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# Treatment of Psoriasis in Patients with Latent Tuberculosis

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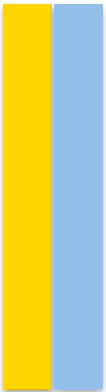

**Treatment of Psoriasis in Patients with Latent Tuberculosis**

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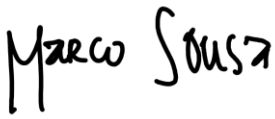

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**Abstract**

**Background:** Psoriasis is a chronic inflammatory skin disease treated with a range of therapies, from topical to systemic agents. Some systemic treatments, due to their immunomodulatory mechanisms, may increase the risk of tuberculosis (TB) reactivation in patients with latent TB infection (LTBI). Given the high global prevalence of LTBI, standardized management protocols have been established in the management of psoriasis patients to mitigate this risk. These protocols often apply uniformly to different therapeutic classes despite variations in their actual TB reactivation risk.

**Objectives:** This article reviews treatment options for psoriasis in patients with LTBI.

**Methods:** A literature search was conducted in PubMed and Google Scholar using the following MeSH terms - [Psoriasis] and ([Tuberculosis] or [Latent Tuberculosis Infection]) and ([Treatment] or [Biological products]). Relevant articles were selected based on title, abstract, and reference screening.

**Discussion:** This discussion examines the safety and efficacy of different psoriasis treatments, emphasizing their implications for LTBI patients. Topical therapies and phototherapy remain first-line options for mild to moderate psoriasis, offering effective disease control with minimal systemic impact, making them safe in this group of patients. Conventional systemic agents, particularly methotrexate and cyclosporine, present a potential yet inconsistent risk of TB reactivation, with current guidelines offering ambiguous screening recommendations. TNF-α inhibitors, by contrast, are strongly associated with TB reactivation, necessitating mandatory screening and prophylaxis. Emerging evidence indicates that IL-17 and IL-23 inhibitors pose no additional risk for TB reactivation, suggesting that existing screening requirements may be outdated and could expose LTBI patients to unnecessary iatrogenic harm. Conversely, IL-12/23p40 inhibitors and TYK2 inhibitors, due to their role in suppressing IL-12—a key cytokine in *Mycobacterium tuberculosis* containment—still warrant screening and prophylaxis. PDE4 inhibitors, with no demonstrated increase in TB risk, have already been exempted from preventive measures in the 2024 guidelines. Psoriasis treatment is evolving with increasingly selective therapies, as well as unconventional approaches such as oral vitamin D and microbiome-based treatments. Although new screening guidelines have already been proposed, they have yet to be implemented.

**Conclusion**: As research continues to evolve, updating clinical protocols to reflect current risk assessments is essential to minimize unnecessary interventions. This article underscores the importance of individualized treatment strategies and the ongoing pursuit of safer and more effective therapeutic options for psoriasis.

**Keywords:** Psoriasis, Tuberculosis, Latent Tuberculosis Infection, Treatment, Biological Products

**Resumo**

**Introdução:** A psoríase é uma doença inflamatória crónica da pele tratada com diversas opções terapêuticas, desde tratamentos tópicos a sistémicos. Alguns destes tratamentos, devido aos seus mecanismos imunomoduladores, podem aumentar o risco de reativação da tuberculose (TB) em pacientes com tuberculose latente. Dada a elevada prevalência global de tuberculose latente, foram estabelecidos protocolos padronizados relativos ao tratamento dos doentes com psoríase para reduzir esse risco. No entanto, estas diretrizes são frequentemente aplicadas de forma uniforme a várias classes terapêuticas apesar das diferenças no risco de reativação da TB.

**Objetivos:** Este artigo analisa as opções terapêuticas para a psoríase em pacientes com tuberculose latente.

**Métodos:** Foi realizada uma pesquisa bibliográfica no PubMed e no Google Scholar, utilizando os seguintes termos MeSH - [Psoriasis] e ([Tuberculosis] ou [Latent Tuberculosis Infection]) e ([Treatment] ou [Biological products]). Os artigos foram selecionados com base na análise do título, resumo e referências.

