Therapeutic Advances in Chronic Disease Review

Secukinumab: a review of the anti-IL-17A biologic for the treatment of psoriasis

Ther Adv Chronic Dis

2018, Vol. 9(1) 5–21

DOI: 10.1177/2040622317738910

© The Author(s), 2017.
Reprints and permissions:
http://www.sagepub.co.uk/journalsPermissions.nav

Jillian Frieder, Dario Kivelevitch and Alan Menter

Abstract: Psoriasis is a systemic inflammatory disease associated with numerous comorbidities and a profound impact on patients' quality of life. While its complex immune pathogenesis is still not fully delineated, current evidence supports a fundamental role of the T-helper-17 (TH-17) pathway and its related interleukin-17 (IL-17) cytokine. Thus, new antipsoriatic therapies have been developed to block this key cytokine and its downstream effects. Secukinumab is a fully humanized, monoclonal anti-IL-17A antibody, and the first in its class to be approved by the US Food and Drug Administration for the treatment of moderate to severe plaque psoriasis. It has also been approved for the treatment of active psoriatic arthritis and ankylosing spondylitis. Its clinical efficacy in plaque psoriasis has been well demonstrated in numerous phase II and III clinical trials. In addition, it has shown superiority in clinical trials to current biologic agents including etanercept and ustekinumab, with a safe adverse event profile. In correlation with excellent skin improvements, secukinumab is also associated with significant improvements in health-related quality of life measures. Thus, secukinumab offers the potential for equal, or improved, therapeutic effects compared with other biologics, and is a valuable addition to our current antipsoriatic armamentarium.

Keywords: biologics, Cosentyx, generalized pustular psoriasis, interleukin 17A, palmoplantar psoriasis, psoriasis, psoriatic arthritis, secukinumab

Received: 11 July 2017; accepted in revised form: 28 September 2017.

Introduction

Psoriasis is a chronic, systemic, immune-mediated disease recognized by its cutaneous manifestation of well demarcated, erythematous, scaly plaques. Numerous clinical phenotypes exist (i.e. plaque, guttate, pustular, inverse), with disease severity ranging from a few scattered plaques to extensive body surface involvement. These skin lesions, often associated with significant pruritus, stinging, and burning, cause substantial psychosocial impairment and overall decreased quality of life (QoL). Extending beyond the skin, this multisystem disease exposes patients with psoriasis to an increased risk of numerous comorbidities including, but not limited to, psoriatic arthritis (PsA), cardiovascular disease, metabolic syndrome, autoimmune conditions (i.e. inflammatory bowel disease, alopecia areata, and vitiligo), malignancies (i.e. lymphoma), and psychiatric disorders (i.e. depression, anxiety, and suicidal ideation).[1–7] Furthermore, severe psoriasis is associated with increased all-cause mortality and an average decreased life expectancy of approximately 4–5 years.[3,8] The extensive impact of psoriasis on virtually all aspects of health emphasizes the necessity for effective disease control.

Classification of psoriasis disease severity accounts for the extent of body surface involvement as well as the body regions affected. Certain areas such as the palms, soles, face, or genitals have been shown to inflict far greater QoL issues, despite smaller body surface area (BSA) involved. The majority of patients with psoriasis have mild to moderate disease (80%) compared with moderate to severe disease (20%).[6] As such, traditional therapies including topical medications, phototherapy, and systemic agents are the mainstay for the majority of patients with psoriasis. Yet, many of these treatment modalities are associated with poor patient satisfaction, in part due to patients' perception of therapeutic inefficacy,

Correspondence to:
Alan Menter
Baylor Scott and White-Division of Dermatology, 3900 Junius Street, Suite 125, Dallas, TX 75246, USA
amderm@gmail.com

Jillian Hadley Frieder
Dario Kivelevitch
Baylor Scott and White-Division of Dermatology, Dallas, TX, USA

inconvenience, and side-effect profiles.[9,10] This poses a challenge to adherence to treatment, clinical responsiveness, and QoL in patients with psoriasis.

