Secukinumab in the Treatment of Palmoplantar, Nail, Scalp, and Pustular Psoriasis

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Introduction

Interleukin (IL)-17A is a key molecule in the T helper (Th) 17 pathway, and it plays a critical role in the pathogenesis of psoriasis as well as a number of other immune-mediated diseases, such as psoriatic arthritis, rheumatoid arthritis, and ankylosing spondylitis.[1,2] Secukinumab is a human monoclonal immunoglobulin G (IgG) antibody that blocks the IL-17A ligand. In Phase 2 and 3 studies, secukinumab has been shown to be highly efficacious in treating moderate-to-severe psoriasis, with early onset action, sustained effect, and an acceptable safety profile.[3–5] It is critically important to investigate the role of secukinumab in the treatment of specialized regions of the body and in other psoriasis phenotypes. In this article, the authors examine the clinical evidence for secukinumab in the treatment of palmoplantar, nail, scalp, and pustular psoriasis.

Palmoplantar Psoriasis

Palmoplantar psoriasis is plaque psoriasis involving the palms and soles. Studies have show that up to 40 percent of patients with plaque psoriasis have some form of palmoplantar involvement.[6] Palmoplantar psoriasis is

TABLE 1. Palmoplantar Investigator's Global Assessment (ppIGA)	
0 = Clear	No signs of psoriasis, postinflammatory hyperpigmentation may be present
1 = Almost clear/minimal	Coloration: normal to pink Thickening: none Scaling: none to minimal focal
2 = Mild	Coloration: pink to light red Thickening: just detectable to mild Scaling: predominantly fine scaling
3 = Moderate	Coloration: dull to bright red, clearly distinguishable Thickening: clearly distinguishable to moderate Scaling: moderate
4 = Severe	Coloration: bright to deep dark red Thickening: severe with hard edges Scaling: severe/coarse covering almost all/all lesions, numerous fissures

associated with disproportionately greater pain, functional limitations, and significant impairment of health-related quality of life.[7] Compared to plaque psoriasis involving other regions, those with palmoplantar psoriasis suffer from more discomfort and disability.[8]

It was generally recognized that palmoplantar psoriasis poses a treatment challenge.[9] Therapies that achieve a certain level of response in other parts of the body often perform relatively poorly in the palmoplantar regions. Patients with palmoplantar involvement but little plaque psoriasis elsewhere on the body are less likely to participate in pivotal trials for new systemic therapies because these trials usually require a body surface area (BSA) of 10 percent or greater.

Few trials have examined the effect of systemic therapies on palmoplantar psoriasis.[10,11] These studies uniformly showed that the currently available systemic medications yield lower efficacy in palmoplantar psoriasis than in generalized psoriasis. Janagond et al[11] performed a head-to-head study comparing efficacy of 0.4mg/kg/week of methotrexate (or 28mg/week in a 70kg patient) to that of acitretin 0.5mg/kg/day (or 35mg/day in a 70kg patient). In this study where 111 patients were randomized to either methotrexate or acitretin, the primary endpoint was the proportion of patients achieving 75-percent improvement or greater on the palmoplantar Psoriasis Area and Severity Index (PPPASI 75). At Week 12, 24 percent of patients in the methotrexate group achieved PPPASI, as compared to eight percent in the acitretin group (p=0.029). Thus, 28mg/week of methotrexate appears to be significantly superior to 35mg/day of acitretin in improving palmoplantar psoriasis in the short-term.

Infliximab was among the first biologics evaluated for its efficacy in the treatment of palmoplantar psoriasis. In a small, randomized, controlled trial, 24 participants were randomized to receive infliximab 5mg/kg at Weeks 0, 2, and 6 versus placebo. At Week 14, 33 percent in infliximab achieved modified PPPASI 75 versus eight percent in placebo (p=0.317).[10]

Study design and study population: The GESTURE study evaluating secukinumab in palmoplantar psoriasis. The investigational program for secukinumab for palmoplantar psoriasis included GESTURE, a double-blind, randomized, placebo-controlled, parallel-group multicenter Phase 3b study. The primary objective of the study was to assess the percentage of patients achieving palmoplantar psoriasis Investigator's Global Assessment (ppIGA) score of 0/1 (i.e., clear or almost clear/minimal and a reduction of at

least 2 points from baseline on the ppIGA scale) at Week 16 (Table 1). In this study, 205 patients were randomized to secukinumab 300mg, secukinumab 150mg, and placebo, with primary endpoint evaluated at Week 16. After 16 weeks, the non-responders from the placebo group are then randomized to secukinumab 300mg, secukinumab 150mg, and placebo. The study follows up with participants until Week 140.

The inclusion criteria for the study are as follows: having chronic moderate-to-severe palmoplantar psoriasis with a ppIGA score of 3 or greater on a 5-point scale at baseline; one or more psoriasis plaques outside of the palms and soles; and psoriasis inadequately controlled by topical treatment, phototherapy, and/or systemic therapy. The study excluded other forms of psoriasis such as pustular psoriasis or palmoplantar pustulosis.

