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Clinical Review: Secukinumab in Psoriatic Diseases

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Clinical Review: Secukinumab in Psoriatic Diseases

INTRODUCTION

ORIGINAL ARTICLES

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Psoriasis Is a Chronic Disease: Long Term Efficacy and Safety of New Biologics Is Important

Leon H. Kircik MD

As clinicians, we tend to eagerly await new drug approvals, especially when the drug represents a new class of treatment and is likely to fulfill an unmet need. We analyze the efficacy data, wondering how the new agent may eventually benefit our patients; if study results are promising, our excitement mounts.

Increased understanding of psoriasis has led to a shift in treatments from non-specific immunosuppressants to targeted biologics. Studies in psoriasis have demonstrated minimal risk and substantial benefit. As a result, dermatologists and patients are more frequently choosing biologics as first-line treatments for moderate-to-severe disease as our biologics options have recently increased.

Cosentyx (secukinumab) is the first in a class of interleukin (IL)-17 inhibitors approved for the treatment of psoriasis and psoriatic arthritis.[1] The drug gained FDA approval for the treatment of moderate-to-severe plaque psoriasis after showing statistically significant efficacy in clinical trials compared to placebo. In addition, the safety profile was very favorable. However, not all clinical trials tell the full story, as initial efficacy and safety data from studies is for a very short period of time (typically three to four months). It is obvious that "psoriasis is a lifelong chronic disease". Therefore, we are in desperate need of long-term efficacy and safety data.

Recently, data from clinical trials up to four years of efficacy and safety have become available for Cosentyx. We now know that psoriasis patients are able to maintain their initial rates of clearance after four years of treatment.[2] In addition, no new safety concerns have been identified. Recently published research has also demonstrated efficacy of this drug in difficult to treat areas of psoriasis such as palmoplantar, nail, and scalp psoriasis from unique and separate studies[3,4] – not as sub-analyses of these special areas from pivotal study data.

What's more, Cosentyx is now additionally approved for the treatment of psoriatic arthritis (PsA). Data suggest that nearly one-third of patients with psoriasis will develop psoriatic arthritis. Unfortunately, some patients with PsA may not even receive a proper diagnosis. As dermatologists, we had for years focused on the skin signs of psoriasis, sometimes overlooking the joint symptoms. As our approach to psoriasis management has evolved, we have become more sensitive to the issue of PsA and the need for effective treatment. In clinical trials, after two years of treatment, the majority of PsA patients treated with Cosentyx maintained their ACR 20 response.[5]

Having these dual indications, moderate-to-severe plaque psoriasis and psoriatic arthritis, is important. Additionally, the dosing schedule is favorable for many patients, with initial doses given at weeks 0, 1, 2, 3, and 4, with maintenance doses provided at four-week intervals.[1] With its documented long-term efficacy and safety, Cosentyx continues to establish itself as an important treatment consideration for patients with moderate to severe plaque psoriasis and psoriatic arthritis.

In the next several pages, my colleagues and I will focus on the long-term efficacy and safety data of Cosentyx for moderate-to-severe plaque-type psoriasis as well as pivotal clinical trials that led the approval for psoriatic arthritis.

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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.

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Secukinumab: A Review of Safety and Efficacy in Psoriatic Arthritis

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INTRODUCTION

Psoriatic arthritis (PsA) is an immune-mediated, inflammatory disease of the peripheral joints, axial spine, and entheses. The frequency of PsA among patients with psoriasis has been estimated at up to 30%, corresponding to a prevalence of up to 1% in the general population in the United States and Europe, with lower numbers seen in other parts of the world based on genetic differences (eg, less commonly among Asian and African populations.)[1-3] Patients experience significant functional disability and suffer from poorer quality-of-life measures than patients with cutaneous psoriasis alone.[4-5]

Interleukin (IL)-17A has been identified as an important component of PsA pathophysiology.[6] Released by T helper 17 cells, IL-17 affects a number of cells to promote an inflammatory response. Interactions with macrophages and dendritic cells cause elevations in keratinocyte proliferation and the proinflammatory cytokines IL-1, IL-6, and tumor necrosis factor (TNF); those with endothelial cells yield thrombosis and tissue destruction; those with fibroblasts and chondrocytes cause cartilage destruction; those with osteoblasts lead to the production of RANK ligand, osteoclastogenesis, and bone erosion.[7-9] Through the upregulation of proteases, IL-17 induces the breakdown of cartilage matrices and inhibits their synthesis.[10] In PsA, affected joints have been shown to contain higher levels of IL-17+T cells, a finding that correlates with disease activity and radiographic erosion.[11] Using the inhibition of IL-17, new biologic therapies offer a means to improve the signs and symptoms of PsA.