**Discussão:** Esta dissertação avalia a segurança e eficácia dos diferentes tratamentos para a psoríase, com ênfase nas suas implicações para pacientes com tuberculose latente. Terapêuticas tópicas e fototerapia continuam a ser as opções de primeira linha para psoríase ligeira a moderada, assegurando um controlo eficaz da doença com impacto sistémico mínimo, sendo, por isso, seguras para este grupo de pacientes. Agentes sistémicos convencionais, como metotrexato e ciclosporina, apresentam um risco variável, mas ainda incerto, de reativação da TB, com diretrizes atuais oferecendo recomendações ambíguas sobre o rastreio. Os inibidores do TNF-α, por outro lado, estão fortemente associados à reativação da TB, tornando o rastreio e a profilaxia obrigatórios. Novos dados sugerem que os inibidores da IL-17 e da IL-23 não aumentam o risco de reativação da TB, indicando que os requisitos de rastreio existentes podem estar desatualizados e expor os pacientes com tuberculose latente a intervenções desnecessárias. Em contrapartida, os inibidores da IL-12/23p40 e da TYK2, devido à sua inibição da IL-12 - citocina essencial na contenção do *Mycobacterium tuberculosis* - ainda requerem rastreio e profilaxia. Os inibidores da PDE4, sem risco demonstrado de reativação da TB, já foram isentos de medidas preventivas nas diretrizes de 2024. O tratamento da psoríase está a evoluir com terapias cada vez mais seletivas e abordagens inovadoras, como a suplementação oral com vitamina D e tratamentos baseados no microbioma. Embora novas *guidelines* de rastreio tenham sido propostas, estas ainda não foram implementadas.

**Conclusão:** À medida que a investigação avança, a atualização dos protocolos clínicos para refletir as avaliações de risco mais recentes é essencial de forma a evitar intervenções desnecessárias. Este artigo destaca a importância de estratégias de tratamento individualizadas e a procura contínua por opções terapêuticas mais seguras e eficazes para a psoríase.

**Palavras chave:** Psoríase, Tuberculose, Tuberculose Latente, Tratamento, Produtos Biológicos

**List of abbreviations**

ADA - Adalimumab
BSA - Body Surface Area
cAMP - Cyclic Adenosine Monophosphate
CTP - Certolizumab-pegol
DLQI - Dermatology Life Quality Index
EADV - European Academy of Dermatology and Venereology
ENT – Etanercept
HBV - Hepatitis B virus
HCV - Hepatitis C virus
HIV - Human immunodeficiency virus
IFN-γ - Interferon-gamma
IFX - Infliximab
IBD - Inflammatory Bowel Disease
IGRA - Interferon-gamma release assay
IL-1 - Interleukine 1
IL-10 - Interleukine 10
IL-12 - Interleukine 12
IL-17 - Interleukine 17
IL-22 - Interleukine 22
IL-23 - Interleukine 23
JAK - Janus kinase
LTBI - Latent Tuberculosis Infection
PASI - Psoriasis Area and Severity Index
PDE4 - Phosphodiesterase 4
PUVA - Psoralen plus Ultraviolet A
RA - Rheumatoid Arthritis
RCT - Randomized Clinical Trials
RORγt - Retinoic acid-related orphan receptor gamma t
TB - Tuberculosis
TNF-α - Tumor Necrosis Factor Alpha
TST - Tuberculin Skin Test
TYK2 - Tyrosine Kinase 2
UVB - Ultraviolet B

**Index**

**Introduction**

Psoriasis is a chronic immune-mediated inflammatory skin disease affecting 0.14% to 5.32% of the population across different geographical regions, being more prevalent in high income countries with peak incidences between 30 and 39 years and 50 and 69 years[1,2]. Extracutaneous comorbidities are frequent and can be associated with an imbalanced immunological response. These include, but are not limited to, cardiovascular, metabolic, psychiatric, renal and gastrointestinal diseases[3,4]. Plaque psoriasis is characterized by well-demarcated, erythematous plaques or papules, symmetrically distributed. Lesions often feature thick silvery-white scaling, and pruritus occurs in about 80% of cases[5].

The primary goal of psoriasis treatment is not only to reduce visible lesions, but also to improve quality of life by enhancing daily functioning[6]. Topical approaches, phototherapy and systemic agents that target various stages of the inflammatory pathway, including tumor necrosis factor alpha (TNF-α) and interleukins (IL) 17 and 23, are the most common treatment options. These treatment modalities are chosen according to disease severity, different clinical variants, potential complications, and patient comorbidities[7]. The involvement of a large surface area, the presence of psoriatic arthritis, and failure of topical treatments often require the use of systemic therapy. However, immunosuppressive and immunomodulatory therapies carry certain drawbacks, with latent infections (tuberculosis, human immunodeficiency virus (HIV) infection, hepatitis B and C) posing a significant concern, particularly due to the risk of reactivation[8].

It is estimated that *Mycobacterium tuberculosis* has infected 23% of the global population, with nearly 11 million active tuberculosis cases in 2024, making it the leading infectious cause of death[9,10]. Tuberculosis infection refers to latent tuberculosis (LTBI), in which individuals remain asymptomatic and noninfectious. In contrast, tuberculosis disease involves active TB, where the patient shows symptoms and is contagious, posing a significant public health risk. These states are not static, as immune system alterations caused by some medications (such as biological agents or chemotherapy) or other conditions can reactivate latent TB[11,12].

