





REVIEW ARTICLE

Treatment of psoriasis with biologic and non-biologic targeted therapies in patients with latent tuberculosis infection or at risk for tuberculosis disease progression: Recommendations from a SPIN-FRT expert consensus

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Abstract

Tuberculosis (TB), caused by *Mycobacterium tuberculosis*, is a significant global health problem. In immunocompetent individuals, the microorganism can remain in a latent, non-contagious form, however, it may become active under conditions of immunosuppression. Tumour necrosis factor (TNF) inhibitors, which are frequently used for the management of immune-mediated disorders like psoriasis, have been associated with a significantly increased risk of reactivating latent TB. Consequently, international guidelines recommend TB screening and preventive treatment before starting anti-TNF therapy. These recommendations have extended to IL-12/23, IL-17, IL-23 and TYK2 inhibitors under a caution principle, despite their different mechanisms of action. However, current evidence suggests that some of these agents are arguably not associated with an increased risk of TB reactivation or development of TB disease after infection, which calls for a critical reassessment of these guidelines. We have conducted a literature search evaluating the risk of TB reactivation associated with these innovative therapies, integrating findings from both randomized clinical trials and real-world evidence. The identified evidence is limited but the low number of identified cases of reactivation with IL-17 and IL-23 inhibitors prompts reconsidering the need for preventive treatment for latent TB in all cases, regardless of biologic class or individual patient's risk of TB reactivation or drug toxicity. This review, along with the clinical insight of a panel of experts on behalf of the SPIN-FRT, led to the development of these consensus recommendations for managing psoriasis treatment in patients with latent TB infection or at risk of TB infection, who are receiving or are intended to receive biologic and non-biologic targeted therapies. These recommendations highlight the need for updates to the existing guidelines, aiming to provide a more differentiated approach that reflects the evolving landscape of psoriasis treatment and its implications for TB management.

For affiliations refer to page 14.

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INTRODUCTION

Psoriasis is a common, chronic, inflammatory skin disease associated with an increased risk of comorbidities such as psoriatic arthritis, metabolic syndrome, cardiovascular diseases and depression.^{1,2}

The interleukin (IL)-23/IL-17 axis and tumour necrosis factor (TNF) are crucial pathways underpinning the immunopathogenesis of psoriasis. The advent of targeted therapies directed to such pathways has markedly transformed psoriasis management. However, these therapies require a nuanced risk–benefit evaluation due to potential complications, including an increased risk of opportunistic infections, such as tuberculosis (TB).

TB, caused by *Mycobacterium (M.) tuberculosis* complex bacteria, represents a significant public health concern, as it is a leading cause of mortality from infectious diseases globally.³ The pathogenesis of TB is initiated by the inhalation or ingestion of *M. tuberculosis*, leading to its phagocytosis by macrophages within the lungs or alimentary tract.^{4,5} Ineffective macrophage response results in the intracellular survival and multiplication of the bacteria, fostering a cycle of bacterial release and re-phagocytosis. In immunocompetent individuals, Th1 lymphocytes are mobilized to initiate a cellular immune reaction through the secretion of cytokines such as interferon (INF)- γ , IL-12 and TNF, which are pivotal in granuloma formation and maintenance.⁶ Consequently, the infection progresses to a latent stage within granulomas, characterized by asymptomatic latency and non-contagiousness, called latent TB infection (LTBI).^{7,8} This ability of Th1 cytokines to promote containment of TB infection is well exemplified by cases of individuals with gene mutations in the IL-12/INF γ axis, who have experienced disseminated infections after Bacillus Calmette–Guérin vaccination.^{9,10}

In immune compromised conditions, such as in cases of human immunodeficiency virus (HIV) infection and other forms of immunosuppression,¹¹ *M. tuberculosis* can escape immune control, leading to TB disease.¹² According to the 2023 World Health Organization (WHO) report, about a quarter of the global population is estimated to have LTBI.^{13,14} In these individuals, the overall lifetime risk of TB reactivation ranges from 5% to 10%.^{3,12}

Considering the widespread prevalence of LTBI and the endemic nature of TB in certain regions, coupled with the chronicity of psoriasis, there is a significant likelihood that patients with psoriasis may have been in contact *M. tuberculosis* at some point in their lives, possibly leading to LTBI or TB disease. Consequently, it becomes vital to assess the potential influence of psoriasis therapies, especially those that modulate the host immune responses, on the reactivation of TB infection.

In that regard, extensive clinical data, including meta-analyses of randomized clinical trials (RCT), pooled safety analyses and real-world clinical observations, have demonstrated that treatment with TNF inhibitors is linked with a high risk of TB infection or LTBI reactivation.^{15–20} This is

Key points

Why was the study undertaken?

- To formulate recommendations for the treatment of psoriasis with biologic and non-biologic targeted therapies in patients with latent tuberculosis infection or at risk for tuberculosis disease progression and to evaluate the risk of tuberculosis reactivation associated with IL-12/23, IL-17, IL-23 and TYK2 inhibitors, and reassess the necessity of preventive treatment before their use.

What does this study add?

- This study provides evidence suggesting a low risk of tuberculosis reactivation with IL-17 and IL-23 inhibitors, prompting a reconsideration of current preventive treatment guidelines for such drugs.

What are the implications of this study for disease understanding and/or clinical care?

- It advocates for updated guidelines that offer a more differentiated approach to managing psoriasis in patients with tuberculosis infection or at risk for tuberculosis disease progression, reflecting new evidence on drug safety.

largely attributed to the crucial role of TNF in both granuloma formation and Th1 cell responses.⁶

As a result, comprehensive guidelines have been established, emphasizing the necessity of TB screening for patients undergoing TNF inhibitors. Standard diagnostic tests include tuberculin skin test (TST), IFN- γ release assays (IGRA) and chest X-ray.^{21,22} If the patient is IGRA- or TST-positive, and in the absence of clinical and radiological evidence of TB disease or detection of *M. tuberculosis* in a microbiological sample, LTBI is diagnosed. In those with LTBI, candidate to biological therapy, the preventive therapy is recommended irrespective of the biologic agent chosen.^{16,23–26} Most protocols of TB preventive therapy include short-course rifampicin monotherapy (600 mg once daily [qd] for 4 months), long-course isoniazid monotherapy (300 mg qd for 6–9 months) or combination rifampicin/isoniazid (600/300 mg qd for 3 months) starting 4 weeks before biologic therapy.²⁷ However, TB preventive therapy is associated with numerous adverse effects and several contraindications for its usage. Isoniazid is associated with hepatotoxicity, peripheral neuropathy, cutaneous adverse drug reactions, gastrointestinal symptoms and neuropsychiatric adverse effects, including cognitive impairment and lethargy.²⁸ Rifampicin is associated with the onset of ‘flu-like’ symptoms, hepatotoxicity, cutaneous adverse drug

reactions, immune-mediated thrombocytopenia, as well as a wide range of drug interactions.²⁹ Also, inadequate or unnecessary use of TB preventive therapy may contribute for the development of drug-resistant TB.

Adopting a cautious approach, current guidelines for TB screening and preventive therapy, except the recently published Austrian consensus,³⁰ are similarly applied to all biologic therapies used in psoriasis treatment, encompassing not only TNF inhibitors but also novel biologics and non-biologic targeted therapies (except for apremilast) that differ significantly in their mechanisms of action. Given the potential contraindications and adverse effects associated with TB preventive therapy regimens, the risk–benefit of starting anti-TB treatment should be carefully weighed. Thus, it is essential to assess the risk of TB reactivation associated with these newer therapeutic classes.³¹

To assess the risk of TB reactivation associated with the various newer biologic and non-biologic targeted therapies, we conducted a thorough literature search to evaluate the clinical evidence from RCTs and real-world clinical studies. This review specifically focused on the potential link between novel biologic and non-biologic targeted therapies for psoriasis (i.e. IL-17 inhibitors, IL-23 inhibitors, IL-12/23 inhibitors, phosphodiesterase 4 (PDE4) inhibitors and TYK2 inhibitors) and the risk of TB reactivation. We also integrated scientific insights on the molecular targets of these drugs and their influence on TB pathogenesis. Our findings, combined with the collective clinical experience of a panel of experts, acting on behalf of Skin Inflammation & Psoriasis International Network–Fondation René Touraine (SPIN-FRT), led to the formulation of recommendations for the treatment of psoriasis with these agents in patients with LTBI or at risk for TB infection.

METHODS

Literature search

Search strategy

A literature search was executed in PubMed, up to 19 March 2024. The queries were as follows:

- a. ((Tuberculosis) OR (TB) OR (LTBI)) AND (ustekinumab),
- b. ((Tuberculosis) OR (TB) OR (LTBI)) AND ((secukinumab) OR (ixekizumab) OR (brodalumab) OR (bimekizumab)),
- c. ((Tuberculosis) OR (TB) OR (LTBI)) AND ((guselkumab) OR (risankizumab) OR (tildrakizumab)),
- d. ((Tuberculosis) OR (TB) OR (LTBI)) AND (apremilast),
- e. ((Tuberculosis) OR (TB) OR (LTBI)) AND (deucravacitinib).

The search strategy was designed to capture keywords across all article fields. Additionally, the reference lists of selected full-text articles and relevant review articles were examined to identify further pertinent studies.

Eligibility criteria

This literature review assesses the available evidence regarding the risk of TB reactivation in patients with LTBI treated with biologic therapies other than TNF inhibitors and non-biologic targeted therapies as specified below.

The following inclusion criteria were applied:

- (i) Systematic reviews, pooled analysis and open-label extensions of randomized clinical trials including data on the reactivation of TB in patients with LTBI treated with IL-17 inhibitors (secukinumab, ixekizumab, brodalumab and bimekizumab), IL-23 inhibitors (guselkumab, risankizumab and tildrakizumab), IL-12/IL-23 inhibitors (ustekinumab), PDE4-inhibitors (apremilast) and TYK2 inhibitors (deucravacitinib).
- (ii) Real-world studies and case reports evaluating the reactivation of TB in patients with LTBI treated with IL-17 inhibitors (secukinumab, ixekizumab, brodalumab and bimekizumab), IL-23 inhibitors (guselkumab, risankizumab and tildrakizumab), IL-12/IL-23 inhibitors (ustekinumab), PDE4-inhibitors (apremilast) and STAT TYK2 inhibitors (deucravacitinib).

Abstracts, conference reports and manuscripts whose full texts were unavailable or written in languages other than English were excluded.

