampin. While these drugs are effective in preventing the progression of LTBI to active TB, it is crucial to acknowledge their potential adverse effects. Isoniazid, for instance, has been known to elicit side effects such skin rashes, liver toxicity, and peripheral neuropathy. Similarly, rifampin may give rise to flu-like symptoms, immune-mediated thrombocytopenia, and liver damage.

Limitation

This study has several limitations. First, some patients included in the analysis were part of the research, leading to missing information on basic demographic data such as sex and age. Second, variability in the duration of

biologic agent use and follow-up periods across studies resulted in the lack of a standardized outcome measure.

Conclusion

Overall, although specific guidelines are lacking, we consider the use of IL-17 and IL-23 inhibitors in psoriasis patients with LTBI to be relatively safe if chemoprophylaxis cannot be well tolerated, while the IL-12/23 inhibitor remains elusive. However, caution is needed before using ustekinumab in psoriatic patients with coexisting LTBI without prior anti-tuberculosis treatment. In the future, large studies are needed to evaluate the safety of IL inhibitors in the LTBI population.

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Data availability statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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