

## BRIEF ARTICLES

**Safe use of Interleukin-17 Inhibitors for Psoriasis and Psoriatic Arthritis in Two Patients with a History of Lymphoproliferative Disease**Stephen Sansone<sup>1</sup>, Yasmin Amir, MD<sup>1</sup>, Mark G. Lebwohl, MD<sup>1</sup><sup>1</sup>Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York, NY

## ABSTRACT

Psoriasis and psoriatic arthritis are chronic, inflammatory, immune-mediated diseases that affect the skin and joints, respectively. The older systemic agents that have been used to treat these conditions are associated with many side effects, including an increased risk of malignancies, specifically lymphoma. In the last few years, there has been a wave of development of novel systemic biologic therapies to target psoriasis and psoriatic arthritis. While long-term safety data is lacking, the newer therapies targeting interleukins 12, 23, and 17 reveal a much more favorable side effect profile, specifically with regards to lymphoma. Here we report two cases of patients with psoriasis and psoriatic arthritis who had histories of lymphoma, both successfully treated with an interleukin-17 inhibitor without any recurrence or worsening of lymphoproliferative disease.

## INTRODUCTION

Psoriasis and psoriatic arthritis are chronic, inflammatory, immune-mediated diseases that affect the skin and joints, respectively. In recent years, systemic agents such as methotrexate, cyclosporine, and the tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) inhibitors, have significantly improved our ability to treat psoriasis and psoriatic arthritis. However, these medications are associated with side effects and concerns for long-term risks, specifically that of an increased risk of malignancies like lymphoma.<sup>1-4</sup> Recent discovery of key components in the pathogenesis of psoriasis has led to the development of novel therapies targeting interleukins (ILs) 12, 23, and 17. Data from clinical trials for these agents reveals favorable, minimal side effect profiles.<sup>5-8</sup> As

these newer medications have only been available for limited time, further studies are needed to determine their long-term safety. Here we report two cases of patients with psoriasis and psoriatic arthritis who had histories of lymphoma, both successfully treated with an interleukin-17 inhibitor without any recurrence of lymphoproliferative disease.

## CASE PRESENTATION

**Patient 1**

A 78-year-old woman with hypertension, chronic obstructive pulmonary disease, psoriasis, psoriatic arthritis, and mycosis fungoides presented to our clinic in 2002. She was diagnosed with mycosis fungoides at that time and the disease has been well

controlled on PUVA in the years since. In 2017, her psoriatic joint pain became severe and debilitating. In light of this, the decision was made to begin systemic medication. She was not a candidate for treatment with TNF- $\alpha$  inhibitors due to her diagnosis of mycosis fungoides. In conjunction with her hematologist-oncologist, secukinumab was initiated at doses of 300mg weekly for the first five weeks, then once every four weeks thereafter. The patient is now five months into her treatment with secukinumab. At this time, she has had great improvement in her arthritis symptoms and remains free of new or worsening mycosis fungoides.

### Patient 2

A 68-year-old woman with hypothyroidism and psoriasis presented to our clinic in 2016. She had psoriasis involving her trunk, buttocks, elbows, ankles, and scalp for over 20 years. She had failed treatment with topical steroids, intralesional steroids, apremilast, and etanercept. In 2004 she was diagnosed with stage I follicular lymphoma, which was successfully treated with lymph node dissection. At the time of presentation in 2016, she had moderate to severe disease, and the decision was made to begin systemic medication. She was not a candidate for treatment with TNF- $\alpha$  inhibitors due to her history of lymphoma. After discussion with her hematologist-oncologist, secukinumab was initiated at doses of 300mg weekly for the first five weeks, then once every four weeks thereafter. The patient initially experienced a greater than 50% improvement in her psoriatic lesions. However, after nine months of therapy with secukinumab, she began to flare. At this point she was switched to brodalumab 210mg at week 0, week 1, week 2, and then every two weeks thereafter. The patient is now twelve months into her treatment with brodalumab. At this time, her skin is clear of psoriasis and

## DISCUSSION

she remains without any evidence of recurrence of lymphoma.

With a broad armamentarium of available treatment options for psoriasis and psoriatic arthritis, it becomes important to separate treatments based on safety profile in specific patient populations. Here, we report two cases in which patients with a known history of lymphoproliferative disease were safely treated with an IL-17 inhibitor. While further studies regarding long-term safety profile are necessary, our cases highlight that the IL-17 inhibitors may be both safe and effective in patients with a history of lymphoproliferative disease.

Psoriasis itself has been associated with an increased risk of lymphoproliferative disorders. This has been evidenced by multiple studies, including a cohort study by Gelfand et al. which compared adults over 65 with psoriasis to adults over 65 without psoriasis and found a three-fold increased risk of lymphoma.<sup>9</sup> As psoriasis itself is associated with an increased risk of malignancy, the interpretation of data regarding the additional risk posed by systemic therapies is challenging.

The biologic small molecules, methotrexate and cyclosporine, have both been associated with an increased risk of malignancy, specifically lymphoproliferative disease, in literature pertaining to both rheumatoid arthritis and psoriasis patients.<sup>4</sup> Importantly, however, the Psoriasis Longitudinal Assessment and Registry (PSOLAR) did not find an increased risk of malignancy, with the exclusion of non-melanoma skin cancer, in patients receiving methotrexate for psoriasis.<sup>10</sup>

The TNF- $\alpha$  inhibitors, infliximab, adalimumab, and etanercept, have all been reported to be associated with hematologic malignancy. The Food and Drug Administration (FDA) package inserts for all three medications include a Black Box Warning for the risk of malignancy, in particular highlighting lymphoma.<sup>1-3</sup> There have been numerous case reports, case series, and meta-analyses of pooled data that have suggested an increased risk of lymphoproliferative disease with the TNF- $\alpha$  inhibitors, both alone and in combination with other immunosuppressive agents. In PSOLAR data, long-term use, defined as greater than twelve months, was found to be associated with malignancy, excluding non-melanoma skin cancer.<sup>10</sup>

While the long-term safety data for the IL-17 inhibitors is lacking at this time, there is some preliminary supporting evidence for their safety with regards to malignancy. Thus far, malignancy incidence rates in patients on these biologic agents have been shown to be less than or comparable to those for the general population.<sup>11</sup>

From a molecular standpoint, multiple experiments have shown that IL-17 plays an essential role in the pathophysiology of cancer, potentially stimulating the formation of tumors via increased expression of antiapoptotic genes and therefore increased tumor cell survival.<sup>12</sup> Additionally, studies in mouse models have found that just as increases in IL-17 have been noted in tumor states, knocking out IL-17 has led to decreased tumor growth.<sup>12</sup> It may therefore be extrapolated that blocking the expression of IL-17 with biologic drugs would not only be safe in patients with malignancy, but that targeting these interleukins may one day actually play a role in decreasing tumor occurrence.

In summary, while there remains a need to further characterize the long-term safety of the new IL-17 inhibitors for the treatment of psoriasis and psoriatic arthritis, there is some preliminary evidence suggesting that these medications may be safe in patients with a history of lymphoproliferative disorders. Here, we describe two cases in which patients with a known history of lymphoproliferative disease were safely treated with IL-17 inhibitors, without evidence of recurrence of their malignancy to date.

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