Managing psoriasis in patients with latent tuberculosis infection poses significant challenges, requiring careful strategies to balance effective symptom control and at the same time minimizing the risk of tuberculosis reactivation. Biologic therapies offer promising options but must be used with an understanding of their limitations. Systemic treatments differ in mechanisms of action and associated risks, underscoring the importance of tailored clinical recommendations.

Current guidelines recommend a conservative approach that includes screening of TB infection in every patient starting a potentially immunosuppressive therapy, regardless of the

specific characteristics of the agent, mechanism of action and risk of TB reactivation[13]. The two major screening tools are TST and IGRA blood test - both assess the immune response to TB antigens[3,14].

According to present recommendations, if the screening test is positive and without clinical or imaging evidence, or microbiological confirmation of *M. tuberculosis* (active TB is excluded), chemoprophylaxis should be initiated prior to starting any biological therapy. A rifamycin-based regimen (rifamycin daily for four months, isoniazid and rifamycin daily for three months, or isoniazid and rifapentine weekly for three months) is generally preferred over isoniazid monotherapy due to higher completion rates and lower toxicity[15,16]. In patients with contraindications to rifamycin, isoniazid monotherapy (6 months or 9 months daily) remains a valid alternative[13]. However, since they are potent inducers of the hepatic CYP450 system, rifamycin and rifapentine have significant drug interactions with commonly used medications, including but not limited to warfarin, dabigatran, hormonal contraceptives, glucocorticoids, statins, beta-blockers, levothyroxine, macrolide antibiotics, and antiretrovirals[17]. Adverse effects include hepatotoxicity, gastrointestinal symptoms and hematologic complications such as cytopenia and acute hemolytic anemia[18]. Regarding treatment with isoniazid, the primary challenge is ensuring adherence, as its side effects can range from mild to life-threatening. Neurological reactions, such as peripheral neuropathy and ataxia, may arise from reduced vitamin B6 activity in neurotransmitter synthesis. While neurotoxicity can be mitigated with pyridoxine supplementation, there remains no definitive solution for isoniazid-induced hepatotoxicity, the most notable side effect[19]. Isoniazid metabolism generates hepatotoxic metabolites, leading to hepatotoxicity in 20% of patients within the first two months of therapy[20]. Approximately 1% of patients develops severe hepatitis[21,22], with reports of fulminant hepatitis that required liver transplant[23] and with fatal outcomes[24–26].

Anti-tuberculosis drug-induced hepatotoxicity is particularly prevalent in complex and high-risk patients, such as those taking other hepatotoxic medications, individuals with HIV, pre-existing liver diseases (hepatitis B and C), alcoholism, female sex, older adults (>60 years) and low body mass index[27,28]. These characteristics are also commonly found in patients with psoriasis. A multinational study involving 14 dermatology centers evaluated adult patients with moderate to severe plaque psoriasis and positive LTBI, who were treated with IL-17 inhibitors over a 7-year period. Of the 405 patients included, 37.8% did not complete or refused chemoprophylaxis due to hepatic toxicity, drug interactions, or physician/patient decision[29].

Given the heightened susceptibility of comorbid patients, it is crucial to carefully weigh the benefits of TB chemoprophylaxis against starting a biological agent with a lower risk of TB

reactivation without treating the latent TB infection. This review evaluates available treatment options for such patients, aiming to provide clear, evidence-based guidance for clinical practice.

**Objectives**

This article aims to review the treatment options for psoriasis in patients with LTBI.

**Methods**

The search for this review was conducted in multiple search engines, including “Pubmed” and “Google Scholar” databases. English-written original and reviewed articles were taken into consideration from 1971 to 2024.

The combination of the following MeSH terms and keywords were employed: [Psoriasis] and ([Tuberculosis] or [Latent Tuberculosis Infection]) and ([Treatment] or [Biological products]).

The search results were filtered by examining the titles and abstracts of the articles, and only those considered pertinent were included. Furthermore, the bibliographic references from the chosen articles were also taken into account.

## Discussion

### Topical therapies and phototherapy

Topical therapies are particularly effective for managing less severe forms of psoriasis or as adjuncts to systemic therapies. In the 2020 Delphi consensus from the International Psoriasis Council, it was established that candidates for topical therapy (mild or mild to moderate psoriasis) typically present a Body Surface Area (BSA) less than 10% and a Dermatology Life Quality Index (DLQI)[30] of 0-10, provided there is no significant involvement of visible areas, major scalp involvement, genital involvement, onycholysis or onychodystrophy of at least two fingernails, severe itch causing scratching, or the presence of recalcitrant plaques. The severity of psoriasis has traditionally been assessed using the Psoriasis Area and Severity Index (PASI); however, its utilization has become less prevalent in recent clinical guidelines[31,32].

