Risk for Deep Fungal Infections During IL-17 and IL-23 Inhibitor Therapy for Psoriasis

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PRACTICE **POINTS**

- The use of IL-17, IL-12/IL-23, and IL-23 inhibitors for psoriasis and other inflammatory conditions does not appear to increase the risk for deep fungal infections.
- Physicians should still be cautiously optimistic in prescribing these medications, as IL-17 and IL-23 play a central role in immunologic defenses, particularly against fungi.
- A high index of suspicion should be maintained for patients from endemic areas who are being treated with biologics.

Psoriasis is an inflammatory disease with both skin and joint manifestations. Focused biologics have been developed to target specific cytokines implicated in psoriasis and are becoming increasingly utilized. Recently, the advent of newer biologics, including IL-17, IL-12/IL-23, and IL-23 inhibitors, have garnered interest as promising treatments for psoriasis and other inflammatory conditions. Although IL-17 and IL-23 have been studied in the pathophysiology of psoriasis, they also play a central role in immunologic defenses, including those against fungi. Therefore, use of these interleukin inhibitors may theoretically impair the immune system against deep fungal infections. We reviewed the available literature investigating the risk for invasive fungal infections in patients treated with IL-17 and IL-23 inhibitors for psoriasis or other inflammatory conditions. Randomized controlled trials (RCTs), including extended trials and clinical trials, were reviewed, and we found that although there was a small number of patients who developed superficial candidiasis, there were no reports of invasive fungal disease. Although these results support the safety and the low risk for deep fungal infection with these biologics, caution is still warranted, as these medications are relatively new. Appropriate screening and management of fungal disease should still be practiced when utilizing these medications in the treatment of psoriasis and other inflammatory conditions.

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Psoriasis is a common chronic, multisystem, inflammatory disease with predominantly skin and joint manifestations that affects approximately 2% of the world's population.[1] It occurs in a variety of clinical forms, from a few well-demarcated, erythematous plaques with a silvery scale to involvement of almost the entire body surface area. Beyond the debilitating physical ailments of the disease, psoriasis also may have psychosocial effects on quality of life.[2] The pathogenesis of psoriasis is not fully understood but represents a complex multifactorial disease with both immune-mediated and genetic components. Characterized by hyperplasia of epidermal keratinocytes, psoriasis is shown to be mediated by infiltration of T-cell lymphocytes with an increase of various inflammatory cytokines, including tumor necrosis factor (TNF) α.[3] More recently, interactions of helper T cells (T_H17) via IL-17 and IL-23 have been supported to play a major role in the pathogenesis of psoriasis.[4,5]

With the growing understanding of the pathophysiology of psoriasis, focused biologics have been developed

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The eTable is available in the Appendix online at www.mdedge.com/dermatology.
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to target specific cytokines implicated in the disease process and have been increasingly utilized. Tumor necrosis factor α inhibitors, including adalimumab, infliximab, and etanercept, along with the IL-12/IL-23 inhibitor ustekinumab, have been revolutionary in psoriasis treatment by providing safe and effective long-term therapy; however, there is concern of life-threatening infections with biologics because of the immunosuppressive effects and mechanisms of action.[6] Specifically, there have been reported cases of deep fungal infections associated with TNF-α inhibitor use.[7]

Recently, the advent of IL-17 and IL-23 inhibitors has garnered notable interest in these biologics as promising treatments for psoriasis. With IL-17 and IL-23 supported to have a major role in the pathogenesis of psoriasis, targeting the cytokine is not only logical but also has proven to be effacacious.[8-10] Secukinumab, ixekizumab, and brodalumab are IL-17 inhibitors that have been approved by the US Food and Drug Administration (FDA) for the treatment of psoriasis. Secukinumab and ixekizumab are anti–IL-17A monoclonal antibodies, whereas brodalumab is an anti–IL-17 receptor antibody. Risankizumab, guselkumab, and tildrakizumab are IL-23 inhibitors that also have been approved by the FDA for the treatment of psoriasis. As with older biologics, there is concern over the safety of these inhibitors because of the central role of IL-17 and IL-23 in both innate and adaptive immune responses, particularly against fungi.[11] Therefore, use of biologics targeting IL-17 and IL-23 may increase susceptibility to deep fungal infections.

