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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