Overall, the baseline characteristics across the study groups were well balanced in the GESTURE study. The patients averaged approximately 50 years of age with males comprising between 50 to 59 percent of the study group population. The mean body weight was approximately 84kg. With regard to baseline ppIGA score, the secukinumab 150mg group had a relatively greater proportion of those with severe disease compared to the placebo and secukinumab 300mg group. In addition, the proportion of patients with prior exposure to biologic psoriasis therapy was lower in the secukinumab 300mg group (9%) compared to secukinumab 150mg group (13%) and the placebo (13%).

Results: The GESTURE study evaluating secukinumab in palmoplantar psoriasis. The GESTURE study is the largest randomized, double-blind, placebo controlled trial of a biologic in palmoplantar psoriasis to date.[12]

The primary endpoint of assessing two doses of secukinumab against placebo in achieving ppIGA 0/1 was met. Specifically, one-third of patients receiving secukinumab 300mg achieved clear or almost clear palms and soles at Week 16. Similar to the Phase 3 studies, efficacy of secukinuamb 300mg was numerically higher than that of secukinumab 150mg.

The secondary endpoint of assessing percentage change in ppPASI over time was also met for both doses of secukinumab. Specifically, palmoplantar disease improved by more than 50 percent in patients on secukinumab 300mg at Week 16, as compared to 35-percent improvement in those receiving secukinumab 150mg at Week 16. Both doses of secukinumab were superior to placebo in achieving palmoplantar disease improvement.

In the GESTURE study, the safety results were consistent with previous studies,[2–5] and no new safety signal was identified. In this difficult population with palmoplantar disease, secukinumab offers a new and effective treatment option.

Nail Psoriasis

The lifetime involvement of nail psoriasis can occur in up to 90 percent of patients with psoriasis.[13] Nail psoriasis is associated with significant functional impairment and psychosocial impairment.[14] In addition, studies have shown that nail psoriasis may be associated with psoriatic arthritis and may predict the onset of psoriatic arthritis in many patients.[14–16] For example, Dalbeth et al[15] showed that nails with onycholysis and hyperkeratosis at baseline were more likely to have corresponding distal phalangeal bone erosion and proliferation on magnetic resonance imaging (MRI).

Because IL-17A is known to play a critical pathogenic role in plaque psoriasis, elucidating the effect of secukinumab on nail psoriasis is of high clinical importance.[2,17]

Study design and study population: The TRANSFIGURE study evaluating secukinumab in nail psoriasis. TRANSFIGURE is a double-blind, randomized, placebo-controlled, parallel-group Phase 3b study evaluating secukinumab in patients with moderate-to-severe psoriasis with nail involvement.[18] The patients were randomized 1:1:1 to receive either secukinumab 300mg, secukinumab 150mg, or placebo up to Week 76. At Week 16, all subjects receiving placebo were re-randomized 1:1 to either 300mg or 150mg secukinumab.

The primary objective is to determine the superiority of secukinumab 300mg and 150mg over placebo by total fingernail Nail Psoriasis Severity Index (NAPSI) percent change from baseline at Week 16. The primary efficacy endpoint is the total fingernail NAPSI—the sum of NAPSI scores of all 10 fingernails. The secondary objectives included NAPSI, PASI 75, and IGA 2011 modified version (mod 2011) 0/1 response over time as well as safety and tolerability.

Patients were included in the study if they had chronic moderate-to-severe psoriasis with significant nail involvement (defined by fingernail NAPSI ≥16 and ≥4 fingernails involved). The patients also had to have psoriasis that was inadequately controlled by topical treatment and/or phototherapy and/or previous systemic therapy.

Results: The TRANSFIGURE study evaluating secukinumab in nail psoriasis. Secukinumab 300mg and secukinumab 150mg resulted in superior efficacy to placebo as measured by NAPSI percent change at Week 16 ($p<0.0001$). Specifically, the mean NAPSI percent change was -45.4 percent for secukinumab 300mg, -38.9 percent for secukinumab 150mg, and -11.2 percent for placebo.

With regard to secondary endpoints, the responses for PASI 75 and modified IGA score of clear or almost clear were significantly higher for both secukinumab 300mg (PASI 75: 87.1% and IGA 0/1: 74.0%) and secukinumab 150mg (PASI 75: 77.0% and IGA 0/1: 68.3%), compared to placebo (PASI 75: 5.1% and and IGA

0/1 3.1%) (p<0.0001). Furthermore, both doses of secukinumab also achieved significantly higher PASI 90 responses compared to placebo (72.5% in secukinumab 300mg, 54.0% in secukinumab 150mg, and 1.7% in placebo, p<0.0001). Finally, the most common adverse events that were reported across secukinumab and placebo arms were nasopharyngitis, headache, and upper respiratory tract infections. The safety profile of secukinumab in the TRANSFIGURE study is similar to that of other Phase 3 studies in plaque psoriasis using secukinumab.