Safety data and discussion of the risk for deep fungal infections from IL-17, IL-12/IL-23, and IL-23 inhibitor use for psoriasis treatment currently are lacking. Given the knowledge gap, we sought to synthesize and review the current evidence on risks for deep fungal infections during biologic therapy in patients with psoriasis, with a focus on IL-17 inhibitor therapies.

METHODS

A PubMed search of articles indexed for MEDLINE from database inception to 2019 (1946-2019) was performed to find randomized controlled trials (RCTs), including extended trials and clinical trials, for IL-17, IL-12/IL-23, and IL-23 inhibitors approved by the FDA for psoriasis treatment. The following keywords were used: *psoriasis* or *inflammatory disease* and *secukinumab, ixekizumab, brodalumab, ustekinumab, risankizumab, guselkumab,* or *tildrakizumab*. Studies were restricted to the English-language literature, and those that did not provide adequate safety data on the specific types of infections that occurred were excluded.

RESULTS

IL-17 Inhibitors

Our search yielded RCTs, some including extension trials, and clinical trials of IL-17 inhibitors used for psoriatic disease and other nonpsoriatic conditions (Table).

Risk for Deep Fungal Infection With Secukinumab—The queried studies included 20 RCTs or clinical trials along with extension trials of 3746 patients with psoriasis or other inflammatory conditions, with follow-up ranging from 12 to 52 weeks. In a 3-year extension study of SCULPTURE, Bissonnette et al[12] reported no new safety concerns for the 340 patients with moderate to severe psoriasis treated with secukinumab. Common adverse events (AEs) included nasopharyngitis, upper respiratory tract infections, and headache, but there were no reports of deep fungal infections.[12] In a subsequent 5-year analysis of 168 patients that focused on the 300-mg fixed interval treatment with secukinumab, the safety profile remained favorable, with 0 reports of invasive fungal infections.[13] A study (FEATURE) of 118 patients with psoriasis treated with a prefilled syringe of 300 or 150 mg of secukinumab also described an acceptable safety profile and reported no deep fungal infections.[14] JUNCTURE, another study utilizing autoinjectors, also found that treatment with 300 or 150 mg of secukinumab was well tolerated in 121 patients, with no deep fungal infections.[15] Common AEs for both studies included nasopharyngitis and headache.[14,15] A 24-week phase 3 study for scalp psoriasis treated with secukinumab also reported 0 deep fungal infections in 51 patients.[16] In an RCT comparing secukinumab and ustekinumab for moderate to severe plaque psoriasis, Blauvelt et al[17] demonstrated that the incidence of serious AEs was comparable between the 2 groups, with no reports of invasive fungal infections in the 334 patients exposed to secukinumab. The CLEAR study, which compared secukinumab and ustekinumab, also found no reported deep fungal disease in the 335 patients exposed to secukinumab.[18] Secukinumab exhibited a similar safety profile to ustekinumab in both studies, with common AEs being headache and nasopharyngitis.[17,18] The GESTURE study investigated the efficacy of secukinumab in 137 patients with palmoplantar psoriasis and reported a favorable profile with no reports of deep fungal disease.[19] In a subanalysis of the phase 3 study ERASURE, secukinumab was shown to have a robust and sustainable efficacy in 58 Japanese patients with moderate to severe plaque psoriasis, and there were no reports of invasive fungal infections.[20] Another subanalysis of 36 Taiwanese patients from the ERASURE study also had similar findings, with no dose relationship observed for AEs.[21] In a phase 2 study of 103 patients with psoriasis, Papp et al[22] demonstrated AE rates that were similar across different doses of secukinumab—3×150 mg, 3×75 mg, 3×25 mg, and 1×25 mg—and described no incidences of invasive fungal disease. In a phase 2 regimen-finding study of 337 patients conducted by Rich et al,[23] the most commonly reported AEs included nasopharyngitis, worsening psoriasis, and upper respiratory tract infections, but there were no reported deep fungal infections.

