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IL-17 INHIBITORS AND THE RISK OF MALIGNANCY

Introduction

The modern era of psoriasis treatment has provided dermatologists with an array of systemic medications to address this serious inflammatory skin disease. In most patients, psoriasis requires chronic treatment and management and, thus, long-term data on medication safety is of utmost importance. The risk of malignancy is a primary concern for both the prescribing dermatologist and the psoriatic patient.

Studies on commonly used systemic agents to treat psoriasis associated with malignancy have been previously reviewed.[1] For example, there have been several reports on Epstein-Barr virus-associated lymphomas in psoriasis patients treated with methotrexate. The use of cyclosporine has been associated with a 2-fold increased risk of overall malignancy, and upward of 6-fold increased risk for squamous cell carcinoma (SCC), specifically. Psoralen combined with ultraviolet A phototherapy (PUVA) has been associated with an increased risk of non-melanoma skin cancers. Tumor necrosis factor alpha (TNFα) inhibitors have also been associated with an increased risk of both SCC and lymphoma. Given their relatively recent introduction, newer biologic agents, such as IL-17 inhibitors, have had limited data regarding malignancy risk.

IL-17 inhibitors

The IL-17 family of cytokines includes IL-17A to IL-17F and is implicated in numerous aspects of immune defense and regulatory function.[2] Increased levels of IL-17 contribute to the development of psoriasis, by inducing the production of antimicrobial peptides and mediating the formation of proliferative and proinflammatory cytokines that affect keratinocyte turnover.[2] IL-17 inhibition through targeted monoclonal antibodies is an efficacious treatment approach for psoriasis, psoriatic arthritis and ankylosing spondylitis. The anti-IL-17 agents currently approved are the anti-IL-17A monoclonal antibodies secukinumab and ixekizumab, as well as the anti-IL-17 receptor monoclonal antibody, brodalumab. This article will provide a focused overview of recently published analyses on the risk of malignancy in patients with psoriasis, psoriatic arthritis (PsA) and ankylosing spondylitis (AS) treated with IL-17 inhibitors. The reader may appreciate that indirect treatment comparisons regarding the risk of malignancy between secukinumab, ixekizumab and brodalumab are challenging given the inherent differences in study design for these agents.

Risk of malignancy in patients treated with IL-17 inhibitors:

Secukinumab

The risk of malignancy in patients with psoriasis, PsA and AS treated with secukinumab from pooled data of 49 clinical trials, as well as post-marketing safety surveillance, has been recently reported.[3] This pooled analysis of 14,519 patients (10,685 psoriasis, 2,523 PsA and 1,311 AS) which represented ~24,000 patient-treated years includes patients followed up to a maximum of five years, with the mean follow up time for patients on secukinumab being 1.54 years for psoriasis, 1.96 years for PsA, and 2.03 years for AS.

The authors evaluated safety using exposure adjusted incidence rates (EAIR; number of cases of malignancy per total exposure time) to report their findings. The EAIR of malignancy was 0.85 per 100 patient treated years [95% confidence interval (CI) 0·74–0·98] in secukinumab-treated patients, corresponding to 204 patients per 23,908 patient treated years, with the most common malignancies being basal cell carcinoma (BCC) (58 cases / 23,988 patient treated years equating to an EAIR of 0.24 per 100 patient treated years), breast cancer, prostate cancer, SCC and thyroid cancer. When compared to an external reference population (United States general population), the authors found that the observed vs. expected number of malignancies from the secukinumab clinical trial data were comparable, as indicated by an SIR of 0·99 (95% CI 0·82–1·19) across indications.

A total of 242 (1.7%) clinical trial patients had a remote history of malignancy greater than 5 years prior (patients with a confirmed malignancy within the previous 5 years prior to screening were excluded, with few exceptions). From the pooled clinical trial data, 25 patients reported a recurrence of malignancy with 18 of the 25 recurrences being non-melanoma skin cancer and 3 out of 25 recurrences being melanoma. The authors also reported post-marketing surveillance data for secukinumab-treated patients (cumulative between 2014-2018). In the post-marketing surveillance analysis, they estimated a malignancy reporting rate of 0.27 per 100 patient treated years with cumulative secukinumab exposure of 285,811 patient treated years.

