

**Joint Position Statement from the National Psoriasis Foundation Medical Board
and the International Psoriasis Council on Routine Testing for Latent
Tuberculosis Infection Prior To and During Treatment of Psoriasis Patients with
IL-17 or Selective IL-23 Inhibitors**

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Testing for latent tuberculosis (TB) infection has been standard clinical practice prior to initiation of biologic therapy for patients with psoriasis.¹ Historically, this practice was largely driven by experience with tumor necrosis factor (TNF) inhibitors. TNF, a prototypic pro-inflammatory cytokine with broad roles in both health and disease, is known to be involved in granuloma formation and function, which helps contain and control *Mycobacterium tuberculosis* infection within tissue.^{2,3} Indeed, treatment of psoriasis and other immune-mediated inflammatory diseases (IMIDs) with TNF inhibitors can inhibit granuloma formation or function and can promote progression of latent TB infection to active disease.⁴⁻⁷ Thus, testing for latent TB infection prior to and during treatment with TNF inhibitors has been an integral and important part of clinical trial designs and clinical practice for decades.

Testing for latent TB infection has also been an integral part of clinical trials and clinical practice prior to and during treatment with other drug classes that can potentially lead to progression of latent TB infection to active disease, including ustekinumab and tyrosine kinase 2 inhibitors, drugs that inhibit both IL-12 and IL-23 actions, and Janus kinase inhibitors, which have broad immunomodulatory effects on a number of cytokines, including interferon- γ . IL-12 and interferon- γ orchestrate Th1 immune responses, which are important for controlling TB infection.^{2,3} Two other classes of biologics used to treat psoriasis, IL-17 inhibitors and selective IL-23 inhibitors, also have requirements for latent TB infection testing. These testing recommendations were primarily based on

early mouse studies⁸⁻¹⁰ and on historic precedent with older biologic therapies, rather than on direct evidence of risk. *Currently, both the biologic basis for this testing and the evidence for progression of latent TB infection to active disease in clinical settings, in both trials and in real-world practice, are limited and weak for both IL-17 and selective IL-23 inhibitors.*¹¹

Recently, international experts have extensively reviewed the roles of IL-17 and IL-23 in TB pathogenesis as well as current clinical evidence for the progression of latent TB infection to active disease during treatment with either IL-17 or selective IL-23 inhibitors; these authorities further suggested several modifications to existing treatment guidelines for these two classes of biologics.^{11,12} Inspired by these efforts, here, the National Psoriasis Foundation Medical Board and the International Psoriasis Council review clinical evidence supporting the safety of IL-17 and selective IL-23 inhibitors regarding the progression of latent TB infection to active disease. A consensus proposal is presented that urges modifications to existing clinical and regulatory guidelines for the routine testing requirement for latent TB infection prior to and during treatment of psoriasis patients with these two newer classes of biologics. Implementing this evidence-based change in future clinical trial designs and clinical practice would avoid unnecessary medical costs, reduce avoidable regulatory burden, alleviate concerns for false positive results, and expedite treatment of patients with psoriasis.

IL-17 Inhibitors

IL-17A and IL-17F are critical cytokines involved in the pathogenesis of psoriasis.¹³

There are now four approved therapies for psoriasis that inhibit function of IL-17 family members: secukinumab and ixekizumab (which both target IL-17A), brodalumab (which targets IL-17RA, a component of the IL-17 receptor), and bimekizumab (which targets IL-17A and IL-17F). Although the exact role for IL-17 family members in the immunopathogenesis of *M. tuberculosis* infection is debated,^{14,15} recent findings in mice have demonstrated that selective inhibition of IL-17A, IL-17F, IL-17RA, or IL-22 does not impair host control of *M. tuberculosis*, while TNF-deficient mice rapidly succumb to infection.^{16,17} Furthermore, using a human microgranuloma model *in vitro*, secukinumab-induced inhibition of IL-17A did not reverse *M. tuberculosis* dormancy, whereas ustekinumab-induced inhibition of IL-12/IL-23 and adalimumab-induced inhibition of TNF promoted *M. tuberculosis* reactivation.^{18,19}

Consistent with these biologic studies in the laboratory and in mice, considerable clinical trial data and post-marketing real-world evidence support the concept that IL-17 inhibitors do not increase the risk of progression of latent TB infection to active disease in humans with psoriasis and other IMIDs.²⁰⁻³² For clinical trials, patients with known latent TB infection were typically eligible for enrollment into IL-17 inhibitor studies, provided that they received preventive TB therapy according to local guidelines before or at the beginning of the trials. No cases of active TB were observed in trials among

such individuals, which numbered in the hundreds.¹¹ Although these data underscore that IL-17 inhibitors are safe in patients with properly treated latent TB infection, administration of prior TB preventive therapy introduces a confounding factor in assessing the specific safety of IL-17 inhibitors in the setting of TB infection.