Our search also resulted in studies specific to the treatment of psoriatic arthritis (PsA) with secukinumab.

IL-17 Inhibitor Exposure Data Summary

Reference	Year	Country	IL-17 Inhibitor	Patients Exposed to IL-17 Inhibitor, n	Data Source	Reported Deep Fungal Infections, n
Bissonnette et al[12]	2017	International	Secukinumab	340	Extension	0
Bissonnette et al[13]	2018	International	Secukinumab	168	Extension	0
Blauvelt et al[14]	2015	International	Secukinumab	118	RCT	0
Paul et al[15]	2015	International	Secukinumab	121	RCT	0
Bagel et al[16]	2017	United States	Secukinumab	51	RCT	0
Blauvelt et al[17]	2017	International	Secukinumab	334	Clinical trial	0
Thaci et al[18]	2015	International	Secukinumab	335	Clinical trial	0
Gottlieb et al[19]	2017	International	Secukinumab	137	RCT	0
Ohtsuki et al[20]	2014	Japan	Secukinumab	58	RCT	0
Wu et al[21]	2017	Taiwan	Secukinumab	36	RCT	0
Papp et al[22]	2013	International	Secukinumab	103	RCT	0
Rich et al[23]	2013	International	Secukinumab	337	RCT	0
McInnes et al[9]	2014	International	Secukinumab	28	RCT	0
Kavanaugh et al[24]	2017	International	Secukinumab	404	RCT	0
McInnes et al[25]	2015	International	Secukinumab	299	RCT	0
Nash et al[26]	2018	International	Secukinumab	277	RCT	0
Sticherling et al[27]	2017	International	Secukinumab	105	Clinical trial	0
Braun et al[28]	2017	International	Secukinumab	200	RCT	0
Marzo-Ortega et al[29]	2017	International	Secukinumab	145	RCT	0
Pavelka et al[30]	2017	International	Secukinumab	150	RCT	0
Callis Duffin et al[31]	2017	United States	Ixekizumab	204	RCT	0
Gordon et al[32]	2016	International	Ixekizumab	2334	RCT	0
Saeki et al[33]	2017	Japan	Ixekizumab	91	Clinical trial	0
Reich et al[34]	2017	International	Ixekizumab	136	Clinical Trial	0
Zachariae et al[35]	2018	International	Ixekizumab	211	Clinical trial	0
van der Heijde et al[36]	2018	International	Ixekizumab	381	RCT	0
van der Heijde et al[37]	2018	International	Ixekizumab	164	RCT	0
Nakagawa et al[38]	2016	Japan	Brodalumab	113	RCT	0
Umezawa et al[39]	2016	Japan	Brodalumab	145	Clinical trial	0
Papp et al[10]	2012	International	Brodalumab	320	RCT	0
Papp et al[40]	2016	International	Brodalumab	441	RCT	0
Papp et al[41]	2014	International	Brodalumab	181	Clinical trial	0
Yamasaki et al[42]	2017	Japan	Brodalumab	30	Clinical trial	0
Mease et al[43]	2014	International	Brodalumab	113	RCT	0
Martin et al[44]	2013	International	Brodalumab	30	RCT	0
Busse et al[45]	2013	International	Brodalumab	226	RCT	0

Abbreviation: RCT, randomized controlled trial.