Category	Combined ixekizumab (N = 5898)	IR[a]
Non-melanoma skin cancer, n (%)	51 (0.9)	0.3
Basal cell carcinoma, n (%)	42 (0.7)	0.2
Squamous cell carcinoma, n (%)	12 (0.2)	0.1
Malignancies excluding NMSC, n (%)	86 (1.5)	0.5
Prostate cancer[b], n (%)	12 (0.3)	0.1
Squamous cell carcinoma, n (%)	6 (0.1)	<0.05
Invasive ducal breast carcinoma, n (%)	5 (0.1)	<0.05
Colon cancer, n (%)	4 (0.1)	<0.05
Lung cancer metastatic, n (%)	3 (0.1)	<0.05

Table 1. Malignancies in ixekizumab pooled analysis; Armstrong et al, 2020
IR incidence rate, N total number of patients, n number of patients in category, NMSC non-melanoma skin cancer
[a] Incidence rates are per 100 patient-years
[b] Calculated in men only; N = 4000 men with 11,714.2 patient-years of exposure

Ixekizumab

Safety data for ixekizumab from 13 pooled clinical trials has been recently reported, with ~17,000 patient years of ixekizumab exposure for 5,898 patients receiving at least one dose of ixekizumab for the treatment of moderate-to-severe psoriasis.[4] Of note, 2,749 patients had ≥4 years of ixekizumab exposure.

A total of 51 of 5,898 (0.9%) patients developed non-melanoma skin cancer of which 42 (0.7%) were BCC and 12 (0.2%) were SCC, resulting in an incidence rate of 0.3 for non-melanoma skin cancers (**Table 1**). The authors highlight that the incidence rate of non-melanoma skin cancers for patients treated with ixekizumab was slightly lower than the rates associated with TNFα inhibitors such as etanercept and adalimumab, as well as the IL-12/23 inhibitor, ustekinumab. Malignancies, excluding non-melanoma skin cancers, occurred in 86 of 5,898 patients (1.5%) and represented an incidence rate of 0.5. From this analysis, prostate cancer was the most reported (n=12) with an incidence rate of 0.1 per 100 patient years in male patients. The results of this pooled analysis of malignancies, other than non-melanoma skin cancers, in patients treated with ixekizumab point to similar malignancy rates

seen in other long-term studies with etanercept, adalimumab and ustekinumab.

A subsequent study by Genovese et al.[5] expanded the original pooled analysis to include ixekizumab clinical trials with data on PsA (4 clinical trials) and axial spondyloarthritis (4 clinical trials), representing a total of 8,228 patients with 20,896 cumulative patient years of ixekizumab exposure. In these analyzed clinical trial populations, the incidence rates of malignancy in ixekizumab-treated patients with arthritis were comparable to those with psoriasis only (IR ≤ 0.8).

Brodalumab

Analyses of pooled data from four clinical trials reported malignancy rates in brodalumab-treated patients with moderate-to-severe psoriasis.[6] Within this analysis, a group of 4,464 patients with a mean duration of 23.3 months of exposure and a total of 9,174 patient years of follow up was studied. The reported time-adjusted event rate for non-melanoma skin cancer was 0.6 per 100 patient years. For malignancies excluding non-melanoma skin cancer, the follow up time-adjusted event rate was 0.4 per 100 patient years, with prostate cancer being the most common. These event rates are in line with malignancy rates seen in psoriasis patients on other IL-17 inhibitor treatments.

A real-world summary based on pharmacovigilance data reported by US patients and healthcare providers from August 15, 2017, through August 14, 2019 of 2,677 brodalumab patients with a cumulative treatment exposure of 1,656 patient years during a two-year analysis was conducted in the United States.[7] The analysis of this pharmacovigilance data revealed a malignancy rate of 0.9 events per 100 patient years, of which none were deemed to be related to brodalumab.