Current guidelines emphasize the safety of topical treatments for psoriasis, as their side effects are generally localized. Common adverse effects include skin atrophy and striae with corticosteroids[33]; pruritus, edema, and peeling with vitamin D analogs[34]; erythema and pruritus with calcineurin inhibitors[35]; folliculitis and contact dermatitis with topical tapinarof[36]; headaches and nasopharyngitis with roflumilast[35]. These therapies don't have significant impacts on systemic immunity, making them suitable for use in patients with latent tuberculosis infection. Consequently, their use does not require screening or prophylactic treatment for chronic infections, including LTBI[37,38].

Phototherapy is a valuable treatment option for patients with chronic non-arthritic psoriasis inadequately controlled by optimized topical therapies[39]. It is particularly effective as an induction therapy for moderate to severe psoriasis. Narrowband ultraviolet B (UVB) phototherapy, the first-line modality, primarily targets psoriatic plaques for clearance, exerting localized effects with minimal systemic impact. As such, it is often categorized within the realm of topical treatments[40]. According to a 2020 statement by the European Academy of Dermatology and Venereology (EADV), UVB therapy is a valid option for patients with contraindications to systemic treatments, including those with recurrent infections or an elevated risk of systemic infections[39]. Nonetheless, UVB phototherapy can be associated with potential side effects, including impacts on immunity, hormone metabolism, and the skin-brain axis. Evidence from murine models indicates that low-dose UVB inhibits the expansion of effector T cells in skin-draining lymph nodes. Clinically, the most significant concern is the long-term risk of cutaneous carcinogenesis, although the overall malignancy risk in UVB-treated patients is not higher than in the general population. UVB is also associated with systemic immunosuppressive effects, such as inhibition of CD8 and cytotoxic T-cell

activation in the spleen and memory T-cell function in the spleen and bone marrow. However, these effects appear to be beneficial, as they enhance protection against autoimmunity[41].

Other phototherapy modalities include psoralen plus ultraviolet A (PUVA), typically reserved for cases unresponsive to UVB therapy but associated with an increased risk of skin cancer, and excimer lasers, which are used for localized lesions. The main contraindications for phototherapy are lupus erythematosus, photosensitive dermatitis, and cutaneous malignancies. However, chronic infections, including LTBI, do not impose any restrictions, making every phototherapy modality a safe and effective option for such patients. Despite its efficacy and safety, the use of phototherapy may be constrained by spatial, financial, logistical, and time limitations[32,42].

## Systemic therapies

### Conventional systemic agents

According to the 2020 Delphi consensus, candidates for systemic therapy include patients meeting at least one of the following criteria: BSA > 10%, involvement of special areas, or failure of topical therapy. Severe disease is typically defined as BSA > 10% or a DLQI > 10[31]. The EuroGuiDerm guidelines, revised in 2024, recommend conventional systemic agents - acitretin, fumarates, ciclosporin, and methotrexate - as first line therapy for patients with moderate to severe plaque psoriasis requiring systemic therapy. These drugs, used for more than 25 years, can be an option for patients with LTBI, although research on reactivation risk remains limited[32]. Studies indicate no evidence of TB reactivation in patients treated with acitretin[43] and fumarates[44].

Cyclosporin has been associated with LTBI reactivation in solid organ transplant recipients[45,46]; nonetheless, no cases have been reported in patients using cyclosporin for psoriasis, likely due to the lower doses employed in this context [47,48].

Regarding methotrexate, some studies, dated 1971–2001 and primarily involving rheumatoid arthritis (RA) patients, have highlighted a potential risk of TB reactivation[49–51], prompting the EADV to recommend LTBI screening and treatment before methotrexate therapy, even in psoriasis patients. More recently, studies have shown inconsistent and contradictory data. Two Canadian studies reported an increased risk of TB reactivation in rheumatoid arthritis patients using methotrexate, with relative risks of 3.4[47] and 1.3[52]. In contrast, studies conducted in high TB burden countries like Taiwan found no significant increase in TB reactivation among psoriasis patients treated with methotrexate[48]. Furthermore, a significant side effect of methotrexate is hepatotoxicity, which can be exacerbated by antituberculosis agents used for LTBI prophylaxis.

Patients with risk factors such as alcohol consumption, obesity, hepatitis, or diabetes mellitus are particularly vulnerable to this hepatotoxic effect[42].

The 2024 EuroGuiDerm guidelines provide no definitive guidance on TB screening before methotrexate or cyclosporine use. While it advises testing for TB prior to methotrexate treatment and notes that some guidelines recommend testing before cyclosporine (such as the 2008 National Psoriasis Foundation[37]), it does not explicitly endorse this practice. Notably, in its recommendations for laboratory monitoring and instructions pre-, during, and post-treatment with cyclosporine and methotrexate, the EADV mentions testing for HBV, HCV, and HIV but does not include IGRA or TST for TB screening. This approach leaves the decision to individual physicians, who must tailor their recommendations based on the patient's history, risk of exposure, and the prevalence of TB in the region. Further research done specifically in psoriasis patients is essential to accurately evaluate the true risk in their clinical context.