McInnes et al[9] conducted a phase 2 proof-of-concept trial for patients with PsA and reported no deep fungal infections in 28 patients exposed to 10 mg/kg of secukinumab. A 2-year follow-up with the cohort from FUTURE 1, a phase 3 clinical trial, also showed no new or unexpected safety signals in 404 patients exposed to 150 or 75 mg of secukinumab, including no reports of invasive fungal disease.[24] FUTURE 2, a phase 3 clinical trial, demonstrated that the most common AE was upper respiratory tract infection in the 299 patients treated with secukinumab, but there were no recorded invasive fungal infections.[25] In FUTURE 3, 277 patients were treated with secukinumab, with 14 nonserious candida infections but no observed deep fungal infections.[26] A study comparing secukinumab to fumaric acid esters reported that 6 of 105 patients treated with secukinumab also experienced superficial candidiasis, but there were no reports of deep fungal disease.[27]

Secukinumab also has been used in the treatment of ankylosing spondylitis in a phase 3 RCT (MEASURE 1) in which 4 cases of superficial candidiasis were reported (0.7 cases per 100 patient-years of secukinumab) that were all resolved with standard antifungal therapy.[28] In MEASURE 2, a 5-year phase 3 RCT, 145 patients were treated with secukinumab for ankylosing spondylitis, with common AEs including nasopharyngitis, diarrhea, and upper respiratory tract infection, but there were no reports of any invasive fungal infections.[29] MEASURE 3 also demonstrated similar results in which no invasive fungal infections were observed.[30]

Risk for Deep Fungal Infection With Ixekizumab—The queried studies included 7 RCTs or clinical trials of 3523 patients with psoriasis or other inflammatory conditions, with follow-up ranging from 12 to 52 weeks. In UNCOVER-A, a phase 3 RCT of the pharmacokinetics and safety of ixekizumab, 204 patients were randomized to a prefilled syringe or autoinjector; 48% of patients experienced AEs, but no invasive fungal infections were observed.[31] In an analysis of 3 phase 3 trials of ixekizumab including a total 2334 patients treated with ixekizumab from UNCOVER-1, UNCOVER-2, and UNCOVER-3, oral candidiasis frequently was reported, but no candidal infections met criteria for serious invasive infection.[32] In UNCOVER-J, a 52-week phase 3 open-label trial of Japanese patients, 91 patients were treated for plaque psoriasis, erythrodermic psoriasis, or generalized pustular psoriasis using ixekizumab; the most common AEs included allergic reactions and injection-site reactions. One case of oral candidiasis was reported, but there were no reported cases of invasive fungal infections.[33] A comparison of ixekizumab vs ustekinumab from the IXORA-S trial demonstrated no substantial differences in AEs between the two, and no cases of deep fungal infections were reported. The most common AE between the 2 groups was nasopharyngitis.[34] An open-label extension over 4 years of a phase 2 RCT treated 211 patients with either 120 or 80 mg of ixekizumab; 87% of patients had experienced at least 1 AE, and all AEs were considered mild or moderate in severity, with no invasive fungal disease.[35]

Our search also resulted in 1 study specific to the treatment of PsA with ixekizumab. A phase 3, 52-week study of patients treated with ixekizumab for PsA observed 2 incidences of oral candidiasis and nail candida infections, but no invasive fungal infections were reported.[36]

We also found 1 study of ixekizumab used in the treatment of ankylosing spondylitis. COAST-V was a phase 3 RCT of patients treated for ankylosing spondylitis in which 164 patients were treated with ixekizumab; no serious AEs were recorded, including 0 deep fungal infections. The most common AEs observed were nasopharyngitis and upper respiratory tract infections.[37]

Risk for Deep Fungal Infection With Brodalumab—The queried studies included 9 RCTs and 3 clinical trials along with extension trials of 1599 patients with psoriasis or other inflammatory conditions, with follow-up ranging from 12 to 120 weeks. In a phase 2 RCT of Japanese patients with moderate to severe plaque psoriasis, 113 patients were treated with 70, 140, or 210 mg of brodalumab, and the most common AEs were nasopharyngitis, diarrhea, and upper respiratory tract inflammation. There were no reported cases of fungal infections in the study.[38] In an open-label extension study of Japanese patients that evaluated the long-term clinical safety of brodalumab, 145 patients were enrolled and observed similar AEs to the RCT, with 7 patients experiencing oral candidiasis and 1 patient having skin candidiasis, but there were no observed deep fungal infections.[39] In AMG 827, which evaluated the efficacy and safety of brodalumab, 320 patients were treated, and only 2 serious AEs were reported, neither of which were deep fungal disease.[10] A phase 3 RCT conducted by Papp et al[40] (AMAGINE-1) also treated 441 patients with moderate to severe plaque psoriasis with brodalumab and observed candida infections in 9 patients that were mild to moderate and responsive to treatment, with no patients discontinuing the study. In a 120-week open-label extension study of 181 patients, Papp et al[41] reported 8% of patients experienced serious AEs, with 1 case of latent tuberculosis that led to withdrawal of treatment. A study also investigated the efficacy and safety of brodalumab in 30 patients with generalized pustular psoriasis or psoriatic erythroderma and observed 2 cases of mild candida infections that resolved with treatment. There were no reports of invasive fungal disease.[42]

