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IL-23 blockade in a patient with psoriasis and *Toxoplasma gondii* reactivation history: Case report and review

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Abstract

Toxoplasma gondii infection can lead to severe disease in immunocompromised patients. Current systemic therapies in psoriasis rely on varying degrees of immunomodulation. Few studies have investigated the involvement of key cytokines targeted by these novel therapies (interleukins 23 and 17) in the immune response against *T. gondii*. We describe a case of a patient with severe plaque psoriasis and a history of frequent ocular toxoplasmosis reactivations successfully treated using anti-IL-23 therapy without *T. gondii* reactivation. A brief scoping review of the literature is presented to address current data on toxoplasmosis and biologic therapy for psoriasis.

Keywords

Psoriasis, toxoplasmosis, interleukin-23, interleukin-12, risankizumab

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Introduction

In the past decades, many targeted monoclonal antibodies have been used to treat moderate-to-severe psoriasis and its associated comorbidities with significant efficacy, including anti-tumour necrosis factor (TNF), anti-interleukin (IL)-17, anti-IL-12/23 and anti-IL-23.[1] However, those therapies can confer varying degrees of immunomodulation.[2–4] Toxoplasmosis is caused by the obligate intracellular protozoan parasite *Toxoplasma gondii.* Although usually mildly symptomatic, this pathogen can cause severe disease in immunocompromised patients.[5] We describe a case of refractory severe plaque psoriasis treated with risankizumab in a patient with a history of frequent ocular toxoplasmosis reactivations and treatment considerations in this clinical context.

Case report

We report the case of a 60-year-old male with extensive plaque psoriasis who previously failed multiple therapies, including topicals, methotrexate before his toxoplasmosis infection, acitretin and phototherapy. Baseline Psoriasis Area and Severity Index was 27 and the body surface area was 30%. His medical history is significant for recurrent episodes of right eye uveitis due to toxoplasmosis reactivation starting previously to 2004 and presenting the latest episode in June 2022 for a total of six episodes including three in the last 2 years. Review of symptoms was otherwise negative. A multidisciplinary approach, including infectious disease and ophthalmology consultations, was performed to assess the risk and management of toxoplasmosis reactivation if a biologic agent was to be initiated. The ophthalmology physician followed up closely on the ocular condition while infectious disease suggested possible prophylaxis with sulfamethoxazole-trimethoprim (TMP-SMX) as well as serial toxoplasmosis whole blood polymerase chain reaction (PCR) for detection of reactivation and systemic involvement. A shared decision was to initiate risankizumab, an anti-IL-23 biologic agent. Patient declined

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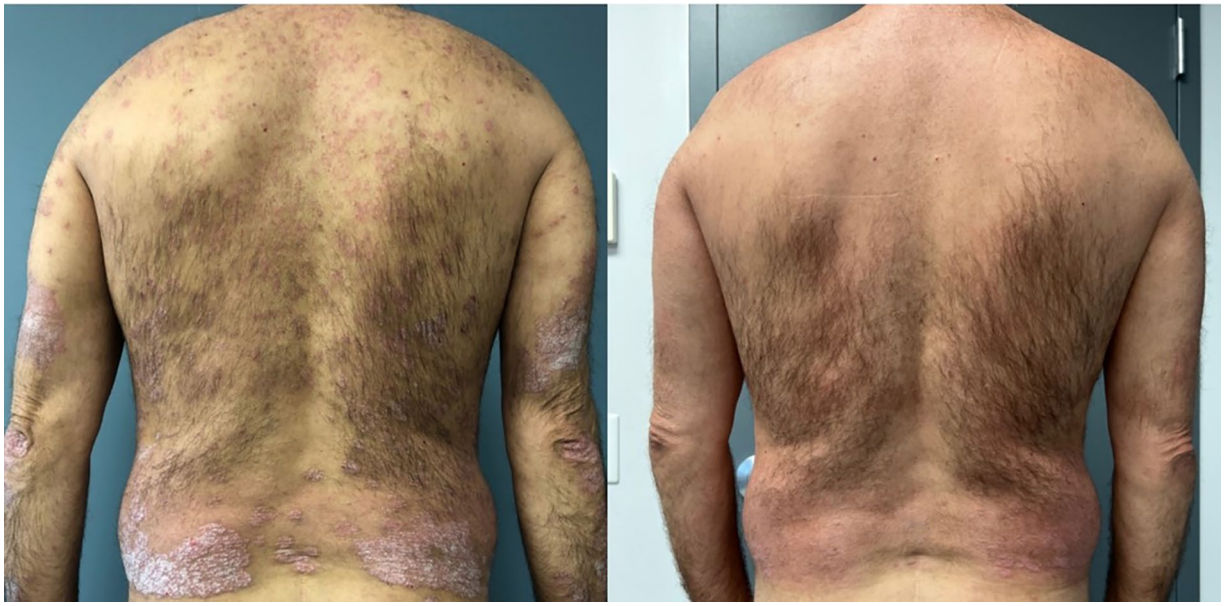

Figure 1: On the left is shown the extension of the patient's plaque psoriasis before treatment in April 2022. On the right is shown the patient's response to Risankizumab in July 2023.

TMP-SMX prophylaxis due to the risk of possible toxicities. After initiation of treatment, psoriatic lesions greatly improved (almost clear) (Figure 1). Monthly *T. gondii* DNA PCR testing and additional ophthalmologic follow-up between January 2023 and October 2024 showed no signs of reactivation.

Discussion

Literature addressing the role of IL-23 in toxoplasmosis immunity is limited and controversial. This case emphasizes the importance of understanding the cytokines targeted for psoriasis treatment and their respective role in various types of infections including intracellular protozoans (Table 1).