### Biological systemic agents

#### TNF-α inhibitors

The introduction of TNF-α inhibitors, such as etanercept (ENT) in 2004, infliximab (IFX) in 2005, adalimumab (ADA) in 2007 and more recently certolizumab-pegol (CTP) 2018, marked a significant advancement in the systemic treatment of psoriasis and other chronic inflammatory diseases[32]. However, their use has long been associated with immunosuppression and its repercussions in patients with rheumatoid and psoriatic arthritis as well as ankylosing spondylitis[53]. In response to *M. tuberculosis*, IL-12 is produced by the innate immune system, promoting the differentiation of Th1 helper cells, which in turn secrete IL-1, TNF-α, and interferon-gamma (IFN-γ)[54]. TNF-α accumulates in the infection site and is responsible for the containment of the tuberculosis infection through the activation of phagocytosis in macrophages, maturation of dendritic cells and formation and maintenance of granulomas. Studies in mice and humans have shown that the *knock-out* of TNF-α or TNF-α receptor leads to severe inflammation, uncontrolled infection and reactivation of latent TB infection [55,56].

Given the direct influence that TNF-α has in controlling *Mycobacterium* infection, TB screening before initiating this biologic therapy was incorporated into practice guidelines in 2001 to enhance patient safety[57]. In addition, TB associated with TNF-α inhibitor use often presents with less typical symptoms and is more frequently extrapulmonary, disseminated, and life-threatening, posing significant challenges for early diagnosis and treatment [58].

Extensive research has firmly established the association between anti-TNF-α agents and an increased risk of infections, including TB, across various disease contexts[59–61], with reported relative risk estimates ranging from 1.6 to 25.1[62]. Data from clinical trials, national registries, and post-marketing surveillance report median incidences of 85.5 cases of TB per 100,000 person-years for etanercept, 284.5 cases per 100,000 person-years for infliximab, and 203 cases per 100,000 person-years for adalimumab. Notably, these TB incidence rates are higher than the background TB rates in the respective countries. This review included patients who underwent different TB screening and treatment protocols, varying from none to complete prophylaxis, with some data predating the 2001 guideline recommending systematic TB screening[57]. The risk of tuberculosis reactivation associated with certolizumab pegol has significantly decreased, from 2630 to 180 cases per 100,000 person-years, following the implementation of LTBI screening. This reduction highlights the effectiveness and necessity of implementing rigorous measures for latent tuberculosis management in psoriasis patients[63]. Since 2001, preventive measures have been estimated to reduce the risk of reactivation by 65%[64].

One major limitation in understanding the exact impact of TNF-α inhibitors on TB reactivation in psoriasis patients is that most studies focus on rheumatologic conditions, particularly RA. While TB appears to be more common in RA compared to inflammatory bowel disease (IBD) or psoriasis (0.29% vs. 0.19%), some studies show that the difference is not statistically significant [65]. The apparent higher prevalence in RA patients may be explained by their more extensive history of immunosuppressive therapy. Research specifically targeting psoriasis patients is scarce, requiring extrapolation of findings from studies conducted on other inflammatory diseases.

Given the overwhelming evidence linking TNF-α inhibitors to an increased risk of LTBI reactivation, current guidelines mandate TST or IGRA testing prior to initiating therapy with ETN, IFX, ADA and CTP. These guidelines also strictly contraindicate the use of these agents in patients with active tuberculosis[32,42].

Anti IL-17

In the realm of biological agents, more selective therapies were later developed, specifically targeting interleukins such as IL-17. IL-17 plays a crucial role in enhancing innate immunity by promoting neutrophil recruitment, stimulating granulopoiesis, driving local inflammatory responses[66] and contributing to granuloma formation[55]. IL-17 inhibition is associated with suboptimal control of certain fungal infections, particularly candidiasis[67], as well as mucocutaneous *Staphylococcus aureus*[68]. Interestingly, studies comparing cytokine roles in TB infection found that while TNF-α neutralization leads to lethal alterations in immune and inflammatory responses, IL-17

cytokine blockage results in only mild changes in gene expression. Lung pathology and survival rates were similar between IL-17 *knockout* murines and wild-type mice[69], indicating that the IL-17 pathway has a redundant role in TB containment as long as the Th1 response remains intact[70].

IL-17 antagonist agents, including secukinumab (approved in 2015), ixekizumab (2016), brodalumab (2018), and bimekizumab (2021), are first-line treatments for moderate to severe psoriasis in patients who fail (or are expected to fail) to achieve satisfactory outcomes with conventional systemic therapies[32]. Current guidelines require screening for tuberculosis infection before initiating IL-17 blockers. However, neither active TB nor LTBI is explicitly listed as a contraindication for their use.

