Secukinumab: Long-term Safety and Efficacy in Psoriasis

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INTRODUCTION

Psoriasis is a chronic, immune-mediated, inflammatory skin disease characterized by erythematous and scaly plaques. The prevalence of psoriasis varies across the globe, with estimates ranging from 0.09% to 5.1% depending on the country.[1] Roughly 3% of the United States population is affected, and approximately 20-30% of those patients suffer from moderate-to-severe disease, which requires more intensive treatments than topical therapies.[2-4]

The perception of psoriasis as a disease entity has evolved over time. Initially considered to be a solely cutaneous disorder, psoriasis is now recognized as a systemic condition, with associated cardiovascular complications, inflammatory arthritis, and depression.[5,6] Poorer quality of life, specifically measured in terms of emotional health and the impact on relationships, is well documented in patients suffering from psoriasis.[7-10]

The development of targeted biologics has improved the treatment outlook of affected patients. The psoriasis area and severity index (PASI) is a commonly used tool to calculate the extent and severity of cutaneous psoriasis. Changes in PASI are the key measure by which the efficacy of therapies is assessed. A 75% improvement in PASI score has long been the established endpoint for determining treatment outcomes. As research into the pathogenesis of psoriasis has progressed, increasingly specific mediators and targeted biologics have been discovered. The success of this translational research has elevated the goals for clearing psoriasis lesions, with the PASI-90 response rate emerging as a new standard.[11]

Interleukin (IL)-17 is now recognized as a fundamental component in the pathogenesis of psoriasis. Produced by mast cells, neutrophils, and T cells, IL-17 causes inflammation through the proliferation and activation of keratinocytes, fibroblasts, and dendritic cells.[12] IL-17-producing γδ T cells have found to be significantly increased in psoriasis plaques.[13] Based on these observations, several medications directed against IL-17 have recently been developed.

Secukinumab (Novartis Pharma AG, Basel, Switzerland) is a fully human IgG1K monoclonal antibody that selectively neutralizes IL-17A. Secukinumab has demonstrated utility in the treatment of moderate-to-severe plaque psoriasis and has exhibited superior efficacy over anti-TNF and anti-IL12/23 therapies.[14-19] Histologically, biopsies taken from patients treated with secukinumab show decreased epidermal hyperplasia and decreased expression of IL-17A.[20] In this article, we review the safety and efficacy data of secukinumab from recent, large-scale clinical trials.

Treatment of Plaque Psoriasis

The CLEAR trial (ClinicalTrials.gov/NCT02074982) was performed to compare the long-term safety and efficacy of secukinumab and ustekinumab.[21] This double-blinded phase IIIb study randomized 676 patients to treatment with either secukinumab 300 mg or ustekinumab (45 mg for weight ≤100 kg and 90 mg for >100 kg). The primary objective of PASI-90 at week 16 was achieved, and the efficacy was significantly higher and sustained over 52 weeks for secukinumab versus ustekinumab (76% versus 61%; $P<.0001$) In addition, higher PASI-100 responses were seen with secukinumab (46% versus 36%; $P=.0103$). Patient-reported measures of pain, itching, and scaling also favored secukinumab. The frequency of adverse events or serious adverse events did not vary significantly between groups. The most common adverse events were nasopharyngitis, upper respiratory tract infection, and headache (consistent with those observed in previous clinical trials).

Different maintenance dosing schedules for secukinumab were examined in the phase III SCULPTURE trial (ClinicalTrials.gov/NCT01406938).[22] The SCULTPURE study measured the degree to which positive responses to secukinumab are maintained using either a dosing regimen of retreatment as needed (RAN) or the standard fixed-interval (FI) dosing every four weeks. In the RAN study arm, secukinumab 300 mg was administered only after a loss of 20% or more of maximum PASI score improvement versus baseline, plus a loss of PASI-75 response. Comparing results from the two treatment arms showed that at week 52, FI dosing maintained PASI-75 responses more effectively than RAN, highlighting the importance of regular and sustained secukinumab administration.

The SCULPTURE trial underwent a 3-year extension period, during which patients from the core study received the same double-blinded maintenance treatment of either four-week FI or RAN dosing.[23] Over this long-term period, the FI regimen

continued to demonstrate superior efficacy relative to RAN (PASI-75 responses of 83.0% and 46.6%, respectively).

During its 4th year, the SCULPTURE study transitioned to an open-label, home-administration design.[24] In an observed data analysis, the 300 mg group exhibited a PASI-75 response rate of 88.5%, PASI-90 rate of 66.4%, and PASI-100 rate of 43.5%. The average PASI improvement was 90.8%, which has consistently remained >90% over the 4-year period. Patients experienced a substantial and lasting reduction in disease symptomatology, with 70.8% indicating that they do not suffer any impact on their quality of life. The safety profile has remained favorable, without increases in adverse events over time.