Secukinumab (Novartis Pharma AG, Basel, Switzerland) is an IgG1K monoclonal antibody that selectively blocks IL-17A.[12] Initially approved for moderate-to-severe plaque psoriasis, secukinumab gained approval for PsA in Europe in October 2015 and in the United States in January 2016.

Prior to secukinumab, the treatment for severe PsA centered on biologic disease-modifying antirheumatic drugs such as anti-TNF agents and ustekinumab. Although anti-TNF medications have greatly improved the therapy paradigm for PsA, additional agents are needed in order to provide options for non-responders, patients who lose response, or those who experience adverse events.

The safety and efficacy of secukinumab in the treatment of PsA have been evaluated in the FUTURE-1 and FUTURE-2 phase III clinical trials. Over 1000 patients were enrolled in these studies, comparing different dosing regimens of secukinumab to placebo. In this review, we examine the principal results from these important trials.

FUTURE-1 Clinical Trial

FUTURE-1 (ClinicalTrials.gov/NCT01392326) is a phase III study of 606 patients with active PsA.[13] Patients were initially randomized to treatment with either secukinumab 150 mg, secukinumab 75 mg, or placebo. Both treatment groups received intravenous secukinumab (10 mg/kg) at weeks 0, 2, and 4. After the first 4 weeks, patients received subcutaneous secukinumab at either 75 mg or 150 mg every 4 weeks. After 16 weeks, placebo responders (defined as those achieving a 20% reduction in tender and swollen joint counts) continued to receive placebo until week 24, whereas placebo non-responders were re-randomized to receive 150 mg or 75 mg of secukinumab. The primary endpoint was the American College of Rheumatology 20 (ACR20) response, which denotes ≥ 20% improvement in joint symptoms. These rates were examined at week 24 in patients treated with either secukinumab 150 mg, secukinumab 75 mg, or placebo.

At week 24, patients in the 150 mg group and 75 mg group showed significantly higher ACR20 responses (50.0% and 50.5%, respectively) compared to placebo (17.3%; $P<.001$ for both secukinumab comparisons). Additional clinical domains that displayed significant improvement were enthesitis, dactylitis, skin and nail disease, physical function, and quality of life. Overall, secukinumab was well tolerated, although patients did experience a modestly higher rate of candidiasis (1% with secukinumab versus 0% with placebo)—a predictable side effect given that IL-17 is involved in host defense against candida infection.

Van der Heijde et al.[14] reviewed the inhibition of radiographic progression of joint disease in FUTURE-1 patients. The

Sharp/van der Heijde score (SHS), a method for assessing erosion and joint space narrowing in the hands and feet of PsA patients, was calculated throughout the study. At week 24, both secukinumab 150 mg and secukinumab 75 mg groups demonstrated less progression of joint erosion and joint space narrowing relative to placebo ($P<.05$). The radiographic progression of disease was inhibited regardless of previous anti-TNF use.

A 2-year review of the FUTURE-1 trial highlighted the sustained efficacy of secukinumab in the treatment of PsA.[15] Results from week 104 showed ACR20 responses of 66.8% in the secukinumab 150 mg group and 58.6% in the 75 mg group (multiple imputation from weeks 28-104). Lack of efficacy was the most common reason for study dropout (5.0% among subjects receiving 150 mg, 6.9% among those receiving 75 mg, and 7.4% in the placebo group).

When patients were stratified according to previous anti-TNF therapy, responses were higher in patients who were anti-TNF-naïve. In the secukinumab 150 mg group, anti-TNF-naïve patients achieved an ACR20 rate of 75.2% versus 48.0% in patients with previous anti-TNF exposure. In the 75 mg group, ACR20 rates were 63.7% and 46.9%, respectively. Both groups experienced an inhibition of joint damage, with radiographic analyses showing an absence of disease progression in 84.3% of patients in the secukinumab 150 mg group and 83.8% of patients in the secukinumab 75 mg group. No new safety signals were identified over the extended follow-up period.