Data extraction

Titles and abstracts were initially reviewed to pinpoint articles that potentially matched the criteria. The full texts of these articles were examined for eligibility. For data extraction, a standardized form was employed, capturing the following items: first author, publication year, study type, location, investigated drug, disease, count of LTBI-positive patients included with complete, incomplete or lacking preventive therapy, reasons for incomplete or lack of preventive therapy, number of TB reactivation cases and duration of follow-up. Review of article abstracts and full texts, and data extraction were independently performed by two authors (NB and TT). Cases of disagreement were resolved by discussion.

Data analysis and results

The search yielded a total of 193 articles, broken down as follows: 85 for query a, 60 for b, 26 for c, 19 for d and 3 for e (see search strategy). An additional 19 studies were retrieved through reference screening, totalling 211 studies. Fifty studies were identified more than once through the search. Out of the 161 unique entries, 23 articles met the criteria (Figure 1). Data were extracted using a standardized form, cohesively synthesized in a narrative format

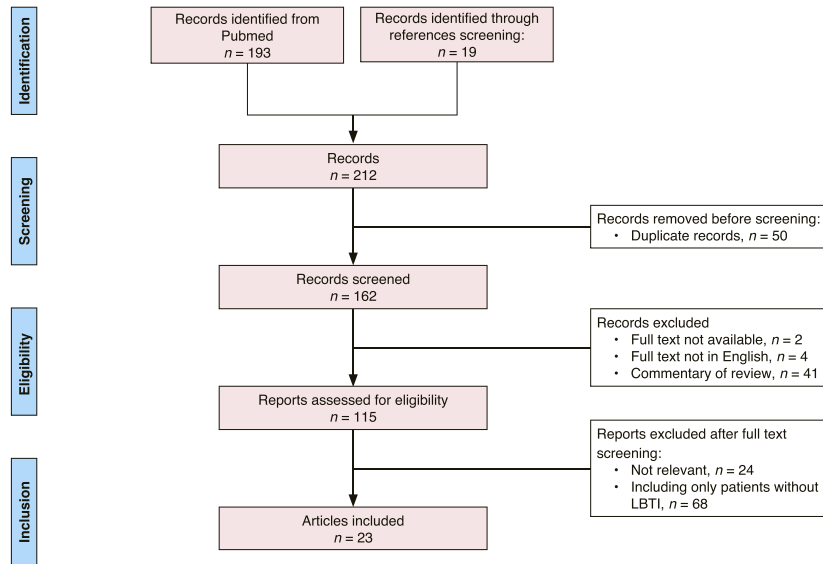


FIGURE 1 Flow chart of the literature search strategy.

and organized into a comprehensive table including studies investigating TB disease reactivation in patients with incomplete or absent LTBI preventive therapy under IL-17 inhibitor or IL-23 inhibitor biologics (Table 1). Documented cases of TB reactivation in patients under ustekinumab are reported in Table 2.

Recommendation development and establishment of consensus

Two experts (TT and LP) utilized the results of the literature search to initially propose a set of recommendations, which were presented to a select panel comprising 14 independent experts, including dermatologists (belonging to the scientific committee of the SPIN-FRT) and infectious diseases specialists. Panel members were invited to either endorse the proposed recommendations or suggest amendments. The feedback received was carefully considered, leading to the refinement of the recommendations. The revised recommendations were subsequently resubmitted to the panel for a vote. This iterative process of review and voting continued until a consensus was reached among all the experts.

Literature search limitations

There is the possibility that certain studies were not captured if their abstracts, titles or keywords did not contain the search terms. All instances of TB disease in patients with the diagnosis of LTBI were classified as cases of TB reactivation. It is important to note that the original study authors did not definitively determine in all cases if it was instances of TB reactivation or de novo infections, although the latter is considered unlikely.

SUPPORTING EVIDENCE: RANDOMIZED CLINICAL TRIALS AND REAL-WORLD EVIDENCE

IL-17 inhibitors: Secukinumab, ixekizumab, brodalumab and bimekizumab

IL-17A is recognized as a pivotal effector molecule in the pathogenesis of psoriasis. Several biologic agents targeting the IL-17 family have been developed: (i) monoclonal antibodies (mAbs) directly targeting IL-17A, such as secukinumab (fully human immunoglobulin [Ig]G1k mAb) and ixekizumab (humanized IgG4 mAb); (ii) a mAb targeting the IL-17RA subunit of the IL-17A receptor, brodalumab (fully human IgG2 mAb), which inhibits the biologic activity not only of IL-17A but also of IL-17C, IL-17E and IL-17F; (iii) a mAb targeting both IL-17A and IL-17F, bimekizumab (humanized IgG1 mAb).

The exact role of IL-17A (and the IL-17 family at large) in the immune response to *M. tuberculosis* is still a matter of debate and seems dependent on the stage of infection. In some models, Th17 response seems crucial for initiating early protective immunity to *M. tuberculosis* infection, aiding in the recruitment of neutrophils, macrophages and Th1 cells to the inflamed tissue.³² In others, IL-17 is implicated in the maturation of granulomas from the nascent to the mature stage.³³ However, IL-17-induced responses seem to be essential for mounting protective immunity against *M. tuberculosis* only when the Th1/IFN- γ axis is compromised.^{34,35} Moreover, recent findings demonstrate that inhibiting Th17 effector responses in mice, either through IL-17A or IL-17F neutralization by antibodies, or via knock-down of IL-17RA or IL-22, does not impair host control of *M. tuberculosis*, while mice deficient in TNF rapidly succumb to infection.^{36,37} Notably, in an in vitro human microgranuloma model, inhibiting IL-17A using secukinumab did

TABLE 1 Cases of LTBI reactivation in patients with incomplete or absent LTBI preventive therapy under IL-17 inhibitors or IL-23 inhibitors.

Drug	Disease	Study type	Study location	# LTBI	# Reactiv.	Follow-up (mean)	Reason for absence /incomplete preventive therapy	References
Secukinumab	Pso	Case report	Italy	1	0	n/a	Incomplete (hepatic toxicity)	Lasagni et al., J Dermatolog Treat. 2018
		Case series	Italy	12	0	52 weeks	Absent (contraindication or refusal)	Ribero et al., Case Rep Dermatol. 2019
		Case series	Portugal	2	0	2 years	Incomplete (<i>n</i> =1, toxicity) or absent (<i>n</i> =1, contraindication)	Machado et al., Eur J Dermatolo. 2020
	Retrospective analysis	Italy	1	0	n/a	n/a		Galluzzo et al., Expert Opin Biol Ther. 2020
		China	17	0	51.5 weeks	Incomplete (<i>n</i> =2) or Absent (<i>n</i> =15, refusal)	Shu et al., Dermatol Ther. 2000	
		Italy	3	0	73 weeks	Absent (contraindication)	Fiorella et al., Clin Case Rep. 2022	
		Italy	10	0	84 weeks	Absent (contraindication or refusal)	Megna et al., J Dermatolog Treat. 2022	
	Retrospective analysis	China	14	0	18.9 months	Absent (contraindication)	Xiao et al., Dermatol Ther. 2023	
		Italy	2	0	23.6 months	n/a	Mastorino et al., ActaDV. 2022	
		Spain	1	0	24 months (median)	Absent (contraindication)	Manzanares et al, J Eur Acad Dermatol Venerol. 2023	
Retrospective analysis	Multi-nation	35	0	32.87 months	Incomplete (<i>n</i> =11, toxicity or non-compliance) or Absent (<i>n</i> =24, contraindication or refusal)	Torres et al., Am J Clin Dermatol. 2024		
Ixekizumab	Pso	Prospective analysis	China	89	0	24 months	Absent (contraindication or refusal)	He et al., Dermatol Ther, 2024
		Retrospective analysis	China	3	0	17.2 months	Absent (refusal)	Liu et al., Clin Rheumatol. 2023
	Retrospective analysis	Italy	2	0	21.6 months	n/a	Mastorino et al., ActaDV. 2022	
	Retrospective analysis	Spain	2	0	24 months (median)	Absent (contraindication)	Manzanares et la, J Eur Acad Dermatol Venerol. 2023	
Pso/PsA	Retrospective analysis	Multi-nation	26	1 ^a	32.87 months	Incomplete (<i>n</i> =4, toxicity or non-compliance) or Absent (<i>n</i> =22, contraindication or refusal)	Torres et al., Am J Clin Dermatol. 2024	
	Prospective analysis	China	8	0	24 months	Absent (contraindication or refusal)	He et al., Dermatol Ther, 2024	
	Pooled safety analysis from 16 trials	Multi-nation	6	0	867–1785 days (range)	n/a	Mrowietz et al, J Am Acad Dermatol. 2020	
Brodalumab	Pso	Retrospective analysis	Italy	4	0	10.3 months	n/a	Mastorino et al., ActaDV. 2022
		Retrospective analysis	Spain	1	0	24 months (median)	Absent (contraindication)	Manzanares et al., J Eur Acad Dermatol Venerol. 2023
	Retrospective analysis	Multi-nation	10	0	32.87 months	Incomplete (<i>n</i> =4, toxicity or non-compliance) or Absent (<i>n</i> =6, contraindication or refusal)	Torres et al., Am J Clin Dermatol. 2024	

(Continues)

TABLE 1 (Continued)

Drug	Disease	Study type	Study location	# LTBI	# Reactiv.	Follow-up (mean)	Reason for absence /incomplete preventive therapy	References
Risankizumab	Pso	Retrospective analysis	Italy	2	0	9.3 months	n/a	Mastorino et al., ActaDV. 2022
		Phase 3 trial (IMMhance)	Multi-nation	31	0	55 weeks	n/a	Blauvelt et al., JAMA Dermatol. 2020
	Retrospective analysis	Spain	21	0	24 months (median)	Absent (contraindication)	Manzanares et al., J Eur Acad Dermatol Venerol. 2023	
		Multi-nation	45	0	32.87 months	Incomplete ($n=15$, toxicity or non-compliance) or Absent ($n=30$, contraindication or refusal)	Torres et al., Am J Clin Dermatol. 2024	
Guselkumab	Pso	Retrospective analysis	Spain	5	0	24 months (median)	Absent (contraindication)	Manzanares et al., J Eur Acad Dermatol Venerol. 2023
		Retrospective analysis	Multi-nation	19	0	32.87 months	Incomplete ($n=3$, toxicity or non-compliance) or Absent ($n=16$, contraindication or refusal)	Torres et al., Am J Clin Dermatol. 2024
Tildrakizumab	Pso	Case report	Ireland	1	0	24 weeks	n/a	Kearney et al., Clin Exp Dermatol. 2020
		Retrospective analysis	Spain	5	0	24 months (median)	Absent (contraindication)	Manzanares et al., J Eur Acad Dermatol Venerol. 2023
Total		Retrospective analysis	Multi-nation	18	0	32.87 months	Incomplete ($n=4$, toxicity or non-compliance) or Absent ($n=14$, contraindication or refusal)	Torres et al., Am J Clin Dermatol. 2024
				423	1			

Note: The study includes secukinumab, ixekizumab, brodalumab, guselkumab, risankizumab and tildrakizumab.