Our search also resulted in studies of brodalumab used in the treatment of PsA and nonpsoriatic diseases. In one phase 2 RCT, 113 patients with PsA were treated with 140 mg, 280 mg, or combined doses of brodalumab, with the most common AEs being nasopharyngitis, upper respiratory tract infection, and diarrhea, but there were no reports of deep fungal infection.[43] In a phase 1b trial of patients with methotrexate-resistant rheumatoid arthritis treated with brodalumab, common AEs

reported included headache, cough, and abdominal pain, with only 1 case of oral candidiasis that was determined not to be drug related.[44] Finally, an RCT of patients with moderate to severe asthma treated 226 patients with brodalumab and reported a greater incidence of oral candidiasis in treatment groups compared with placebo (3.5% vs 0%) but saw no instances of invasive fungal infection.[45]

IL-12/IL-23 Inhibitor

Risk for Deep Fungal Infection With Ustekinumab—The queried studies included 4 RCTs of 954 patients with psoriasis treated with ustekinumab (eTable).[46-49] Within these trials, there were no reported cases of serious infections involving deep fungal organisms during the stated follow-up period. The literature search also found long-term safety data from the ACCEPT and PHOENIX trials that included 5437 patients with psoriasis treated with ustekinumab.[66,67] There also were no demonstrated incidences of invasive fungal disease in these studies, with most cases of infection being common bacterial or viral infections.

IL-23 Inhibitors

Risk for Deep Fungal Infection With Risankizumab, Guselkumab, and Tildrakizumab—The queried studies included 16 RCTs or clinical trials for psoriatic patients treated with IL-23 inhibitors, including 5 with risankizumab,[50-54] 9 with guselkumab,[55-63] and 2 with tildrakizumab.[64,65] Within these trials there were no observed cases of serious infections with deep fungal disease.

COMMENT

Our literature review has demonstrated that there does not appear to be an increased incidence of deep fungal infections for patients treated with IL-17, IL-12/IL-23, or IL-23 inhibitors for psoriatic disease. All of the reviewed studies found no cases of invasive fungal infections for patients with psoriasis treated with secukinumab, ixekizumab, brodalumab, ustekinumab, risankizumab, guselkumab, or tildrakizumab. Patients with other inflammatory conditions, such as ankylosing spondylitis, rheumatoid arthritis, and asthma, also did not appear to show an increased incidence of deep fungal disease.

Although these results show promising safety data for the use of these biologic therapies in treating inflammatory conditions, caution still is warranted, as these medications still are relatively new, with FDA approvals within the last 5 years. Safety data among different study populations also cannot be derived without further investigation, and much of the available literature is limited in long-term data. More extended trials or registry data from a large, broadly representative cohort are necessary to establish the long-term safety and risk for deep fungal infections with IL-17 and especially the newer IL-23 inhibitors.