The development of immunogenicity remains an important consideration in the use of biologics. Reich et al.[25] examined the immunogenicity of secukinumab over several clinical trials in subjects followed up to 60 weeks. Patients treated with secukinumab for plaque psoriasis were monitored for antidrug antibodies (ADAs) at baseline and weeks 12, 24, 52, and 60. Among 2842 patients, only 0.4% developed ADAs from treatment, demonstrating the low immunogenicity of secukinumab. Importantly, these neutralizing antibodies were scarce for patients treated with FI dosing or RAN dosing and were not correlated with a loss of efficacy. Such results show promise for secukinumab in maintaining clinical responses over time.

Treatment of Palmoplantar Psoriasis

Palmoplantar psoriasis may affect up to 40% of psoriasis patients and remains notoriously resistant to treatment.[26] The GESTURE trial (ClinicalTrials.gov/NCT01806597) evaluated secukinumab in the treatment of moderate-to-severe palmoplantar psoriasis.[27] The study randomized 205 subjects to treatment with either secukinumab 300 mg, 150 mg, or placebo. At week 16, the percentage of patients who achieved an Investigator Global Assessment (IGA) of 0 or 1 (clear or almost clear) was 33.3% in the secukinumab 300 mg group, 22.1% in the secukinumab 150 mg group, and 1.5% in the placebo group (P<.001 versus secukinumab groups).

Follow-up data at 1.5 years revealed a durable response, with 57% of patients who received secukinumab 300 mg achieving an IGA of 0 or 1.[28] The safety profile was comparable to previously reported secukinumab trials. Although lacking an active comparator, the GESTURE study demonstrated high rates of efficacy in treating palmoplantar psoriasis.

Treatment of Nail Psoriasis

Nail involvement is common in psoriasis, with a prevalence estimated at roughly 40% to 80% of psoriasis patients.[29-31] Studies have shown that over half affected patients report pain due to nail changes, with many noting restrictions in their daily activities or work as a result of the disease.[32]

The TRANSFIGURE trial (ClinicalTrials.gov/NCT01807520) examined secukinumab in the treatment of nail psoriasis.[33] Patients with moderate-to-severe plaque psoriasis and significant nail involvement were randomized to treatment with either secukinumab 300 mg, secukinumab 150 mg, or placebo. Changes in nail involvement were measured using the Nail Psoriasis Severity Index (NAPSI). At week 16, NAPSI scores improved by 45.3% in the 300 mg group, 37.9% in the 150 mg group, and 10.8% in the placebo group (P<.0001 versus secukinumab groups). The high rates of efficacy continued over time, with week 32 results showing 63.2% improvement in the 300 mg group.

Nail psoriasis has also been examined in the FUTURE-2 study (ClinicalTrials.gov/NCT01752634). (34) The trial evaluated patients with active psoriatic arthritis who were randomized to treatment with secukinumab 300 mg, 150 mg, 75 mg, or placebo. Changes in nail disease were assessed with the modified NAPSI (mNAPSI). At week 24, the 300 mg group showed 10.30% improvement in mNAPSI scores, compared to 4.85% in the placebo group (P<.01).

CONCLUSION

Phase III clinical trials have established the long-term safety and efficacy of secukinumab in the treatment of moderate-to-severe psoriasis. Treatment has been associated with a modest increase in non-serious monilial infections (1.2% with 300 mg versus 0.3% with placebo),[35] which is to be expected given that IL-17 is involved in host defense against fungal pathogens. With 4-year data now available, the clinical benefits of secukinumab have been shown to remain consistent over an extended timeframe, without increases in safety signals. No risks of malignancy, major adverse cardiac events, depression, or tuberculosis reactivation have been found. To date, secukinumab is the only IL-17A inhibitor to demonstrate these results through such prolonged follow-up. Of particular importance, secukinumab has shown to be effective in palmoplantar psoriasis, a challenging disease. The success of secukinumab reinforces the importance of IL-17A in the pathogenesis of psoriasis and the significance of selectively inhibiting this cytokine. Given its favorable safety profile, high efficacy, and monthly maintenance dosing schedule, secukinumab represents a key treatment option for patients affected by moderate-to-severe disease.

DISCLOSURES

Dr. Lebwohl is an employee of Mount Sinai which receives research funds from: Abbvie, Amgen, Boehringer Ingelheim, Celgene, Eli Lilly, Janssen / Johnson & Johnson, Kadmon, Medimmune/Astra Zeneca, Novartis, Pfizer and ViDac. Dr. Kircik receives compensation for his editorial support from JDD and serves either as consultant, speaker, or an investigator for Novartis, Eli Lilly, Amgen, Abbvie, Boehringer Ingelheim, Janssen,

Celgene, Valeant, Pfizer, Cellceutix, Promius, and Xenoport. Dr. Hashim has no conflicts.

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