Abbreviations: axSpA, axial spondyloarthritis; HS, hidradenitis suppurativa; LTBI, latent tuberculosis infection; Pso, psoriatic arthritis; Pso, psoriasis. Intestinal tuberculosis after 14 months of treatment.

TABLE 2 Documented cases of TB reactivation/active TB disease with ustekinumab treatment.

Disease	Study type	Study location	# Reactivation/TB disease	Timing	Preventive therapy	Comments	References
Pso	Case report	Italy	1 (LTBI react/pulmonary TB)	First week after second UST injection	Preventive therapy done The patient received isoniazid because of QFT positivity at screening. UST introduced while keeping isoniazid and steroid therapies.	A 36-year-old healthy man, with a 7-year history of moderate to severe psoriasis 1 week after the 2nd UST injection, the patient was hospitalized for the onset of cough, fever and anorexia. The positive result of sputum mycobacterial culture and the miliary change detected by chest radiograph and computed tomography were consistent with pulmonary miliary TB. No sign/symptom of extrapulmonary TB.	Enrichetti et al., Eur J Dermatol. 2014
Pso PsA	Case report	Ireland	1 (LTBI react/Peritoneal TB)	Not specified	Preventive therapy/treatment done The patient was treated for 9 months with isoniazid and pyridoxine due to positive TST at initial screening (prior to starting a treatment attempt with etanercept, 5 years before initiating UST)	A 36-year-old Filipino female, with a 5-year history of severe psoriasis and PsA. Under UST, laparotomy examination found chronic inflammatory bowel deposits, omental caking and abdominal and pelvic adhesions typical of peritoneal TB. A chest radiograph showed no evidence of TB. Polymerase chain reaction and mycobacterial culture confirmed <i>M. tuberculosis</i> . NOTE: Once successfully treated, the patient started secukinumab therapy. No reactivation of TB after 9 months.	Lynch et al., JAAD Case Rep. 2017
CD	Case report	Japan	1 (LTBI react/Tuberculous pericarditis)	38 months after UST initiation	Preventive therapy/treatment done The patient was treated with ISO, RIF, EB and streptomycin after extrapulmonary TB and tuberculous lymphadenitis under Infliximab. Once TB was considered resolved, she switched to UST.	A 28-year-old woman with CD 38 months after UST initiation, transthoracic echocardiography showed pericardial effusion, right atrial collapse, and no thrombus or shunt in the left atrium or left ventricle. Chest CT showed pericardial effusion, and the patient was diagnosed with pericardial tamponade. Tuberculous pericarditis was diagnosed based on positive PCR.	Tominaga et al., Healthcare. 2021

Abbreviations: BAL, bronchoalveolar lavage; CD, Crohn's disease; LTBI, latent tuberculosis infection; PCR, polymerase chain reaction; PsA, psoriatic arthritis; Pso, psoriasis; QFT, QuantiFERON-TB test; TB, tuberculosis; TST, tuberculin skin test; UST, ustekinumab.

not reverse *M. tuberculosis* dormancy, whereas the IL-12-p40 inhibitor ustekinumab, the TNF inhibitor adalimumab and the recombinant IL-1 receptor antagonist (IL-1RA) anakinra promoted *M. tuberculosis* reactivation, establishing a mechanistic connection to human therapeutics.^{38,39}

Recent reviews^{40,41} and comprehensive cohort safety studies,^{42–47} have thoroughly analysed data from Phase I, II and III clinical trials and post-marketing studies, focusing on IL-17 inhibitors (secukinumab, ixekizumab and brodalumab) used in treating psoriasis, psoriatic arthritis, ankylosing spondylitis and hidradenitis suppurativa. It is important to emphasize that patients with LTBI were typically eligible for enrolment in these trials, and they received TB preventive therapy in accordance with local guidelines. These analyses consistently found no evidence of TB reactivation in patients with LTBI undergoing treatment with IL-17 inhibitors together with preventive treatment for TB. The clinical significance of this observation is reinforced by the inclusion in these studies of several thousand patients, accounting for tens of thousands of patient-years' exposure. Notably, this figure reaches up to 112,280 patient-years in a pooled safety analysis for secukinumab when post-marketing exposure was included.⁴⁷ Also, for the latest IL-17A/IL-17F dual inhibitor (bimekizumab) pooled analysis of safety data from Phase III clinical trials⁴⁸ and extension studies up to 3 years are available,^{49,50} with no cases of TB reported.

Although these studies offer encouraging evidence regarding the relative safety of IL-17 inhibitors in treating patients with LTBI, the administration of prior preventive therapy introduces a significant confounding factor. A meaningful exception consists of a subgroup of 6 LTBI-negative patients who became LTBI-positive while receiving ixekizumab but did not undergo concurrent TB preventive therapy. This finding was highlighted in a pooled safety analysis encompassing 16 trials for psoriasis and psoriatic arthritis.⁴⁶ Similarly, a separate pooled safety analysis of 5 trials involving secukinumab for psoriasis included 25 patients with a history of treated pulmonary TB disease who tested IGRA-negative at screening. These patients were treated with secukinumab without undergoing TB preventive therapy.³⁹ In both patient cohorts, no cases of TB reactivation were reported, underscoring the arguable safety of these treatments in this specific population.^{39,46}

Numerous retrospective studies and case reports have been recently published, describing cases of patients with LTBI receiving IL-17 inhibitors in the absence of adequate TB preventive therapy.^{51–63} The primary reasons for patients not receiving appropriate preventive therapy included liver disease or toxicity, contraindications due to existing comorbidities or potential pharmacological interactions, along with cases of patient's refusal. A subset of patients initiated preventive treatment but were unable to complete it, due to poor adherence or the emergence of safety concerns.

These reports, which corroborate and expand the insights gained from clinical trials,^{39,46} offer a unique chance to conduct an unbiased assessment and provide meaningful insights into the usefulness of preventive therapy for LTBI

patients undergoing such therapies. Table 1 provides a comprehensive list of the available studies, categorizing them according to the specific IL-17 inhibitors used.

Aggregating data from various studies reveals that a total of 212 patients with LTBI, lacking appropriate preventive therapy, were treated with secukinumab over a period ranging from 12 to 32 months.^{51–53,55,57–63} Within this cohort, 169 patients did not undergo any form of preventive therapy, 15 patients ceased their prescribed preventive therapy prematurely, failing to complete it and 25 had been previously treated for TB disease. Data regarding interruption or absence of preventive therapy were unavailable for the remaining 3 patients. Additionally, 38 patients without proper preventive therapy were administered ixekizumab for periods between 21 and 32 months, and 15 patients received brodalumab for 10–32 months.^{56,57,62,63} In these latter groups, 32 and 7 patients on ixekizumab and brodalumab, respectively, did not receive any TB preventive therapy, while the rest discontinued their prophylactic course before completion (in some cases the information was lacking).

Only one of these patients exhibited signs of TB disease reactivation.⁶² Considering the unique characteristics of the patient cohort included in real-world settings, which includes individuals with contraindications to or with high risk of toxicity to standard TB preventive therapy, the rare occurrence of TB reactivation in these cases is particularly noteworthy.

The evidence described above highlights the safety of IL-17 inhibitors in patients with LTBI, even in the absence of preventive therapy, as they are unlikely to increase the risk of TB reactivation.

IL-23 (p19) inhibitors: Guselkumab, risankizumab and tildrakizumab

IL-23, a member of the IL-12 cytokine family, is composed of two distinct subunits: p40, which is shared with IL-12, and p19, exclusive to IL-23. The role of IL-23 in the pathogenesis of psoriasis is crucial, acting as an upstream regulatory cytokine in the Th17/IL-17 pathway.⁶⁴

Like IL-17A, IL-23 seems implicated in protective responses to *M. tuberculosis*⁶⁵; however, its significance appears to be overshadowed by Th1 responses, being important only when the Th1/IFN γ axis is compromised.

Selective inhibition of IL-23 is accomplished through the neutralization of its unique p19 subunit by mAbs such as guselkumab (a fully human IgG1 lambda mAb), risankizumab (a humanized IgG1 mAb) and tildrakizumab (a humanized IgG1 kappa mAb). The safety and efficacy of these agents is well-established through extensive RCTs and real-world clinical experience.

As reported in the case of IL-17 targeted therapies, comprehensive reviews^{41,66–68} have specifically focused on investigating the occurrence of TB reactivation in patients with LTBI. Pooled safety studies,^{69–71} encompassing data from multiple RCTs (including Phase I, II, and III for

psoriasis and psoriatic arthritis), offer corroborative evidence in this regard. No cases of TB reactivation were reported in clinical trials for targeted IL-23 therapies. This finding is relevant considering the substantial number of patients involved: 2072 patients treated with risankizumab with an exposure of 7927 patient-years (PY),⁶⁹ 4399 patients treated with guselkumab with an exposure of 10,787 PY⁷⁰ and 1413 patients treated with tildrakizumab, with exposures ranging from 4 to 76 weeks.⁷¹ Similar findings were observed in Phase 2 and Phase 3 studies with guselkumab and risankizumab in inflammatory bowel disease (ulcerative colitis and for patients with Crohn's disease).^{72–76} However, it is important to note that patients with LTBI were typically included in these studies only after undergoing preventive therapy, introducing a potential confounding bias. Despite this, there were exceptions within these cohorts, providing valuable insights. In the IMMhance Phase III clinical trial, designed to evaluate risankizumab for the treatment of psoriasis, there was a subset of 31 patients who were IGRA-positive during screening but did not receive LTBI preventive therapy.⁷⁷ These individuals were exposed to risankizumab for a duration of 55 weeks. Additionally, in a pooled analysis from two Phase III studies focusing on guselkumab, a group of 7 patients began TB preventive treatment concurrently with guselkumab therapy, and 5 more initiated preventive treatment after starting guselkumab.⁷⁸ In both cohorts, no cases of TB reactivation were reported.