Three-year data from the FUTURE-1 trial has recently been presented.[16] Of the original 606 patients, 435 patients have completed assessments up to week 156. Statistical analyses used multiple imputation for binary variables. At week 156, ACR 20 responses rates were 76.8% in the 150 mg group and 65.2% in the 75 mg group. Previous TNF treatment continues to demonstrate an effect on responses; in the 150 mg group, ACR20 rates were 81.0% for anti-TNF-naïve patients and 61.5% for anti-TNF-exposed patients. In the 75 mg group, ACR20 rates were 67.3% and 55.6% for anti-TNF-naïve and anti-TNF-exposed patients, respectively. Adverse events have been consistent with those previously reported.

FUTURE-2 Clinical Trial

The FUTURE-2 trial (ClinicalTrials.gov/NCT01752634) expanded upon the dosing regimens of the FUTURE-1 study. Three hundred ninety-seven patients were evenly randomized to receive either subcutaneous secukinumab 300 mg, 150 mg, 75 mg, or placebo once weekly until week 4 and then every 4 weeks afterwards.[17] At week 16, patients were classified as either responders or non-responders based on whether ≥20% improvement in tender and swollen joints had been achieved. Patients receiving placebo were re-randomized to either secukinumab 300 mg or 150 mg at week 24 (in responders) or at week 16 (in non-responders). The primary endpoint was ACR20 response at week 24.

Week 24 results showed response rates of 54% in the 300 mg group ($P<.0001$ versus placebo), 51% in the 150 mg group ($P<.0001$ versus placebo), 29% in the 75 mg group ($P=.0399$ versus placebo), and 15% in the placebo group. Significant improvements in physical function and quality of life occurred. Candida infections were reported in 11 subjects, all of whom had been part of secukinumab treatment groups; cases were mild-to-moderate and did not lead to study discontinuation.

Similar to the FUTURE-1 trial, 2-year data from the FUTURE-2 trial demonstrated long-term safety and efficacy in the treatment of PsA.[18] The ACR20 responses were 69.9% in the 300 mg group, 64.7% in the 150 mg group, and 50.1% in the 75 mg group (multiple imputation). The ACR50 responses were 50.8% in the 300 mg group, 36.2% in the 150 mg group, and 28.2% in the 75 mg group.

Dactylitis and enthesitis were examined as distinct clinical manifestations in the FUTURE-2 trial. The endpoints evaluating treatment success were the proportion of patients with resolution of dactylitis or enthesitis at weeks 24 and 52, in addition to the change from baseline in dactylitis digit and enthesitis site counts at weeks 24 and 52. Of the 397 subjects randomized in the FUTURE-2 trial, 138 subjects (35%) were affected with dactylitis, and 253 subjects (64%) suffered from enthesitis.

Secukinumab administration was associated with the rapid resolution of dactylitis. At week 24, the proportion of patients who experienced a resolution of dactylitis was significantly greater in the 300 mg group (56.5%) and 150 mg group (50.0%) relative to placebo (14.8%; $P<.01$ versus secukinumab). These results were sustained over a 52-week period, with both treatment groups demonstrating >60% resolution at that time. Measuring the dactylitis count at week 24, a significant reduction in affected digits was seen in the 300 mg group (-2.56) compared to placebo (-0.97; $P<.05$), although statistically significant differences were not reached in the other treatment groups.

Enthesitis also showed high rates of resolution with secukinumab treatment. At week 24, 48.2% of affected patients in the 300 mg group reached disease resolution ($P<.01$ versus placebo), along with 42.2% in the 150 mg group ($P<.05$ versus placebo). These rates remained largely stable over the 52-week period. Of note, the treatment improvements in enthesitis and dactylitis were observed regardless of baseline disease severity.

CONCLUSION

Taken together, the results from FUTURE-1 and FUTURE-2 demonstrate the ability of secukinumab to significantly ameliorate the signs and symptoms of PsA over long-term periods. Clinical

improvements have been observed in both anti–TNF-naïve and anti–TNF-exposed subjects, although anti-TNF-naïve patients experienced greater benefit. Additional phase III studies, including FUTURE-3 (ClinicalTrials.gov/NCT01989468), FUTURE-4 (ClinicalTrials.gov/NCT02294227), and FUTURE-5 (ClinicalTrials.gov/NCT02404350), are planned in order to further assess dosing regimens and patient outcomes. Given the increasingly recognized role of IL-17A in PsA, secukinumab represents an important therapeutic agent in treatment algorithms.

DISCLOSURES

Dr. Papp has been a consultant and speaker and has served on steering committees and advisory boards and has received research grants from Novartis. Dr. Mease has served as a consultant and speaker and has received research grants from Novartis. Dr. Hashim has no conflicts.

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