A 2024 review encompassing thirty retrospective and prospective analyses, case reports, case series, and clinical trials evaluated 276 LTBI patients from regions with varying TB burdens who received anti-IL-17 therapy (except bimekizumab) without completing chemoprophylaxis. Among these patients, only one case of TB reactivation was identified[71]. This case, reported in a multinational retrospective analysis, involved a patient who refused prophylaxis due to concerns about isoniazid-related hepatotoxicity. The patient developed intestinal TB 14 months after starting ixekizumab therapy. Biological therapy was discontinued, and standard four-drug anti-tuberculosis treatment was initiated. The patient subsequently made a full recovery without long-term TB-related complications[29]. Given the typical progression rate of untreated LTBI to active TB (5–10%)[72] and the fact that most biologic-induced reactivations occur within the first six months of therapy[73,74], it remains unclear whether this reactivation was directly linked to IL-17 inhibition or a natural progression of the infection. These findings suggest a low likelihood of TB reactivation with anti-IL-17 therapy, even in the absence of prophylactic treatment. Although bimekizumab has been available only recently, safety data from randomized clinical trials (RCT) have not identified any TB cases in patients with ankylosing spondylarthritis over 52 weeks in a phase III RCT[75] and 156 weeks in a phase IIb RCT[76], or in patients with psoriatic arthritis over 3 years in a phase IIb RCT[77].

Nonetheless, a discrepancy exists between current clinical practice recommendations and evidence suggesting that IL-17 therapy does not increase TB risk in psoriasis patients. This misalignment often results in LTBI patients undergoing potentially avoidable treatments associated with side effects that should not be disregarded.

<u>Anti IL23p19</u>

IL-23 is pivotal in the differentiation of Th17 cells, which produce key cytokines such as IL-17A, IL-17F, and IL-22. Unlike IL-12, which it partially overlaps with by sharing the p40 subunit, IL-23 contains a unique p19 subunit. Therapeutic agents targeting IL-23 introduced in clinical practice

in 2017 to 2019 (guselkumab, tildrakizumab, risankizumab) primarily act by neutralizing this subunit. Additionally, IL-23 promotes IFN-γ-producing Th1 cells in the absence of IL-12p70[78]. IL-23 blockers inhibit IL-17 production, suggesting that the considerations outlined in the previous topic regarding IL-17 also extend to IL-23. This interleukin primarily functions as a regulatory cytokine and is not essential for the immune response to *Mycobacterium*.

In the above mentioned 2024 review, anti-IL-23 therapies were also assessed and no cases of TB reactivation were reported among 147 LTBI patients who did not complete chemoprophylaxis[71]. A significant advantage of anti-IL-17/23 studies is that the majority of the data concerns to psoriasis patients, providing a more precise risk assessment within the context of this specific disease. This evidence reshapes the understanding of these biotherapies, suggesting that the risk of TB reactivation is minimal, even in the absence of preventive LTBI treatment. Nonetheless, as with anti-IL-17 recommendations, TST or IGRA testing remains a mandatory prerequisite before initiating IL-23 targeted therapies.

Anti IL 12/23p40

Ustekinumab, introduced in 2009, is a monoclonal antibody targeting the shared p40 subunit of IL-23, thereby functioning as a nonselective inhibitor of both IL-12 and IL-23. The IL-12 pathway is a key player against intracellular pathogens, by inducing Th1 responses and facilitating the migration of dendritic cells to lymph nodes through the p40 subunit[79]. Studies have demonstrated that defects in IL-12/23-mediated immunity, including the absence of IL-12p40 or IL-12Rβ1, are associated with increased tuberculosis incidence[80,81].

A 2012 review of five phase III trials of ustekinumab involving 3177 treated patients found that only one patient, who did not receive prior anti-tuberculosis treatment, developed asymptomatic pulmonary TB. No cases were reported among the 167 psoriasis patients with latent TB who received isoniazid prophylaxis[82]. Three cases of TB reactivation have been reported in patients who received chemoprophylaxis – two psoriasis cases in Italy with pulmonary TB (2014) and in Ireland in with peritoneal TB (2017) and one Crohn's disease case in Japan with tuberculosis pericarditis (2021)[83–85]. These findings appear to corroborate the essential role of IL-12 in controlling and maintaining *M. tuberculosis* infection latency. Further data on the safety profile of ustekinumab is needed, but in light of these findings, it seems reasonable to continue to require mandatory TB screening and treatment prior to initiating anti-IL-12/23p40 therapies.