In real-world clinical settings, as summarized in Table 1, a total of 68 LTBI patients who did not receive adequate TB preventive therapy were treated with risankizumab for periods ranging from 9 to 32 months.^{56,57,62,77} Fifty-one patients did not undergo any preventive therapy, 15 did not complete the preventive regimen, and information was lacking for 33 patients. Furthermore, 25 additional patients (21 without preventive therapy, 3 with incomplete preventive therapy and 1 with no available information) were treated with guselkumab for 24–32 months.^{56,62,79} Regarding tildrakizumab, 23 patients (19 without preventive therapy and 4 with incomplete preventive therapy) received treatment for 24–32 months.^{62,80} Remarkably, there were no documented cases of TB reactivation, a fact that reinforces the safety profile of targeted IL-23 inhibitors in patients with LTBI who lacked standard prophylactic care.

Thus, as with IL-17 inhibitors, existing evidence reinforces the safety profile of IL-23 inhibitors in patients with LTBI in the absence of preventive therapy, due to the likely non-increased risk of TB reactivation.

IL-12/23 (p40) inhibitor: Ustekinumab

Ustekinumab, a fully human IgG1 kappa mAb targeting the p40 subunit, is a non-selective IL-23 inhibitor. As p40 is also a component of IL-12, ustekinumab also targets this cytokine. This becomes especially important in the context of infection, as IL-12 is involved in promoting Th1 cell

responses, which are vital for granuloma formation and effective responses against *M. tuberculosis*.⁸¹

A pooled analysis of 5 RCTs in psoriasis and 6 Phase II/III studies in inflammatory bowel disease reported no cases of TB reactivation in patients undergoing TB preventive therapy starting at baseline.^{82,83} However, in the PEARL Phase III study on psoriasis, one of 167 LTBI patients who had an abnormal chest X-ray but normal TST/IGRA and did not receive preventive therapy developed asymptomatic pulmonary TB.⁸⁴ Subsequent real-world clinical data (Table 2) reported three additional cases of TB reactivation in patients who had received complete preventive therapy and were treated with ustekinumab for different conditions (psoriasis, psoriatic arthritis and Crohn's disease).^{85–89} The time to reactivation varied, ranging from 15 days to 38 months after treatment initiation, though most cases occurred within the first 2 months.

Although data on TB reactivation with ustekinumab are limited, the reported cases warrant further investigation into the risk of TB reactivation with IL-12/23 inhibition. The currently available evidence combined with the potential impact of IL-12 inhibition on immune defence against TB infection suggests that caution is warranted in waiving TB preventive therapy before initiating ustekinumab.

Non-biologic targeted therapies: PDE4 and TYK2 inhibitors

PDE4 inhibitors: Apremilast

Cyclic adenosine monophosphate (cAMP), a ubiquitous secondary messenger, plays a crucial role in modulating various cellular responses. In psoriasis, cAMP activates a series of molecular events leading to the suppression of pro-inflammatory cytokine release and keratinocyte proliferation, key pathogenetic factors in this disease. The degradation of cAMP is mediated by phosphodiesterases, with PDE-4 being the predominant isoenzyme in immune cells. Targeted inhibition of PDE-4 stabilizes cAMP levels, thus offering a therapeutic approach in psoriasis by reducing inflammation and modulating the dysregulated immune response. Apremilast was the first orally available PDE-4 inhibitor approved by the FDA in 2014 for the treatment of moderate-to-severe plaque psoriasis.⁹⁰

A series of randomized Phase III trials evaluated apremilast for psoriasis⁹¹ and psoriatic arthritis,^{92–95} encompassing 1184 patients with psoriasis with exposure extending up to 3 years and 1348 patients with psoriatic arthritis throughout an exposure period of 24–52 weeks. These trials excluded patients with TB disease or a history of incompletely treated TB, and they did not mandate LTBI testing prior to enrolment. There were no reported cases of TB disease. This observation is significant, as it implies that patients with LTBI may have been included and treated with apremilast without prophylactic measures, yet no reactivation events were documented. In fact, and unlike other biologic and non-biologic

targeted therapies, apremilast was approved by the regulatory authorities without the need for TB screening or mandatory LTBI treatment before initiating apremilast.

Several real-world studies have been conducted and none reported instances of TB reactivation.^{96,97} A comprehensive retrospective analysis utilizing a large US-based claims database, including patients diagnosed with psoriasis and/or psoriatic arthritis who were administered at least one dose of apremilast between 2014 and 2018, identified only two cases of TB disease among 10,074 patients treated with apremilast.⁹⁸

This evidence collectively strengthens the fact that apremilast is unlikely to be associated with a significant increased risk of reactivating latent TB.

TYK2 inhibitors: Deucravacitinib

TYK2 is a member of the Janus kinase (JAK) family and plays a crucial role in the signalling pathways downstream several pro-inflammatory cytokine receptors, notably IL-12, IL-23 and Type I IFNs, which are crucial in the pathogenesis of psoriasis and other autoimmune disorders. The selective inhibition of TYK2, therefore, results in a decrease in inflammation and modulation of the immune response, offering a targeted therapeutic approach in the management of these conditions. Deucravacitinib, a selective oral TYK2 inhibitor, received its first approval by the FDA in 2022 for treatment of adults with moderate-to-severe plaque psoriasis, demonstrating superior efficacy in pivotal Phase III trials compared to apremilast.^{99,100}

RCTs of deucravacitinib have not reported any case of TB reactivation and there have been no real-world clinical reports of TB reactivation in patients treated with deucravacitinib (without or without preventive therapy), although the data are limited to this point. Nevertheless, preventive therapy is advised for patients with LTBI.¹⁰¹ This caution is justified because TYK2 inhibition impairs function of IL-12, a cytokine known to play a role in fighting granulomatous infections through the induction of a Th1 response, which may increase the risk of TB reactivation.

EXPERT CONSENSUS RECOMMENDATIONS

The data reviewed herein—albeit acknowledging its potential limitations, such as underreporting—indicate a significantly different risk of TB reactivation in patients with LTBI treated with IL-17, IL-23 or PDE4 inhibitors compared with TNF inhibitors and a potentially different risk compared with IL-12/23 or TYK2 inhibitors (even though data on TB reactivation with ustekinumab and deucravacitinib is limited or not yet available, the mechanisms of action of these drugs and their implications regarding the immunopathology of granuloma maintenance support the recommendations provided below).

Thus, there is a rationale for adopting a distinct therapeutic approach for psoriasis in patients with LTBI or at risk for TB disease progression depending on the selected agent, particularly due to the non-negligible risks associated with TB preventive therapy. This contrasts with almost all the current recommendations, which do not make any difference based on the therapeutic agent used for psoriasis.^{16,23–25} The exception is the Austrian consensus that no longer recommends preventive treatment for patients being treated with IL-17 inhibitors.³⁰

Moreover, the accessibility to these therapeutic options, particularly newer targeted therapies, may be influenced by several factors such as financial constraints, reimbursement policies or other issues, at least as first-line treatments. For instance, in many countries, TNF inhibitors (both biosimilars and originals) are often prescribed as the first line due to their lower cost, provided there are no contraindications for the patient. Consequently, patients from certain regions, especially those from economically disadvantaged areas, may lack access to newer biologics and non-biologic targeted treatments. This situation is likely to persist as additional biosimilars, such as those of ustekinumab, are approved and made available.

Based on these premises, the existing guidelines and the current clinical practice, the expert group authoring this manuscript, within the framework of the SPIN-FRT, proposes specific recommendations for the treatment of psoriasis with biologic and non-biologic target therapies in patients with LTBI or at risk for TB disease progression.

The recommendations reported below, which account for these potential scenarios, are organized into four categories:

1. Screening for LTBI/TB disease before initiating targeted therapies, and management of patients who test positive or negative (Figure 2).
2. Management of patients with previously treated TB disease or previously treated LTBI (with preventive treatment) (Figure 3).
3. Management of patients being treated with biologic and non-biologic targeted therapies who develop TB disease (Figure 4).
4. Periodic TB screening in patients being treated with biologic and non-biologic targeted treatments (Figure 5).

An all-encompassing decision tree, which encapsulates these recommendations, is presented in Figure 1.

These recommendations take into account the currently available biologic and non-biologic targeted therapies for psoriasis and may potentially be extrapolated to other agents of the same therapeutic classes as they become available. As agents from new therapeutic classes become available or new evidence emerges, these recommendations may be updated.

1. Screening for LTBI/TB disease before initiating targeted therapies:

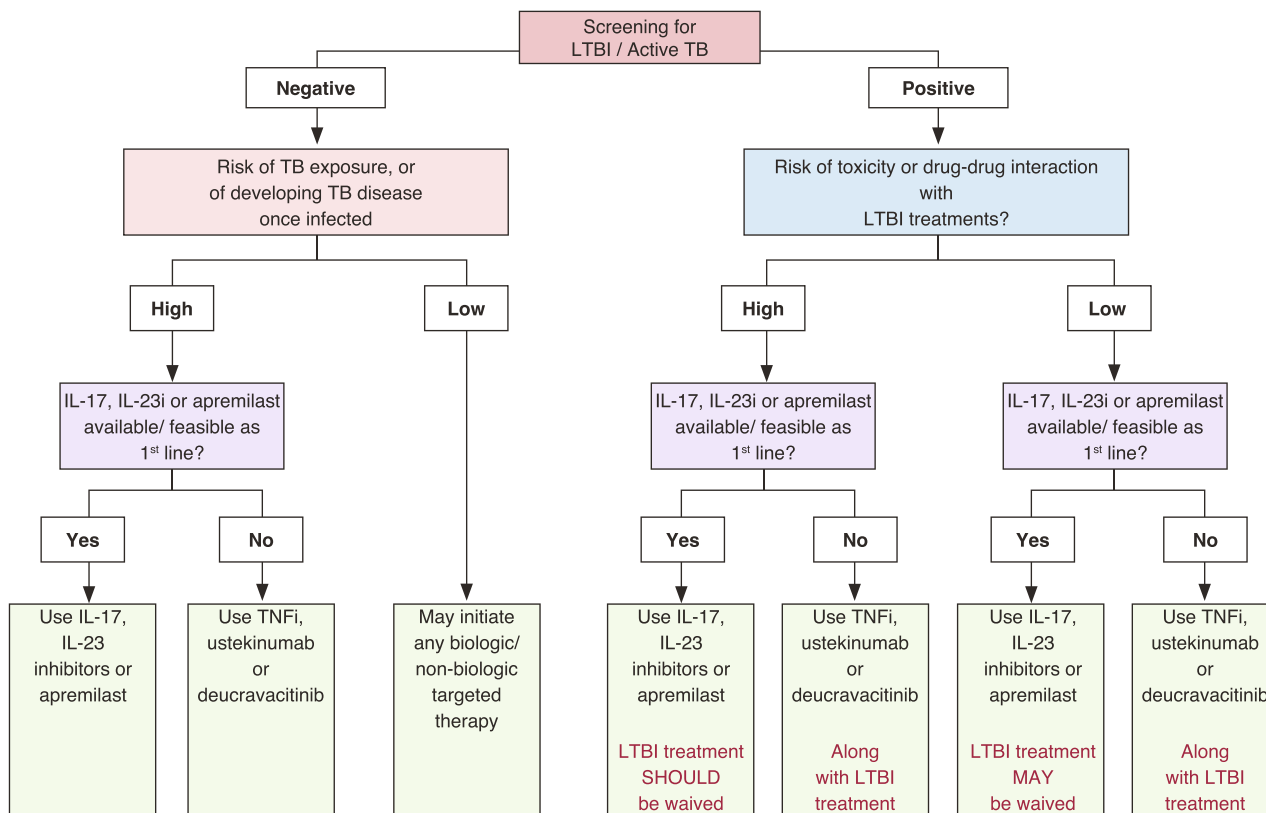


FIGURE 2 Proposed recommendation for patients who were never treated for TB or LTBI.