It is important to note that, among prospective, placebo-controlled trials evaluating nail psoriasis, secukinumab in the TRANSFIGURE study achieved the highest efficacy at Week 16 reported to date.

Scalp Psoriasis

Scalp is usually the first site of psoriasis onset, and scalp psoriasis affects approximately 80 percent of psoriasis patients.[19–22] Scalp psoriasis is particularly associated with marked decrease in quality of life due to desquamation, psychosocial stress, and itching.[23,24]

Just as with psoriasis affecting other specialized areas, different assessment instruments are used for scalp psoriasis. Namely, the psoriasis scalp severity index (PSSI) is used to measure severity of scalp psoriasis. PSSI is similar to PASI in that it measures erythema, induration, and scaling, which are graded from 0 to 4 and multiplied by a categorical area score. The distinction is that PSSI measures scalp only. Another tool used to measure severity of scalp psoriasis is the scalp Physician's Global Assessment (PGA), which is a measurement of plaque morphology limited to scalp lesions only.

Topical treatments have been variably effective in scalp psoriasis.[20] Topical treatments have significant limitations for scalp psoriasis due partly to the thick scale in plaque psoriasis that prevents deep penetration of topical medications into the dermis. Furthermore, the itching in scalp psoriasis often results in chronic scratching and koebnerization of the lesions. Therefore, in patients with isolated but difficult-to-treat scalp psoriasis recalcitrant to topical therapies or in patients with generalized, moderate-to-severe plaque psoriasis that also involve the scalp, systemic treatments can be considered.

Systemic treatments for scalp psoriasis have included traditional agents, such as cyclosporine or methotrexate, but large, randomized, controlled trials assessing their efficacies are lacking. Apremilast has been shown to achieve a scalp PGA of clear or almost clear in 46 percent of apremilast-treated patients compared to 17 percent of patients on placebo (p<0.0001) at Week 16.[25] Biologics, such as etanercept, adalimumab, and infliximab, have shown good efficacy in clearing scalp psoriasis.[26–28]

The role of IL-17 inhibitors in scalp psoriasis had not been previously studied. In the poster by Lebwohl et al[29] at the 2015 American Academy of Dermatology meeting, the investigators presented the study design for an ongoing study assessing the efficacy and safety of secukinumab in scalp psoriasis.

In this currently ongoing, Phase 3b, multicenter, randomized, double-blind, placebo-controlled, parallel-group study, the investigators aimed to evaluate the efficacy of secukinumab 300mg compared to placebo in patients with moderate-to-severe scalp psoriasis at Week 12 with respect to PSSI 90 response rate.

A total of 94 patients across 20 study sites in the United States are randomized 1:1 to placebo or secukinumab 300mg. Adults with psoriasis were included in the study if they had chronic moderate-to-severe scalp psoriasis defined by PSSI score of 12 or greater, modified IGA of 3 or greater, and greater than 30 percent scalp surface involvement. They also had to be deemed to be candidates for systemic therapy by the investigators. The results of this study are pending and will contribute substantially to our understanding of the role of secukinumab in scalp psoriasis.

Pustular Psoriasis

Pustular psoriasis is a form of psoriasis that is characterized by sterile pustules. Pustular psoriasis can be categorized into generalized versus localized forms. Generalized pustular psoriasis (GPP) can involve most of the body and is considered a potentially life-threatening condition. Few treatment options currently exist for GPP.

Study design and study population: Secukinumab in generalized pustular psoriasis. In a study by Imafuku et al,[30] Japanese investigators evaluated the efficacy and safety of secukinumab in Japanese patients with GPP in a multicenter, single arm, open label Phase 3 study. A total of 12 patients with GPP received secukinumab 150mg at baseline, Weeks 1, 2, 3, and 4. At Week 8, patients without notable improvement based on Clinical Global Impression (CGI) were assigned to secukinumab 300mg, whereas patients with sufficient improvement remained on secukinumab 150mg every four weeks.

Results: Secukinumab in generalized pustular psoriasis. Of the 12 enrolled patients, 10 patients continued on 150mg, one patient up-titrated to 300mg at Week 8, and one patient discontinued due to protocol deviation. Primary endpoint was achieved in 10 patients with CGI evaluated as "Very much improved" (9 patients) or "Much improved" (1 patient) at Week 16. The PASI 75 response was achieved by 10 patients at Week 16. The most common adverse events were nasopharyngitis and urticaria. Two patients had experienced liver injury and upper gastrointestinal hemorrhage; no deaths were reported. This is among the few studies investigating the role of biologic agents in treating GPP. In this open-label

study, secukinumab was found to be effective in treating GPP in Japanese patients.

The role of secukinumab in the treatment of psoriasis involving specialized regions of palms and soles, nail, and scalp is continually elucidated. Its role in GPP illustrates the utility of IL-17A inhibitors for other phenotypes of psoriasis beyond plaque psoriasis. It is important to continually study IL-17 inhibitors for both their efficacy as well as monitoring their long-term safety in the various phenotypes of psoriasis.

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