## Non-Biological systemic agents

### Phosphodiesterase 4 inhibitors

Apremilast, a small molecule non biological systemic treatment introduced in 2015, is a selective phosphodiesterase 4 (PDE4) inhibitor that elevates intracellular cyclic adenosine monophosphate (cAMP) levels, leading to the suppression of pro-inflammatory cytokines like TNF-α, IL-17, IFN-γ and promotion of anti-inflammatory mediators like IL-10. This immunomodulatory, rather than immunosuppressive, mechanism reduces inflammation in immune and non-immune cells, effectively mitigating psoriasis-related chronic inflammation without significantly impairing overall immune function[86,87]. Apremilast targets an earlier stage of the inflammatory pathway compared to TNF-α antagonists and IL-17/23 blockers. Due to their less aggressive mechanism of action, PDE4 inhibitors have demonstrated lower efficacy compared to biological agents. Real-world data indicates that these therapies are often prescribed to patients with a PASI score of 10–11 and limited prior exposure to biological treatments. However, they offer the significant advantage of being suitable for patients with chronic infections, including hepatitis B, hepatitis C, HIV, and TB. In phase III trials which included 7 patients previously treated for TB (4 with latent TB and 3 with active TB), overall a 156 week period to evaluate apremilast safety, no case of opportunistic infection or TB reactivation was reported[88].

In phase II and III clinical trials conducted between 2012 and 2017, where latent TB screening was not required but cases of active TB or incomplete TB treatment were excluded, no instances of opportunistic infections or TB reactivation were reported[89–93]. Based on evidence indicating that apremilast does not elevate TB risk, mandatory screening is not required in the updated 2024 EuroGuiDerm guidelines[32].

### Tyrosine Kinase 2 inhibitors

Deucravacitinib, a novel pharmaceutical introduced in 2023, is a selective tyrosine kinase 2 (TYK2) inhibitor that blocks the signaling pathways of cytokines implicated in psoriasis, including IL-12, IL-23, and type I interferons. It achieves this by allosterically binding to the TYK2 regulatory pseudokinase domain, locking it into an inhibitory conformation and preventing downstream activation. This high selectivity for TYK2, with minimal inhibition of the Janus kinase (JAK) 1, JAK 2 and JAK 3, gives deucravacitinib a favorable safety profile and positions it as an effective treatment for moderate-to-severe plaque psoriasis[94,95].

The Phase III POETYK trials evaluating the safety and efficacy of deucravacitinib over one- and two-year periods reported one case of TB. This case involved a 33-year-old patient from Russia

(high burden TB setting) with a negative IGRA result at baseline but with pre-existing fibrosis of the upper lung lobes. Investigators deemed this a moderate TB case unrelated to the study treatment[96]. Notably, active TB and positive IGRA results were an exclusion criteria in the PSO-1 and PSO-2 Phase III double-blinded, 52-week randomized controlled trials, making it challenging to determine the true risk of TB reactivation with TYK2 selective therapy[97,98]. It should also be noted that the mentioned trials were conducted during the SARS-CoV-2 pandemic, and the majority of adverse events reported were coronavirus infections. However, given the mechanism of action involving IL-12, which plays a significant role in defense against mycobacteria as already discussed, current guidelines recommend TB screening and treatment for LTBI before initiating therapy, pending further research and clearer evidence, ideally conducted in a more typical epidemiological context.

## Future Perspectives

### Novel treatments

The treatment of chronic inflammatory diseases has become increasingly selective, aiming to reduce side effects while improving efficacy and convenience, such as through oral administration. In psoriasis management, the goal remains to aggressively resolve psoriatic plaques while minimizing immunosuppressive effects—a balance that has yet to be fully achieved[99].

Ongoing research focuses on novel inflammatory targets for severe psoriasis, with several agents in phase I, II, and III trials. These include JAK inhibitors (tofacitinib, baricitinib), though safety concerns persist[100–102]; the TYK2/JAK1 pathway inhibitor brepocitinib[103]; adenosine A3 receptor agonists like piclidenoson [104]; ROCK2 inhibitors such as belumosudil, which elevate IL-10 levels to downregulate Th17 T-cells without compromising immunity[105]; and selective retinoic acid-related orphan receptor gamma t (RORγt) antagonists, including vimirogant and cedirogant[106].

Future perspectives for the treatment of psoriasis also include innovative approaches that address underlying factors beyond traditional inflammatory pathways. One promising approach involves the use of oral vitamin D, which has demonstrated significant antimycobacterial activity in vitro and plays a critical role in host defense and inflammation[107]. Historically utilized alongside UVB phototherapy for tuberculosis treatment[108], higher vitamin D levels have been associated with reduced TB transmission[109]. While not explicitly endorsed by the National Psoriasis Foundation, recent evidence supports oral vitamin D as a safe and effective therapy for improving plaque psoriasis, with recurrence observed upon discontinuation and improvement upon resumption[110]. Another possible unconventional treatment is the correction of gut microbiota imbalances that are implicated in dermatological conditions like psoriasis, atopic dermatitis, and acne[111]. Gut microbiota

dysbiosis in psoriasis patients correlates with disease severity, inflammation markers, and altered microbial composition, such as decreased *Akkermansia muciniphila* and increased *Ruminococcus* species. This dysbiosis impacts immune responses, particularly via the IL-23/Th17 axis, promoting inflammation and highlighting the therapeutic potential of microbiome-targeted interventions and dietary modulation[112]. Therapies targeting intestinal microbiome have shown promise as safe and effective interventions that need more investigation in order to be implemented in real-life clinical practice.