FIGURE 3 Proposed recommendation for patients with previously treated TB disease or previously treated LTBI.

Recommendation

All patients starting with biologic and non-biologic targeted therapies, such as TNF inhibitors, IL-12/23 inhibitors, IL-17 inhibitors, IL-23 inhibitors or TYK2 inhibitors, should be screened for LTBI/TB disease following local guidelines (screening for LTBI/TB disease may include an epidemiological anamnesis, clinical observation, chest X-ray, IGRA, tuberculin test (TST) and sputum tests for *M. tuberculosis* detection). In the case of PDE4 inhibitors, screening for LTBI/TB disease, it is not required.

1.1 If negative for LTBI:

1.1.1 People at high risk for TB exposure:

- Close contacts of persons exposed to contagious cases of TB.

- Individuals, including children, who have immigrated from high TB endemic areas within the last 5 years.
- Residents and employees of high-risk institutional settings (prisons, nursing homes, homeless shelters, drug addiction treatment facilities and healthcare facilities).
- Healthcare providers who care for high-risk persons.
- Some medically underserved, populations at risk of poverty or social exclusion as defined locally.
- High-risk minority populations defined locally as having an increased prevalence of TB.
- Infants, children and adolescents exposed to contagious cases of TB.
- Persons who inject illicit drugs or any other locally identified high-risk substance users.
- Persons who live in, regularly visit or work in countries with high TB incidence.

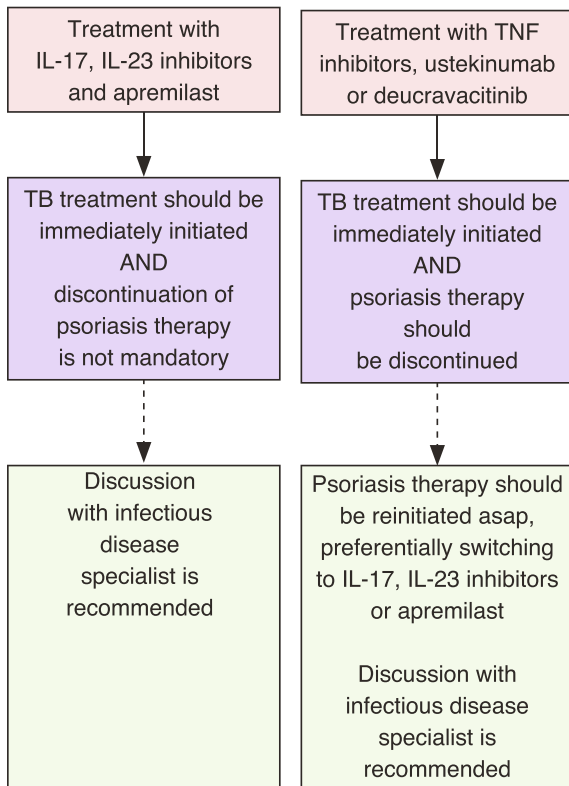


FIGURE 4 Proposed recommendation for patients being treated with biologic and non-biologic targeted therapies who develop TB disease.

1.1.2 People at high risk of developing TB disease once infected

- Persons with human immunodeficiency virus (HIV) infection.
- Persons who have underlying medical conditions known to increase the risk of progression to TB disease, such as diabetes, silicosis, chronic renal failure, malignancies (haematological malignancies and solid tumours), low body weight (<90% of ideal body weight), gastrectomy or jejunioleal bypass, malnutrition and high alcohol consumption (>60 g/day).
- Persons who inject illicit drugs or any other locally identified high-risk substance users.
- Person who are receiving immunosuppressive therapy, such as patients having received organ or bone marrow/haematopoietic precursors transplantation or patients with immune-mediated diseases besides psoriasis.

Recommendation

These high-risk patients should preferentially be treated with IL-17 inhibitors, IL-23 inhibitors or PDE4 inhibitors.

If IL-17 inhibitors, IL-23 inhibitors or PDE4 inhibitors are not available/feasible as first-line treatment or clinically

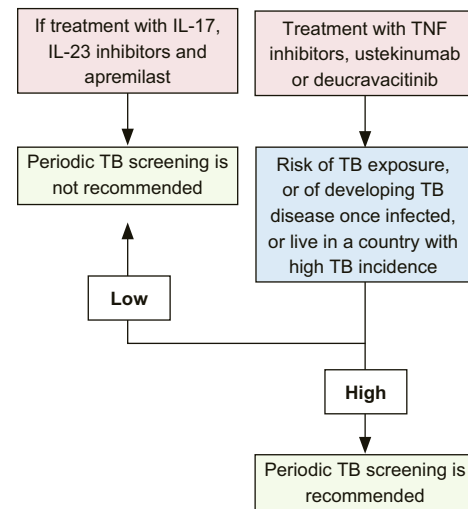


FIGURE 5 Proposed recommendation for periodic TB screening in patients being treated with biologic and non-biologic targeted therapies. [Correction added on 22 August 2024, after first online publication: Figure 5 has been revised.]

indicated, these high-risk patients may initiate treatment with TNF inhibitors, IL-12/23 inhibitors or TYK2 inhibitors.

Periodic TB screening should be performed as recommended below in Point 4. In the event of exposure to *M. tuberculosis* or screening tests becoming positive during treatment, TB disease should be excluded and psoriasis treatment should be managed accordingly (as below in Point 1.2). Those resulting as not infected after exposure *M. tuberculosis*, may continue their psoriasis treatment. In case of development of TB disease, patients should be managed accordingly (as below in Point 3).

1.1.3 People at low risk of TB exposure or of TB disease development once infected

Recommendation

These non-high-risk patients may initiate any biologic/non-biologic targeted therapy.

Periodic TB screening should be performed as recommended below in Point 4. In the event of exposure to *M. tuberculosis* or screening tests becoming positive during treatment, TB disease should be excluded and psoriasis treatment should be managed accordingly (as below in Point 1.2). Those not getting infected after exposure may continue their psoriasis treatment. In case of development of TB disease, patients should be managed accordingly (as below in Point 3).

1.2 If positive for LTBI

1.2.1 Patients with high risk of toxicity to LTBI treatment, which include

- age >60 years
- poor nutritional status (body weight loss >15%)
- alcohol consumption (>60 g/day)
- anaemia
- HIV co-infection
- albumin deficiency
- hepatitis C or hepatitis B infection
- other liver diseases (cirrhosis)
- concomitant consumption of hepatotoxic drugs
- abnormal baseline liver or kidney function
- thrombocytopenia
- diabetes
- slow acetylator NAT2 and CYP2E1 c1/c1 genotypes (cf frequencies in different populations, e.g. Egypt and Middle East)

1.2.2 Patients with potential risk of clinically relevant drug–drug interactions with TB treatments (isoniazid or rifampicin)

Recommendation

These patients should preferentially be treated with IL-17 inhibitors, IL-23 inhibitors or PDE4 inhibitors, and TB preventive treatment **should** be waived. Discussion with infectious diseases specialist is recommended in case of patients with HIV co-infection.

If IL-17 inhibitors, IL-23 inhibitors or PDE4 inhibitors are not available/feasible as first-line treatment or clinically indicated, TNF inhibitors, 12/23 inhibitors or TYK2 inhibitors may be initiated along with TB preventive treatment, according to local guidelines with close safety supervision. If patients develop side effects to preventive treatment (requiring discontinuation), psoriasis treatment should be switched to IL-17 inhibitors, IL-23 inhibitors or PDE4 inhibitors (if available) and preventive treatment should be discontinued/modified (discussion with infectious diseases specialist is recommended).

1.2.3 Patients with low risk of LTBI treatment toxicity or drug–drug interactions

Recommendation

These patients should preferentially be treated with IL-17 inhibitors, IL-23 inhibitors or PDE4 inhibitors, and TB preventive treatment **may** be waived.

If IL-17 inhibitors, IL-23 inhibitors or PDE4 inhibitors are not available/feasible as first-line treatment, or are not clinically indicated, TNF inhibitors, IL-12/23 inhibitors or TYK2 inhibitors may be initiated along with TB preventive treatment, according to local guidelines. If patients do not tolerate preventive treatment (requiring discontinuation), psoriasis treatment should be switched to IL-17 inhibitors, IL-23 inhibitors or PDE4 inhibitors (if available), and preventive treatment should be discontinued/modified (discussion with infectious diseases specialist is recommended).

In patients starting TB preventive treatment, it is recommended, though without strong evidence, that they receive at least 1 month of preventive treatment before starting TNF inhibitors, IL-12/23 inhibitors or TYK2 inhibitors, whenever possible. TNF inhibition (and perhaps IL-12 or TYK2 as well) might facilitate reactivation before preventive therapy takes effect. If a shorter duration is intended, consultation with an infectious disease specialist is advised. This period can be reduced for patients treated with IL-17 or IL-23 inhibitors.

2. Patients with previously treated TB disease or previously treated LTBI

Recommendation

The risk of reactivation should be addressed:

- If previous treatment of TB disease or LTBI is deemed adequate, consider the patient as negative for LTBI and treat accordingly (see Recommendation 1.1).
- If previous treatment of TB disease or LTBI is uncertain or inadequate, consider as positive for LTBI and treat accordingly (see Recommendation 1.2).