In addition to IFN-γ, both IL-12 and IL-23 have previously been hypothesised to have a role in the immune response against *T. gondii*.[21,22] Both share the p40 subunit, but differ on the second subunit, p35 and p19 respectively. Multiple immune pathways have been identified in acute toxoplasmosis, including NK-cell and T-cell responses dependent on the p40 subunit for the development of Th1-driven immunity to *T. gondii*.[23,24] NK-cell response via IFN-γ in acute toxoplasmosis infection was found to be dependent on both IL-12 and IL-23 in vivo using cytokine specific knockdown mice models (IL-12p70, IL-12p35 and IL-23p19).[25] Furthermore, toxoplasmosis naïve NK-cells were not intrinsically different from previously sensitized NK-cells suggesting that extrinsic immune pathways were more likely to explain the unique response to secondary *T. gondii* infection.[25] In these models, T-cells were not necessary for NK-cells to mount an IFN-γ driven immune response.[25] IL-12 blockade using anti-IL-12p40 induced a complete absence of NK-cell IFN-γ production while anti-IL-12p70 showed an incomplete reduction in the immune response suggesting two independent mechanisms. Interestingly, anti-IL-23p19 treatment reduced the absolute number of NK-cells but did not reduce the frequency of IFN-γ^+ NK-cells nor their production of IFN-γ.[25] The same author also demonstrated that the maturation of NK-cells was reduced, by decreasing KLRG1$^+$ rates, in the absence of IL-23 (KO) or with anti-IL-23p19 treatment but the impact of this diminished maturation on NK-cell capacities to control *T. gondii* reactivation was uncertain.

Table 1. Number of reported toxoplasmosis infections in the literature under biologic psoriasis treatments.

Treatment	Number of toxoplasmosis cases reported to date
Anti-TNF	$N = 4$[6,7]
Anti-IL-12/23 ustekinumab	$N = 7$[8–11]
Anti-IL-17	
Ixekizumab	$N = 1$[12]
Secukinumab	$N = 5$[13,14]
Brodalumab	$N = 0$[15]
Bimékizumab	$N = 0$[16,17]
Anti-IL-23	
Risankizumab	$N = 0$[18]
Guselkumab	$N = 0$[19]
Tildrakizumab	$N = 0$[20]

TNF, tumour necrosis factor; IL, interleukin.

In terms of the T-cell-driven immune response to *T. gondii*, p40-deficient and p35-deficient mice's splenocytes showed absent IFN-γ production, highlighting the fundamental role of IL-12, but not IL-23 alone, in the production of IFN-g. In this model, the addition of IL-12, but not IL-23, to p40 or p35-deficient mice increased IFN-g production. However, the addition of IL-23 to p40-deficient mice reduced the acute parasite burden 7 days post-infection suggesting a limited role of IL-23 in acute toxoplasmosis clearance that is not dependent on IFN-γ but only demonstrated in the absence of IL-12.[21] Thus, using an anti-IL-23 treatment had potentially less to no theoretical infectious risks in a patient with a history of frequent toxoplasmosis reactivation compared to anti-IL-12/23 treatments. This has some clinical correlates as one case of disseminated and some cases of localized toxoplasmosis has been described in a patient on ustekinumab.[8–11]

As for other cytokines targeted in psoriasis, TNF and IL-17 blockade have a different theoretical infectious risk.[26] TNF-α blockade has been associated in clinical trials and registries with an increased risk of latent tuberculosis reactivation and rare toxoplasmosis as it is implicated in *T. gondii* immunity in vitro.[6,27,28] As for IL-17A, it is overexpressed in active toxoplasmosis but its impact is still unclear because of its dual role in balancing between its pro-inflammatory effect helping to control the infection and its neuroprotective, homeostasis maintenance and cell apoptosis prevention properties.[29] In IL-17RA deficient mouse, better survival and diminished tissue destruction after *T. gondii* infection as well as allowing increased production of IFN-γ and IL-10 was described.[30] On the other hand, IL-17R$^{(-/-)}$ mouse had normal adaptative immunity against *T. gondii* but presented an increased mortality in the early stages of the disease.[31] In addition, there were cases of acute toxoplasmosis described in patients receiving anti-IL-17a biologic agents.[12–14]

When investigating the infectious risk in anti-IL-23 treated patients in clinical trials and real-world evidence studies, no opportunistic infections or increased latent tuberculosis reactivation were identified in a phase III programme of guselkumab with a follow-up spanning up to 5 years,[19] and risankizumab whether prophylaxis was given or not during the course of treatment.[18]

As for other advanced small oral molecules used to treat psoriasis, namely apremilast and deucravacitinib, their profile in this context is different. For deucravacitinib, inhibiting TYK2 decreases type 1 IFN and its use has been associated with rare cases of latent tuberculosis and one case of active tuberculosis in psoriasis phase 3 studies.[32] Apremilast has a good infectious safety profile in phase 3 and real-world studies but opportunistic infections, although at very low rates and comparable to placebo, were described in the literature.[33]

In conclusion, warranted analysis of the existing, albeit limited, literature focusing on the involvement of IL-23 in the immune response against *T. gondii* primary and secondary infections suggests the safety of the IL-23 blockade in chronic toxoplasmosis infection. As for the other biologics used to treat psoriasis, anti-TNF and anti-IL-12/23 are contraindicated or should be used with great caution in these patients while data is limited in anti-IL-17 therapies with rare cases described.

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Patient consent

Patient provided consent for medical distribution of clinical history and anonymized pictures.

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