Further research involving larger patient populations is essential to thoroughly explore these innovative and alternative therapeutic approaches.

### Updating guidelines

In light to new data, experts' opinion has started to shift. Both a 2019 review published in the Journal American Academy of Dermatology and the Austrian 2023 consensus on managing LTBI suggest that IL-17 antagonists do not impose a higher TB reactivation risk and do not require TST/IGRA testing, agreeing that they are a safe option in LTBI patient. However, they also state that additional safety data is needed to make the same assumptions for IL-23 blockers[43,113].

More recently, the 2024 SPIN-FRT expert consensus, involving 14 dermatology and infectious disease specialists, proposed updated recommendations for managing psoriasis with biological and nonbiological therapies in patients at risk of TB exposure, at risk of TB disease, with LTBI and with active TB disease. The changes were particularly relevant when it comes to IL-17 and IL-23 antagonists and have major implications concerning screening timing after beginning therapy, first line psoriasis treatments for LTBI patients and management of active TB in patients under systemic therapy[71].

The consensus advises LTBI screening for all patients initiating systemic treatments, except for apremilast. Periodic testing with TST or IGRA is recommended only for patients treated with TNF-α inhibitors, IL-12/23 inhibitors, or TYK2 inhibitors who lack a history of TB and simultaneously have specific risk factors for TB exposure or active disease. Screening is not required for patients without these risk factors regardless of the therapy they are using or any patient treated with IL-17 inhibitors, IL-23 inhibitors, or PDE4 inhibitors.

Regarding best treatment options for patients with known TB infection, for individuals with a high risk of toxicity to antituberculosis drugs (those over 60 years old, with diabetes or other comorbidities), IL-17/23 blockers and PDE4 inhibitors are preferred, and chemoprophylaxis is unnecessary. For low-risk patients, the decision to initiate preventive LTBI treatment should be

individualized. If TNF-α inhibitors, ustekinumab, or deucravacitinib are selected as the therapeutic agents, chemoprophylaxis is recommended.

In cases where TB disease develops during treatment with IL-17/23 blockers or apremilast, TB therapy should begin without necessarily stopping psoriasis treatment, with decisions made on a case-by-case basis. For patients on TNF-α inhibitors, ustekinumab, or TYK2 inhibitors, psoriasis treatment must be discontinued, TB treatment initiated, and psoriasis therapy switched to IL-17/23 blockers or apremilast[71].

To optimize the use of valuable medical resources and minimize the risk of iatrogenic harm from unnecessary medical interventions, it is essential to revise current guidelines to align with the safety profiles of each drug.

**Conclusions**

Managing psoriasis in patients with LTBI is a nuanced challenge that demands personalized, evidence-based care. Psoriasis, which is frequently associated with comorbidities, requires a treatment approach that not only targets the dermatological condition but also takes into account the patient's broader clinical context, including the implications of coexisting conditions such as a LTBI diagnosis.

Topical therapies and phototherapy, though long-standing approaches, remain effective options for managing mild to moderate psoriasis. Conventional systemic agents like acitrecin and fumarates are 1$^{st}$ line therapy in severe plaque psoriasis as well as methotrexate and cyclosporine, although they must be prescribed with caution in high burden TB regions. However, the therapeutical arsenal in the 21st century has expanded. TNF-α antagonists, while effective, carry a heightened risk of TB reactivation, needing stringent screening protocols. Novel treatment options like - IL-17 inhibitors, IL-23 inhibitors, IL-12/23 inhibitors, apremilast, and TYK2 inhibitors, - offer promising personalized care-tailoring alternatives with potentially lower TB reactivation risks.

In the past, when TNF-α inhibitors were the only biological treatment available, the strict guidelines, including universal TB screening and chemoprophylaxis, were justifiable. However, as new therapies emerge, guidelines must evolve to reflect these advancements. The one-size-fits-all approach is outdated. It assumes that the benefits of preventive treatment, using isoniazid or rifamycin-based regimens, always outweighs the risks, overlooking the possibility of hepatotoxicity and drug interactions, which are particularly concerning in complex psoriasis patients.

Ultimately, a more flexible and personalized approach to managing psoriasis in LTBI patients is necessary. This should involve updated guidelines that take into account the differential risks of systemic therapies and exploring cutting-edge, alternative, non-traditional approaches to treatment, thereby ensuring safer and more effective management for these patients.

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