3. Patients being treated with biologic and non-biologic targeted therapies who develop TB disease

3.1 Patients being treated with IL-17 inhibitors, IL-23 inhibitors and PDE4 inhibitors

Recommendation

TB treatment should be immediately initiated according to the local guidelines, and discontinuation of psoriasis treatments is not mandatory (decision for discontinuation may consider current severity of psoriatic disease). Discussion with infectious diseases specialist is recommended.

3.2 Patients being treated with TNF inhibitors, IL-12/23 inhibitors or TYK2 inhibitors

Recommendation

TB disease treatment should be immediately initiated according to the local guideline, and psoriasis therapy should be discontinued (risk of psoriasis flare and immune reconstitution syndrome should be considered). Psoriasis treatment should be reinitiated as soon as possible (discussion with infectious diseases specialist about time to reinitiate psoriasis treatment is recommended) and should preferentially be switched to IL-17 inhibitors, IL-23 inhibitors or PDE4 inhibitors (if available).

4. Periodic TB screening in patients being treated with biologic and non-biologic targeted therapies:

Recommendation

- In cases requiring periodic TB screening, the use of TST or IGRA is only recommended for patients with no previous diagnosis of LTBI or TB disease. In those with previously treated TB or previously treated LTBI screening should include an epidemiological anamnesis, and clinical observation to identify any new contact with *M. tuberculosis* and the emergence of clinical symptoms/signs of TB disease.
- In patients being treated with IL-17 inhibitors, IL-23 inhibitors or PDE4 inhibitors there is no need for periodic TB screening under treatment. In patients being treated with TNF inhibitors, IL-12/23 inhibitors or TYK2 inhibitors who are at high risk of TB exposure or of developing active TB disease once infected (see definition: 1.1.1 and 1.1.2), or live in countries with high TB incidence, periodic TB screening is recommended (should be discussed with infectious diseases specialist).
- In all other patients (low risk of TB exposure or of developing active TB disease once infected, or living in countries with low TB incidence) being treated with TNF inhibitors, IL-12/23 inhibitors or TYK2 inhibitors there is no need for periodic TB screening under treatment.
- In any patient with known exposure to TB, screening and ruling out of TB disease should be performed.

CALL TO ACTION

The treatment of psoriasis in patients with LTBI or those at elevated risk of TB disease poses a considerable challenge. Almost all current guidelines largely stem from the well-documented TB reactivation safety concerns associated with TNF inhibitors, which were seemingly extrapolated to all subsequent biologic and non-biologic targeted treatments (except for apremilast) under a principle of caution, recommending TB preventive therapy for all such patients, regardless of the agent chosen. However, TB preventive therapy may be associated with serious adverse events, including liver failure and death, and contribute for the development of drug-resistant TB. The increased understanding of the pathophysiological mechanisms underlying both psoriasis and TB, coupled with the availability of pooled RCT safety analyses and real-world clinical data for newer targeted therapies, invites a re-evaluation of these guidelines, especially regarding drugs with mechanisms of action distinct from TNF inhibition. Recently, in 2023, a Austrian consensus no longer recommend preventive treatment for patients being treated with IL-17 inhibitors, although maintaining this recommendation for patients being treated with IL-23 inhibitors.³⁰ This clearly shows the beginning of a paradigm change.

Based on the available data, this review proposes updated recommendations, based on an expert consensus, for the use of novel biologics and non-biologic targeted therapies in psoriasis patients diagnosed with LTBI or at risk of developing TB. The authors, within the framework of the SPIN-FRT,

advocate for a reassessment and revision of current guidelines to reflect the latest evidence and emerging insights.

AUTHOR CONTRIBUTIONS

Conceptualization, formal analysis and interpretation and writing original draft: TT, LP and NB. Data interpretation, revision of intellectual content and editing: RGL, RBW, DT, AGAK, JLP, ALG, AN, MS, DG, MA, PS and WHB. Final approval of the version to be published: All authors.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available on PubMed.

ETHICS STATEMENT

Ethics committee approval was not required for this study as it did not involve human participants or personal data.

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REFERENCES

- Boehncke WH, Schon MP. Psoriasis. *Lancet*. 2015;386(9997):983–94.
- Griffiths CEM, Armstrong AW, Gudjonsson JE, Barker JNWN. Psoriasis. *Lancet*. 2021;397(10281):1301–15.
- MacNeil A, Glaziou P, Sismanidis C, Maloney S, Floyd K. Global epidemiology of tuberculosis and Progress toward achieving global targets—2017. *MMWR Morb Mortal Wkly Rep*. 2019;68(11):263–6.
- Aiello A, Najafi-Fard S, Goletti D. Initial immune response after exposure to mycobacterium tuberculosis or to SARS-COV-2: similarities and differences. *Front Immunol*. 2023;14:1244556.
- Kock R, Michel AL, Yeboah-Manu D, Azhar EI, Torrelles JB, Cadmus SI, et al. Zoonotic tuberculosis—the changing landscape. *Int J Infect Dis*. 2021;113(Suppl 1):S68–S72.
- Caavalcanti YV, Brelaz MCA, de Andrade Lemoine Neves JK, Ferraz JC, Pereira VRA. Role of TNF-alpha, IFN-gamma, and IL-10 in the development of pulmonary tuberculosis. *Pulm Med*. 2012;2012:745483.
- Alsayed SSR, Gunosewoyo H. Tuberculosis: pathogenesis, current treatment regimens and new drug targets. *Int J Mol Sci*. 2023;24(6):5202.
- Goletti D, Delogu G, Matteelli A, Migliori GB. The role of IGRA in the diagnosis of tuberculosis infection, differentiating from active tuberculosis, and decision making for initiating treatment or preventive therapy of tuberculosis infection. *Int J Infect Dis*. 2022;124(Suppl 1):S12–S19.
- Casanova JL, Abel L. Genetic dissection of immunity to mycobacteria: the human model. *Annu Rev Immunol*. 2002;20:581–620.
- Castro KG. Tuberculosis as an opportunistic disease in persons infected with human immunodeficiency virus. *Clin Infect Dis*. 1995;21(Suppl 1):S66–S71.
- Goletti D, Pisapia R, Fusco FM, Aiello A, van Crevel R. Epidemiology, pathogenesis, clinical presentation and management of TB in patients with HIV and diabetes. *Int J Tuberc Lung Dis*. 2023;27(4):284–90.
- Ai JW, Ruan QL, Liu QH, Zhang WH. Updates on the risk factors for latent tuberculosis reactivation and their managements. *Emerg Microbes Infect*. 2016;5(2):e10.
- WHO. *Global tuberculosis report 2023*. 2023.
- Houben RM, Dodd PJ. The global burden of latent tuberculosis infection: a Re-estimation using mathematical modelling. *PLoS Med*. 2016;13(10):e1002152.
- Zhang Z, Fan W, Yang G, Xu Z, Wang J, Cheng Q, et al. Risk of tuberculosis in patients treated with TNF-alpha antagonists: a systematic review and meta-analysis of randomised controlled trials. *BMJ Open*. 2017;7(3):e012567.
- Cantini F, Nannini C, Niccoli L, Iannone F, Delogu G, Garlaschi G, et al. Guidance for the management of patients with latent tuberculosis infection requiring biologic therapy in rheumatology and dermatology clinical practice. *Autoimmun Rev*. 2015;14(6):503–9.
- Cantini F, Niccoli L, Goletti D. Adalimumab, etanercept, infliximab, and the risk of tuberculosis: data from clinical trials, national registries, and postmarketing surveillance. *J Rheumatol Suppl*. 2014;91:47–55.
- Miller EA, Ernst JD. Anti-TNF immunotherapy and tuberculosis reactivation: another mechanism revealed. *J Clin Invest*. 2009;119(5):1079–82.