Some particular patient scenarios are notable from the clinical trial literature on IL-17 inhibitors and TB infection. Six patients receiving ixekizumab tested negative for latent TB infection before entering clinical studies, but later tested positive during the trials. These patients did not receive treatment for latent TB infection, continued receiving ixekizumab, and did not develop active TB.²⁶

A considerable body of real-world evidence also exists on the safety of IL-17 inhibitors in patients with latent TB infection, even in the absence of TB preventive therapy.³²⁻⁴⁵ Indeed, details from these reports reveal hundreds of patients with IMIDs who were treated with IL-17 inhibitors and did not receive appropriate TB preventive therapy for a variety of reasons, including concomitant liver disease, contraindications due to existing co-morbidities or potential drug-drug interactions, and patient preference. Only one patient in these reports exhibited signs of progression of latent TB infection to active disease,⁴⁴ which falls well within the 5-10% lifetime risk for progression of latent TB infection to active disease.¹ Whereas TNF inhibitor-associated progression of latent TB infection to active disease is typically observed within 12 months of starting treatment,⁴⁶ atypical extra-pulmonary TB was observed in this patient 14 months after starting an IL-

17 inhibitor. It is likely that the cause for progression to active TB was independent of biologic treatment.⁴⁴ No progression of latent TB infection to active disease was reported in all other cases, underscoring the relative safety of IL-17 inhibitor treatment for psoriasis and other IMIDs in the setting of latent TB infection.

Selective IL-23 inhibitors

IL-23 plays a critical role in the pathogenesis of psoriasis.⁴⁷ IL-23 consists of two protein subunits, p40 and p19; the former subunit is shared with IL-12, whereas p19 is specific for IL-23. Selective IL-23 inhibitors, which block p19, are important treatment options for psoriasis patients; they include guselkumab, tildrakizumab, and risankizumab. Similar to IL-17A, IL-23 has been implicated in protective responses against *M. tuberculosis* infection. However, IL-12-mediated Th1 responses are dominant in controlling TB infection, with IL-23/Th17 responses playing a protective role only in the setting where Th1 responses are compromised.⁴⁸

Many reviews have highlighted the safety of selective IL-23 inhibitors in treating psoriasis and other IMIDs, including in the setting of latent TB infection.^{21,49,50} Extensive data from clinical trials have been pooled and analyzed on this issue.⁵¹⁻⁵³ Analyses that included 4,399 patients treated with guselkumab with an exposure of 10,787 patient-years,⁵¹ 1,413 patients treated with tildrakizumab,⁵² and 2,072 patients treated with risankizumab with an exposure of 7,927 patient-years⁵³ revealed no cases of

progression of latent TB infection to active disease in clinical trials utilizing selective IL-23 inhibitors. Similarly, no cases of progression of latent TB infection to active disease have been reported in clinical trials utilizing selective IL-23 inhibitors to treat other IMIDs, such as psoriatic arthritis, ulcerative colitis, and Crohn's disease.^{51,54-58} As discussed above with IL-17 inhibitor trials, patients with latent TB infection were typically included in these selective IL-23 inhibitor studies only if they had previously received TB preventive therapy, which introduces confounding bias when fully evaluating the safety of these drugs in the setting of latent TB infection.

Some patient cohorts in selective IL-23 inhibitor clinical trials are noteworthy. For example, a subset of 31 patients in the IMMhance risankizumab trial for psoriasis tested positive for latent TB infection during screening, but did not receive TB preventive therapy prior to study initiation; these individuals were exposed to risankizumab for 55 weeks and none reported progression of latent TB infection to active disease.⁵⁹ In a pooled analysis from two guselkumab studies, a subset of 7 patients began TB preventive therapy concurrently with the initiation of guselkumab therapy and 5 additional patients began TB preventive therapy after starting guselkumab; none of these 12 patients experienced progression of latent TB infection to active disease.⁶⁰

Real-world data on psoriasis patients being treated with selective IL-23 inhibitors provides additional support for the safety of these drugs in the setting of latent TB infection. Twenty-five patients who tested positive for latent TB infection, yet were either

untreated or inadequately treated, received guselkumab for 24-32 months, with no cases of progression of latent TB infection to active disease reported.^{38,44,61} Similarly, 23 patients with latent TB infection who did not receive or received inadequate TB preventive therapy were treated for 24-32 months with tildrakizumab, again with no cases of progression of latent TB infection to active disease reported.^{44,62} Lastly, 68 patients with latent TB infection, but who received either no or inadequate TB preventive therapy, were treated with risankizumab for periods ranging from 9 to 32 months; no cases of progression of latent TB infection to active disease were reported in this cohort.^{38,39,44,59}