Discussion

The lack of head-to-head randomized controlled trials comparing different IL-17 inhibitors in terms of malignancy rates is a key consideration in the interpretation of this pooled analysis data. Additionally, the mean duration of follow up in these reported analyses ranges from 1.9 years to 3.2 years. Therefore, the potential for increased rates of malignancy beyond these timepoints cannot be determined which highlights the need for patient registries and ongoing pharmacovigilance studies in real-world populations to better follow the patients outside of a clinical trial setting. Furthermore, the baseline demographics of the study populations included in these analyses do not allow us to easily translate learnings to clinical practice. For example, patients in these pooled analyses were, on average, relatively young (mean age of pooled data from trials of secukinumab: 57.8 years, ixekizumab: 45.8 years and brodalumab: 44.8 years) which may further confound malignancy risk in a population in whom de novo malignancy rates would not be expected to be high to begin with. Finally, the data from these analyses are predominantly from a Caucasian population (percentage from pooled data from trials of secukinumab: 94%, ixekizumab: 88% and brodalumab: 90%), which does not fully account for the potential risk of malignancy of IL-17 inhibitor treatment in patients of varying skin tones.

This article provided a general overview of published analyses on the risk of malignancy in IL-17 inhibitors. Psoriasis itself confers a slight increase in the development of non-melanoma skin cancers and lymphomas[8] and ongoing research continues to demonstrate an increased risk of other malignancies.

Although excluded from clinical trials, the reality of dermatology practice today is that clinicians will inevitably encounter patients with malignancies that may be recently diagnosed, remitting or relapsing. Although there have been case reports and case series on the use of IL-17 inhibitors in patients with malignancy[9], there are no large-scale studies demonstrating the use of biologics in treating psoriasis patients with active malignancies. Ultimately, the risk-benefit considerations are centered on the patient, with the need to balance the risk of progression and recurrence of malignancy with the need to treat severe and debilitating psoriasis in the hopes of improving the patient's quality of life.

The continued study of the long-term malignancy risk of IL-17 inhibitors, and other biologic molecules, will better assist clinicians in treating patients with psoriasis, PsA, AS and possibly other inflammatory conditions.

References:

1. Kaushik SB, Lebwohl MG. Psoriasis: Which therapy for which patient. Journal of the American Academy of Dermatology. 2019;80(1):27-40. doi:10.1016/j.jaad.2018.06.057

2. Berry SPD-G, Dossou C, Kashif A, et al. The role of IL-17 and anti-IL-17 agents in the immunopathogenesis and management of autoimmune and inflammatory diseases. International Immunopharmacology. 2022;102:108402. doi:10.1016/j.intimp.2021.108402

3. Lebwohl M, Deodhar A, Griffiths CEM, et al. The risk of malignancy in patients with secukinumab-ttreated psoriasis, psoriatic arthritis and ankylosing spondylitis: analysis of clinical trial and postmarketing surveillance data with up to five years of follow-up. British Journal of Dermatology. 2021;185(5):935-944. doi:10.1111/bjd.20136

4. Armstrong A, Paul C, Puig L, et al. Safety of Ixekizumab Treatment for up to 5 Years in Adult Patients with Moderate-to-Severe Psoriasis: Results from Greater Than 17,000 Patient-Years of Exposure. Dermatology and Therapy. 2020;10(1):133-150. doi:10.1007/s13555-019-00340-3

5. Genovese MC, Mysler E, Tomita T, et al. Safety of ixekizumab in adult patients with plaque psoriasis, psoriatic arthritis and axial spondyloarthritis: data from 21 clinical trials. Rheumatology. 2020;59(12):3834-3844. doi:10.1093/rheumatology/keaa189

6. Gottlieb A, Lebwohl M, Liu C, Israel RJ, Jacobson A. Malignancy Rates in Brodalumab Clinical Studies for Psoriasis. American Journal of Clinical Dermatology. 2020;21(3):421-430. doi:10.1007/s40257-020-00512-4

7. Lebwohl M, Leonardi C, Wu JJ, et al. Two-Year US Pharmacovigilance Report on Brodalumab. Dermatology and Therapy. 2021;11(1):173-180. doi:10.1007/s13555-020-00472-x

8. Mastorino L, Dapavo P, Avallone G, et al. Biologic treatment for psoriasis in cancer patients: should they still be considered forbidden? The Journal of Dermatological Treatment. Published online August 30, 2021: 1-8. doi:10.1080/09546634.2021.1970706

9. Bellinato F, Gisondi P, Maurelli M, Girolomoni G. IL-17A inhibitors in patients with chronic plaque psoriasis and history of malignancy: a case series with systematic literature review. Dermatologic Therapy. Published online February 17, 2021. doi:10.1111/dth.14889