19. Souto A, Maneiro JR, Salgado E, Carmona L, Gomez-Reino JJ. Risk of tuberculosis in patients with chronic immune-mediated inflammatory diseases treated with biologics and tofacitinib: a systematic review and meta-analysis of randomized controlled trials and long-term extension studies. *Rheumatology (Oxford)*. 2014;53(10):1872–85.
20. Wang Q, Wen Z, Cao Q. Risk of tuberculosis during infliximab therapy for inflammatory bowel disease, rheumatoid arthritis, and spondyloarthritis: a meta-analysis. *Exp Ther Med*. 2016;12(3):1693–704.
21. Chiacchio T, Petruccioli E, Vanini V, Cuzzi G, Massafra U, Baldi G, et al. Characterization of QuantiFERON-TB-plus results in latent tuberculosis infected patients with or without immune-mediated inflammatory diseases. *J Infect*. 2019;79(1):15–23.
22. Goletti D, Petrone L, Ippolito G, Niccoli L, Nannini C, Cantini F. Preventive therapy for tuberculosis in rheumatological patients undergoing therapy with biological drugs. *Expert Rev Anti Infect Ther*. 2018;16(6):501–12.
23. Ahn CS, Dothard EH, Garner ML, Feldman SR, Huang WW. To test or not to test? An updated evidence-based assessment of the value of screening and monitoring tests when using systemic biologic agents to treat psoriasis and psoriatic arthritis. *J Am Acad Dermatol*. 2015;73(3):420–8. e1.
24. Diel R, Schaberg T, Nienhaus A, Otto-Knapp R, Kneitz C, Krause A, et al. Joint statement (DZK, DGRh, DDG) on the tuberculosis risk with treatment using novel non-TNF-alpha biologics. *Pneumologie*. 2021;75(4):293–303.
25. Rodriguez-Jimenez P, Mir-Viladrich I, Chicharro P, Solano-López G, López-Longo FJ, Taxonera C, et al. Prevention and treatment of tuberculosis infection in candidates for biologic therapy: a multidisciplinary consensus statement adapted to the dermatology patient. *Actas Dermosifiliogr (Engl Ed)*. 2018;109(7):584–601.
26. WHO. *Latent tuberculosis infection: updated and consolidated guidelines for programmatic management*. 2018 Geneva.
27. Sterling TR, Njie G, Zenner D, Cohn DL, Reves R, Ahmed A, et al. Guidelines for the treatment of latent tuberculosis infection: recommendations from the National Tuberculosis Controllers Association and CDC, 2020. *MMWR Recomm Rep*. 2020;69(1):1–11.
28. Denholm JT, McBryde E, Eisen DP, Penington JS, Chen C, Street AC. Adverse effects of isoniazid preventative therapy for latent tuberculosis infection: a prospective cohort study. *Drug Healthc Patient Saf*. 2014;6:145–9.
29. Lee SH, Yim J-J, Kim HJ, Shim TS, Seo HS, Cho YS, et al. Adverse events and development of tuberculosis after 4 months of rifampicin prophylaxis in a tuberculosis outbreak. *Epidemiol Infect*. 2012;140(6):1028–35.
30. Rath E, Bonelli M, Duftner C, Gruber J, Mandl P, Moazedi-Furst F, et al. National consensus statement by the Austrian societies for rheumatology, pulmonology, Infectiology, dermatology and gastroenterology regarding the management of latent tuberculosis and the associated utilization of biologic and targeted synthetic DMARDS (disease modifying antirheumatic drugs). *Z Rheumatol*. 2023;82(2):163–74.
31. Cantini F, Blandizzi C, Niccoli L, Petrone L, Goletti D. Systematic review on tuberculosis risk in patients with rheumatoid arthritis receiving inhibitors of Janus kinases. *Expert Opin Drug Saf*. 2020;19(7):861–72.
32. Khader SA, Bell GK, Pearl JE, Fountain JJ, Rangel-Moreno J, Cillely GE, et al. IL-23 and IL-17 in the establishment of protective pulmonary CD4⁺ T cell responses after vaccination and during mycobacterium tuberculosis challenge. *Nat Immunol*. 2007;8(4):369–77.
33. Okamoto Yoshida Y, Umemura M, Yahagi A, O'Brien RL, Ikuta K, Kishihara K, et al. Essential role of IL-17A in the formation of a mycobacterial infection-induced granuloma in the lung. *J Immunol*. 2010;184(8):4414–22.
34. Khader SA, Pearl JE, Sakamoto K, Gilmartin L, Bell GK, Jelley-Gibbs DM, et al. IL-23 compensates for the absence of IL-12p70 and is essential for the IL-17 response during tuberculosis but is dispensable for protection and antigen-specific IFN-gamma responses if IL-12p70 is available. *J Immunol*. 2005;175(2):788–95.
35. Aujla SJ, Dubin PJ, Kolls JK. Th17 cells and mucosal host defense. *Semin Immunol*. 2007;19(6):377–82.
36. Segueni N, Jacobs M, Ryffel B. Innate type 1 immune response, but not IL-17 cells control tuberculosis infection. *Biom J*. 2021;44(2):165–71.
37. Segueni N, Tritto E, Bourigault ML, Rose S, Erard F, le Bert M, et al. Controlled mycobacterium tuberculosis infection in mice under treatment with anti-IL-17A or IL-17F antibodies, in contrast to TNFalpha neutralization. *Sci Rep*. 2016;6:36923.
38. Arbues A, Brees D, Chibout S-D, Fox T, Kammüller M, Portevin D. TNF-alpha antagonists differentially induce TGF-beta1-dependent resuscitation of dormant-like mycobacterium tuberculosis. *PLoS Pathog*. 2020;16(2):e1008312.
39. Kammüller M, Tsai T-F, Griffiths CE, Kapoor N, Kolattukudy PE, Brees D, et al. Inhibition of IL-17A by secukinumab shows no evidence of increased *Mycobacterium tuberculosis* infections. *Clin Transl Immunol*. 2017;6(8):e152.
40. Fowler E, Ghamrawi RI, Ghiam N, Liao W, Wu JJ. Risk of tuberculosis reactivation during interleukin-17 inhibitor therapy for psoriasis: a systematic review. *J Eur Acad Dermatol Venereol*. 2020;34(7):1449–56.
41. Nogueira M, Warren RB, Torres T. Risk of tuberculosis reactivation with interleukin (IL)-17 and IL-23 inhibitors in psoriasis—time for a paradigm change. *J Eur Acad Dermatol Venereol*. 2021;35(4):824–34.
42. Elewski BE, Baddley JW, Deodhar AA, Magrey M, Rich PA, Soriano ER, et al. Association of secukinumab treatment with tuberculosis reactivation in patients with psoriasis, psoriatic arthritis, or ankylosing spondylitis. *JAMA Dermatol*. 2021;157(1):43–51.
43. Gottlieb AB, Deodhar A, McInnes IB, Baraliakos X, Reich K, Schreiber S, et al. Long-term safety of Secukinumab over five years in patients with moderate-to-severe plaque psoriasis, psoriatic arthritis and ankylosing spondylitis: update on integrated pooled clinical trial and post-marketing surveillance data. *Acta Derm Venereol*. 2022;102:adv00698.
44. Genovese MC, Mysler E, Tomita T, Papp KA, Salvarani C, Schwartzman S, et al. Safety of ixekizumab in adult patients with plaque psoriasis, psoriatic arthritis and axial spondyloarthritis: data from 21 clinical trials. *Rheumatology (Oxford)*. 2020;59(12):3834–44.
45. Genovese MC, Mysler E, Tomita T, Papp KA, Salvarani C, Schwartzman S, et al. Corrigendum to: safety of ixekizumab in adult patients with plaque psoriasis, psoriatic arthritis and axial spondyloarthritis: data from 21 clinical trials. *Rheumatology (Oxford)*. 2021;60(11):5485.
46. Mrowietz U, Riedl E, Winkler S, Xu W, Patel H, Agada N, et al. No reactivation of tuberculosis in patients with latent tuberculosis infection receiving ixekizumab: a report from 16 clinical studies of patients with psoriasis or psoriatic arthritis. *J Am Acad Dermatol*. 2020;83(5):1436–9.
47. Deodhar A, Mease PJ, McInnes IB, Baraliakos X, Reich K, Blauvelt A, et al. Long-term safety of secukinumab in patients with moderate-to-severe plaque psoriasis, psoriatic arthritis, and ankylosing spondylitis: integrated pooled clinical trial and post-marketing surveillance data. *Arthritis Res Ther*. 2019;21(1):111.
48. van der Heijde D, Deodhar A, Baraliakos X, Brown MA, Dobashi H, Dougados M, et al. Efficacy and safety of bimekizumab in axial spondyloarthritis: results of two parallel phase 3 randomised controlled trials. *Ann Rheum Dis*. 2023;82(4):515–26.
49. Baraliakos X, Deodhar A, Dougados M, Gensler LS, Molto A, Ramiro S, et al. Safety and efficacy of Bimekizumab in patients with active ankylosing spondylitis: three-year results from a phase IIb randomized controlled trial and its open-label extension study. *Arthritis Rheumatol*. 2022;74(12):1943–58.
50. Coates LC, McInnes IB, Merola JF, Warren RB, Kavanaugh A, Gottlieb AB, et al. Safety and efficacy of Bimekizumab in patients with active psoriatic arthritis: three-year results from a phase IIb