FDA Adverse Event Reporting System (FAERS) Database Search

To further investigate the possible role of IL-17 inhibitors and selective IL-23 inhibitors in the progression of latent TB infection to active disease, the FDA Adverse Event Reporting System (FAERS) was searched for cases of extra-pulmonary internal organ TB, which generally occur in patients with underlying immune compromising conditions. A total of 96,351 safety reports from the US associated with the use of IL-17 or selective IL-23 inhibitors for the treatment of psoriasis were revealed in the FAERS database (**Table**). For IL-17 inhibitors (secukinumab, ixekizumab, brodalumab, and bimekizumab) and selective IL-23 inhibitors (guselkumab, tildrakizumab, and risankizumab), no cases of extra-pulmonary internal organ TB and no cases of disseminated TB associated with the use of these medications were found. As a positive control, cases of extra-pulmonary internal organ TB in US patients treated with TNF inhibitors were queried. Among 139,825 safety reports associated with use of TNF inhibitors (etanercept,

infliximab, adalimumab, and certolizumab) for the treatment of psoriasis, 26 reports of extra-pulmonary internal organ TB were found, including 8 cases of disseminated TB (**Table**). Thus, despite nearly a decade of use of biologics that target IL-17 or IL-23 for the treatment of psoriasis in the US, no signal was detected in the FAERS database for types of TB infection associated with immunosuppression, but this signal was confirmed with TNF inhibitors.

Joint Position Statement

There are 32 members of the Medical Board of the National Psoriasis Foundation, a U.S.-based non-profit organization focused on advancing clinical care, patient advocacy, and research on psoriatic disease. Membership to the Medical Board is by invitation only and includes dermatologists, rheumatologists, nurse practitioners, and physician assistants generally recognized as national/international experts on psoriatic disease. The International Psoriasis Council is a global non-profit organization focused on psoriasis. Membership into the council occurs through a comprehensive vetting process and includes approximately 200 individuals worldwide, including dermatologists, rheumatologists, other physicians, and basic research scientists who are generally recognized as international experts in psoriasis. Members of the Medical Board of the National Psoriasis Foundation and the Councilors of the International Psoriasis Council have agreed (pending vote) on the following statement:

Routine testing for latent tuberculosis infection is not required prior to or during treatment of psoriasis patients with IL-17 or selective IL-23 inhibitors.

Although this new joint position statement from the NPF and the IPC represents a change from current drug labeling and current sponsor and regulatory practices, which assume screening for latent TB infection is obligated, it is based on biologic, clinical trial, and real-world evidence that support the safety of IL-17 and selective IL-23 inhibitors in the setting of latent TB infection. This recommendation is applicable to both current clinical practice as well as future clinical trials. Regarding the latter, emerging oral medications for psoriasis that selectively target IL-17 or IL-23 have not shown signals that increase the risk of progression of latent TB infection to active disease,⁶³ and thus should also not have routine testing performed for latent TB infection before or during treatment.

This new joint position statement allows for exceptions, which may occur for specific patients and in certain clinical conditions where continued testing for latent TB infection would be prudent or warranted. These other types of patients may be on concomitant medications, such as prednisone or other immunosuppressants, that may increase the risk of progression of latent TB infection to active disease. Lastly, leading experts who utilize IL-17 and selective IL-23 inhibitors to treat IMIDs other than psoriasis, such as psoriatic arthritis, ankylosing spondylitis, hidradenitis suppurativa, and inflammatory bowel disease, are encouraged to make similar position statements. In summary,

avoiding routine TB testing that is scientifically and medically unwarranted would alleviate regulatory burden, save healthcare costs, alleviate concerns for false positive tests, and expedite treatment of psoriasis patients with IL-17 or selective IL-23 inhibitors.

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Table. FAERS reports of extra-pulmonary internal organ TB in patients with psoriasis treated with IL-17, IL-23, or TNF inhibitors in the United States.

Exposure		Total no. of adverse event reports (any cause)	No. of extra-pulmonary internal organ TB reports
IL-17 inhibitors	Secukinumab	43725	0
	Ixekizumab	12078	0
	Brodalumab	1913	0
	Bimekizumab	286	0
Selective IL-23 inhibitors	Guselkumab	7630	0
	Tildrakizumab	513	0
	Risankizumab	30206	0
TNF inhibitors	Etanercept	67566	7
	Infliximab	1765	4
	Adalimumab	66359	15
	Certolizumab	4135	0