A small percentage of patients from the reviewed literature did develop superficial candidiasis. This outcome can be expected, as the central role of IL-17 and IL-23 has been recognized in immunologic protection against infections, specifically against fungi.[11] Because all of the fungal infections reported for patients on IL-17 inhibitors were superficial candidiasis, guides for practical management and treatment should be implemented to standardize future research and care. A proposed screening algorithm for patients on these biologic therapies involves safety monitoring, including inspection of the oral cavity, folds, and genitals, along with inquiring about symptoms such as burning, dysgeusia, and dysuria.[68] If infection is suspected, confirmation by culture, molecular method, or optimally with esophagoscopy can be performed, and appropriate treatment may be initiated.[68] Patients with candida infections of the oral cavity, folds, or genitals can be placed on topical therapy such as nystatin, amphotericin B, ciclopirox, or other azoles, while those with infections of the esophagus can be started on oral fluconazole.[68]

Although there were no reported cases of deep fungal infections, the theoretical risk for developing one while on IL-17 and IL-23 inhibitors may warrant further screening prior to beginning therapy. The TNF inhibitors approved for the treatment of psoriasis currently contain a black box warning for risk for disseminated and extrapulmonary histoplasmosis, coccidioidomycosis, blastomycosis, and other invasive fungal infections, which may highlight the importance of thorough evaluation and awareness of endemic areas for patients on biologics. Prior to initiating treatment with TNF inhibitors, current suggestions involve performing a thorough examination along with keeping a high index of suspicion for invasive fungal infections in patients who live in or have traveled to endemic regions.[69]

Screening for invasive fungal infections for patients on TNF inhibitors involves questioning about potential exposures, such as demolition of old buildings, bird roosts, or spelunking.[70] Serologies or antigen testing can be used routinely, but as these tests are insensitive, empiric antifungal therapy should be initiated if there is high enough clinical suspicion.[71] Currently, there are no clinical guidelines regarding fungal screening and initiation of IL-17 and IL-23 inhibitors for treatment of psoriasis and other inflammatory conditions, but careful stewardship over using these effective medications should still be practiced.

Upon review of the available safety data on the use of IL-17 and IL-23 inhibitors for the treatment of psoriasis and other inflammatory conditions, there does not appear to be an increased incidence of deep fungal infections. Physicians, however, should still be cautiously optimistic in prescribing these medications, as there is a theoretical risk for infection for all patients on biologics. A high index of suspicion for patients presenting with symptoms of fungal infections should be maintained, and

appropriate diagnosis and management should be initiated if they do occur.

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APPENDIX

eTABLE. IL-12/IL-23 and IL-23 Inhibitors Exposure Data Summary

Reference	Year	Country	Biologic	Patients Exposed to Biologic, n	Data Source	Reported Deep Fungal Infections, n
Igarashi et al[46]	2012	Japan	Ustekinumab	126	RCT	0
Krueger et al[47]	2007	International	Ustekinumab	256	RCT	0
Leonardi et al[48]	2008	International	Ustekinumab	511	RCT	0
Tsai et al[49]	2011	International	Ustekinumab	61	RCT	0
Gordon et al[50]	2018	International	Risankizumab	598	RCT	0
Krueger et al[51]	2015	International	Risankizumab	31	RCT	0
Ohtsuki et al[52]	2019	Japan	Risankizumab	113	RCT	0
Papp et al[53]	2017	International	Risankizumab	126	Clinical trial	0
Reich et al[54]	2019	International	Risankizumab	301	Clinical trial	0
Blauvelt et al[55]	2017	International	Guselkumab	329	RCT	0
Deodhar et al[56]	2018	International	Guselkumab	100	RCT	0
Gordon et al[57]	2015	International	Guselkumab	825	RCT	0
Langley et al[58]	2018	International	Guselkumab	135	Clinical trial	0
Nemoto et al[59]	2018	Japan	Guselkumab	20	RCT	0
Ohtsuki et al[60]	2018	Japan	Guselkumab	128	RCT	0
Reich et al[61]	2017	International	Guselkumab	496	RCT	0
Reich et al[62]	2019	International	Guselkumab	534	Clinical trial	0
Terui et al[63]	2018	Japan	Guselkumab	25	RCT	0
Papp et al[64]	2015	International	Tildrakizumab	309	RCT	0
Reich et al[65]	2017	International	Tildrakizumab	617	RCT	0

Abbreviation: RCT, randomized controlled trial.