- randomized controlled trial and its open-label extension study. *Arthritis Rheumatol.* 2022;74(12):1959–70.
51. Fiorella C. Treatment with secukinumab for plaque psoriasis in patients with infectious comorbidities and latent tuberculosis: a multi-case report analysis. *Clin Case Rep.* 2022;10(1):e05302.
 52. Galluzzo M, D'Adamio S, Silvaggio D, Lombardo P, Bianchi L, Talamonti M. In which patients the best efficacy of secukinumab? Update of a real-life analysis after 136 weeks of treatment with secukinumab in moderate-to-severe plaque psoriasis. *Expert Opin Biol Ther.* 2020;20(2):173–82.
 53. Lasagni C, Bigi L, Conti A, Pellacani G. Successful therapy of plaque-type psoriasis with secukinumab in patients with multiple comorbidities treated with previous biologic therapies. *J Dermatolog Treat.* 2018;29(sup2):5–8.
 54. Liu S, He Z, Wu W, Jin H, Cui Y. Safety of secukinumab in the treatment of patients with axial spondyloarthritis and concurrent hepatitis B virus infection or latent tuberculosis infection. *Clin Rheumatol.* 2023;42(9):2369–76.
 55. Machado A, Abreu M, Torres T. Safety of secukinumab in psoriasis patients with latent tuberculosis infection. *Eur J Dermatol.* 2020;30(6):740–1.
 56. Manzanares N, Vilarrasa E, López A, Alonso ML, Velasco M, Riera J, et al. No tuberculosis reactivations in psoriasis patients initiating new generation biologics despite untreated latent tuberculosis infection: multicenter case series of 35 patients. *J Eur Acad Dermatol Venereol.* 2023;38(1):e26–e28.
 57. Mastorino L, Dapavo P, Trunfio M, Avallone G, Rubatto M, Calcagno A, et al. Risk of reactivation of latent tuberculosis in psoriasis patients on biologic therapies: a retrospective cohort from a tertiary Care Centre in Northern Italy. *Acta Derm Venereol.* 2022;102:adv00821.
 58. Megna M, Patruno C, Bongiorno MR, Gambardella A, Guarneri C, Foti C, et al. Lack of reactivation of tuberculosis in patients with psoriasis treated with secukinumab in a real-world setting of latent tuberculosis infection. *J Dermatolog Treat.* 2022;33(5):2629–33.
 59. Ribero S, Licciardello M, Quaglino P, Dapavo P. Efficacy and safety of Secukinumab in patients with plaque psoriasis and latent tuberculosis. *Case Rep Dermatol.* 2019;11(Suppl 1):23–8.
 60. Shu D, Zhang Z, Zhou EY, Ma X, Zhao Y. Is chemoprophylaxis necessary for all latent tuberculosis infection patients receiving IL-17 inhibitors? A cohort study. *Dermatol Ther.* 2020;33(6):e14512.
 61. Xiao Y, Mi W, Wang J, Wen D, Wang Y, Gu Y, et al. A propensity score-matched study on the changes of TB status and TB-IGRA values in patients with psoriasis with latent TB receiving Secukinumab. *Dermatol Ther (Heidelb).* 2023;13(10):2387–401.
 62. Torres T, Chiricozzi A, Puig L, Lé AM, Marzano AV, Dapavo P, et al. Treatment of psoriasis patients with latent tuberculosis using IL-17 and IL-23 inhibitors: a retrospective, multinational, multicentre study. *Am J Clin Dermatol.* 2024;25:333–42.
 63. He CX, Wu C, Zhang L, Jin HZ. Interleukin-17A inhibitors in patients with psoriasis and tuberculosis infection: a 2-year prospective study on safety without preventive treatment. *Dermatol Ther (Heidelb).* 2024;14:893–906.
 64. Gaffen SL, Jain R, Garg AV, Cua DJ. The IL-23-IL-17 immune axis: from mechanisms to therapeutic testing. *Nat Rev Immunol.* 2014;14(9):585–600.
 65. Shen H, Chen ZW. The crucial roles of Th17-related cytokines/signal pathways in *M. tuberculosis* infection. *Cell Mol Immunol.* 2018;15(3):216–25.
 66. Blauvelt A, Chiricozzi A, Efst BD, Lebwohl MG. Safety of IL-23 p19 inhibitors for the treatment of patients with moderate-to-severe plaque psoriasis: a narrative review. *Adv Ther.* 2023;40(8):3410–33.
 67. Cantini F, Nannini C, Niccoli L, Petrone L, Ippolito G, Goletti D. Risk of tuberculosis reactivation in patients with rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis receiving non-anti-TNF-targeted biologics. *Mediators Inflamm.* 2017;2017:8909834.
 68. Zabotti A, Goletti D, Lubrano E, Cantini F. The impact of the interleukin 12/23 inhibitor ustekinumab on the risk of infections in patients with psoriatic arthritis. *Expert Opin Drug Saf.* 2020;19(1):69–82.
 69. Gordon KB, Lebwohl M, Papp KA, Bachelez H, Wu JJ, Langley RG, et al. Long-term safety of risankizumab from 17 clinical trials in patients with moderate-to-severe plaque psoriasis. *Br J Dermatol.* 2022;186(3):466–75.
 70. Strober B, Coates LC, Lebwohl MG, Deodhar A, Leibowitz E, Rowland K, et al. Long-term safety of Guselkumab in patients with psoriatic disease: an integrated analysis of eleven phase II/III clinical studies in psoriasis and psoriatic arthritis. *Drug Saf.* 2023;47:39–57.
 71. Blauvelt A, Reich K, Papp KA, Kimball AB, Gooderham M, Tyring SK, et al. Safety of tildrakizumab for moderate-to-severe plaque psoriasis: pooled analysis of three randomized controlled trials. *Br J Dermatol.* 2018;179(3):615–22.
 72. Danese S, Panaccione R, Feagan BG, Afzali A, Rubin DT, Sands BE, et al. Efficacy and safety of 48 weeks of guselkumab for patients with Crohn's disease: maintenance results from the phase 2, randomised, double-blind GALAXI-1 trial. *Lancet Gastroenterol Hepatol.* 2024;9(2):133–46.
 73. Peyrin-Biroulet L, Allegretti JR, Rubin DT, Bressler B, Germinaro M, Huang KH(G), et al. Guselkumab in patients with moderately to severely active ulcerative colitis: QUASAR phase 2b induction study. *Gastroenterology.* 2023;165(6):1443–57.
 74. Gao X, Fujii T, Ye BD, Chou JW, Sugimoto K, Cao Q, et al. Efficacy and safety of risankizumab for Crohn's disease in patients from Asian countries: a post hoc subanalysis of the global phase 3 ADVANCE, MOTIVATE, and FORTIFY studies. *J Gastroenterol Hepatol.* 2024;39(1):55–65.
 75. Ferrante M, Panaccione R, Baert F, Bossuyt P, Colombel JF, Danese S, et al. Risankizumab as maintenance therapy for moderately to severely active Crohn's disease: results from the multicentre, randomised, double-blind, placebo-controlled, withdrawal phase 3 FORTIFY maintenance trial. *Lancet.* 2022;399(10340):2031–46.
 76. Ferrante M, Feagan BG, Panés J, Baert F, Louis E, Dewit O, et al. Long-term safety and efficacy of Risankizumab treatment in patients with Crohn's disease: results from the phase 2 open-label extension study. *J Crohns Colitis.* 2021;15(12):2001–10.
 77. Blauvelt A, Leonardi CL, Gooderham M, Papp KA, Philipp S, Wu JJ, et al. Efficacy and safety of continuous Risankizumab therapy vs treatment withdrawal in patients with moderate to severe plaque psoriasis: a phase 3 randomized clinical trial. *JAMA Dermatol.* 2020;156(6):649–58.
 78. Puig L, Tsai TF, Bhutani T, Uy J, Ramachandran P, Song M, et al. Safety in moderate-to-severe plaque psoriasis patients with latent tuberculosis treated with guselkumab and anti-tuberculosis treatments concomitantly: results from pooled phase 3 VOYAGE 1 & VOYAGE 2 trials. *J Eur Acad Dermatol Venereol.* 2020;34(8):1744–9.
 79. Kearney N, Byrne N, Kirby B, Hughes R. Successful use of guselkumab in the treatment of severe hidradenitis suppurativa. *Clin Exp Dermatol.* 2020;45(5):618–9.
 80. Motolese A, Ceccarelli M, Macca L, Li Pomi F, Ingrassiotta Y, Nunnari G, et al. Novel therapeutic approaches to psoriasis and risk of infectious disease. *Biomedicine.* 2022;10(2):228.
 81. Cooper AM, Solache A, Khader SA. Interleukin-12 and tuberculosis: an old story revisited. *Curr Opin Immunol.* 2007;19(4):441–7.
 82. Tsai TF, Ho V, Song M, Szapary P, Kato T, Wasfi Y, et al. The safety of ustekinumab treatment in patients with moderate-to-severe psoriasis and latent tuberculosis infection. *Br J Dermatol.* 2012;167(5):1145–52.
 83. Ghosh S, Feagan BG, Ott E, Gasink C, Godwin B, Marano C, et al. Safety of Ustekinumab in inflammatory bowel disease: pooled safety analysis through 5 years in Crohn's disease and 4 years in ulcerative colitis. *J Crohns Colitis.* 2024;18:1091–101.
 84. Tsai TF, Chiu HY, Song M, Chan D. A case of latent tuberculosis reactivation in a patient treated with ustekinumab without

- concomitant isoniazid chemoprophylaxis in the PEARL trial. *Br J Dermatol.* 2013;168(2):444–6.
85. Cho SI, Kang S, Kim YE, Lee JY, Jo SJ. Ustekinumab does not increase tuberculosis risk: results from a national database in South Korea. *J Am Acad Dermatol.* 2020;82(5):1243–5.
 86. Errichetti E, Piccirillo A. Latent tuberculosis reactivation in a patient with erythrodermic psoriasis under treatment with ustekinumab and a low dose steroid, despite isoniazid chemoprophylaxis. *Eur J Dermatol.* 2014;24(4):508–9.
 87. Lynch M, Roche L, Horgan M, Ahmad K, Hackett C, Ramsay B. Peritoneal tuberculosis in the setting of ustekinumab treatment for psoriasis. *JAAD Case Rep.* 2017;3(3):230–2.
 88. Renoux MC, Dutronc S, Kollen L, Theret S, Moreau J. A case of disseminated tuberculosis in a child with Crohn's disease after treatment with Azathioprine, Adalimumab and Ustekinumab. *Arch Bronconeumol.* 2021;57(8):552–4.
 89. Tominaga K, Tanaka T, Kanazawa M, Watanabe S, Nemoto R, Abe K, et al. A case of Crohn's disease with cardiac tamponade caused by tuberculous pericarditis: assessment of a rare phenomenon. *Healthcare (Basel).* 2021;9(6):695.
 90. Torres T, Puig L. Apremilast: a novel Oral treatment for psoriasis and psoriatic arthritis. *Am J Clin Dermatol.* 2018;19(1):23–32.
 91. Crowley J, Thaçi D, Joly P, Peris K, Papp KA, Goncalves J, et al. Long-term safety and tolerability of apremilast in patients with psoriasis: pooled safety analysis for ≥ 156 weeks from 2 phase 3, randomized, controlled trials (ESTEEM 1 and 2). *J Am Acad Dermatol.* 2017;77(2):310–7. e1.
 92. Cutolo M, Myerson GE, Fleischmann RM, Lioté F, Díaz-González F, van den Bosch F, et al. A phase III, randomized, controlled trial of Apremilast in patients with psoriatic arthritis: results of the PALACE 2 trial. *J Rheumatol.* 2016;43(9):1724–34.
 93. Edwards CJ, Blanco FJ, Crowley J, Birbara CA, Jaworski J, Aelion J, et al. Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with psoriatic arthritis and current skin involvement: a phase III, randomised, controlled trial (PALACE 3). *Ann Rheum Dis.* 2016;75(6):1065–73.
 94. Kavanaugh A, Mease PJ, Gomez-Reino JJ, Adebajo AO, Wollenhaupt J, Gladman DD, et al. Treatment of psoriatic arthritis in a phase 3 randomised, placebo-controlled trial with apremilast, an oral phosphodiesterase 4 inhibitor. *Ann Rheum Dis.* 2014;73(6):1020–6.
 95. Wells AF, Edwards CJ, Kivitz AJ, Bird P, Nguyen D, Paris M, et al. Apremilast monotherapy in DMARD-naive psoriatic arthritis patients: results of the randomized, placebo-controlled PALACE 4 trial. *Rheumatology (Oxford).* 2018;57(7):1253–63.
 96. Abignano G, Fadl N, Merashli M, Wenham C, Freeston J, McGonagle D, et al. Apremilast for the treatment of active psoriatic arthritis: a single-centre real-life experience. *Rheumatology (Oxford).* 2018;57(3):578–80.
 97. Favalli EG, Conti F, Selmi C, Iannone F, Bucci R, D'Onofrio F, et al. Retrospective evaluation of patient profiling and effectiveness of apremilast in an Italian multicentric cohort of psoriatic arthritis patients. *Clin Exp Rheumatol.* 2020;38(1):19–26.
 98. Hagberg KW, Persson R, Vasilakis-Scaramozza C, Niemcryk S, Peng M, Paris M, et al. Herpes zoster, hepatitis C, and tuberculosis risk with Apremilast compared to biologics, DMARDs and corticosteroids to treat psoriasis and psoriatic arthritis. *Clin Epidemiol.* 2020;12:153–61.
 99. Armstrong AW, Gooderham M, Warren RB, Papp KA, Strober B, Thaçi D, et al. Deucravacitinib versus placebo and apremilast in moderate to severe plaque psoriasis: efficacy and safety results from the 52-week, randomized, double-blinded, placebo-controlled phase 3 POETYK PSO-1 trial. *J Am Acad Dermatol.* 2023;88(1):29–39.
 100. Strober B, Thaçi D, Sofen H, Kircik L, Gordon KB, Foley P, et al. Deucravacitinib versus placebo and apremilast in moderate to severe plaque psoriasis: efficacy and safety results from the 52-week, randomized, double-blinded, phase 3 program for evaluation of TYK2 inhibitor psoriasis second trial. *J Am Acad Dermatol.* 2023;88(1):40–51.
 101. Kingston P, Blauvelt A, Strober B, Armstrong AW. Deucravacitinib: a novel TYK2 inhibitor for the treatment of moderate-to-severe psoriasis. *J Psoriasis Psoriatic Arthritis.* 2023;8(4):156–65.

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