The recent advent of antipsoriatic biologic agents over the past 16 years has elevated the standards of psoriasis treatment outcomes, and is serving the unmet needs of hundreds of thousands of patients with psoriasis. Often used as first-line treatment in moderate to severe psoriasis, biologics are also routinely used in cases of treatment failure with one or more traditional systemic therapies, intolerable adverse effects, or patients with multiple comorbidities. Updated treatment guidelines reflect the importance of initiating a biologic as initial therapy in patients with more severe disease who will inevitably fail to respond to previously implemented first-line treatments.[7] Minimizing the duration between treatment onset and acceptable clinical response contributes to increased patient satisfaction associated with biologic agents compared with traditional systemic therapies (e.g. methotrexate).[9,11] In a relatively short time span, there have been tremendous advancements in the development of biologics through the identification of key cytokines integral to the psoriasis inflammatory process.

This article will review the pharmacology and clinical data of the new anti-interleukin 17A (IL-17A) monoclonal antibody, secukinumab, primarily focusing on its use in the treatment of moderate to severe plaque psoriasis. We will also briefly discuss its use in other forms of psoriasis and PsA.

IL-17 in the pathogenesis of psoriasis

As the complex pathogenesis of psoriasis is further elucidated, newer, more targeted therapies are being developed to treat this debilitating disease. The current understanding centers on immune dysregulation, which is influenced by an intricate combination of environmental factors and genetic susceptibility. The identification of T-helper-17 (Th17) cells in psoriatic lesional skin implicated this T-cell population as a key contributor to the proinflammatory state of psoriasis.[12,13] In response to several cytokines, namely IL-6 and transforming growth factor β (TGF-β), naïve CD4+ T cells differentiate into Th17 cells. In addition to T-cell differentiation, these cytokines induce Th17 expression of IL-23R and IL-17A. After necessary exposure of developing Th17 cells to IL-23, there is augmented production of other effector cytokines, that is, IL-17A, IL-17F, IL-22, and tissue necrosis factor α (TNF-α).[14,15]

The IL-17 cytokine family consists of six members (IL-17A through IL-17F), with IL-17A the primary effector cytokine of the Th17 cell lineage. In addition to T cells, mast cells and neutrophils have been identified as cellular sources of IL-17 in psoriasis, as well as in a number of immune-mediated diseases.[16–18] The IL-17 cytokines exert their biologic functions through binding to their respective transmembrane IL-17 receptor (IL-17R), a heterodimer composed of five different subunits (IL-17RA–IL-17RE) (see Figure 1). Sharing the greatest homology, IL-17A and IL-17F signal through the same receptor subunits (IL-17RA and IL-17RC). However, IL-17A is approximately 10–30 times more potent than IL-17F in activating gene expression, owing to different ligand-receptor affinities.[19,20] IL-17A receptors are expressed on the surface of keratinocytes, making these cells the primary target in psoriasis. Upon IL-17A binding, there is increased keratinocyte expression of numerous chemokines (i.e. CCL20, CXCL1, and CXCL8), which play a role in recruiting inflammatory cells to lesional skin and stimulating the innate immune system; this complex interaction ultimately contributes to epidermal hyperproliferation and skin barrier dysfunction, important factors in psoriasis pathogenesis.[21,22] The effects of IL-17A are augmented by other inflammatory mediators, particularly, TNF-α. The synergistic effects of IL-17A and TNF-α on keratinocytes maintain a positive feedback loop for increased production of TNF-α and other mediators, as well as upregulation of genes involved in the psoriasis gene signature.[15,23]

In psoriasis, expression of IL-17 mRNA is higher in lesional compared with nonlesional skin.[24] Additionally, IL-17A levels are significantly correlated to disease severity.[25,26] One cohort study demonstrated a threefold increase in serum IL-17A levels in patients with psoriasis with a Psoriasis Area and Severity Index (PASI) score greater than 10 compared with those with scores less than 10.[27] Blockade of IL-17 is shown to reduce keratinocyte hyperproliferation, T-cell infiltration into the dermis, and mRNA expression of key disease-propagating genes.[28] Thus, there are considerable data supporting the central role of IL-17 in the pathogenesis of psoriasis, and the importance of IL-17-targeted biologic therapy

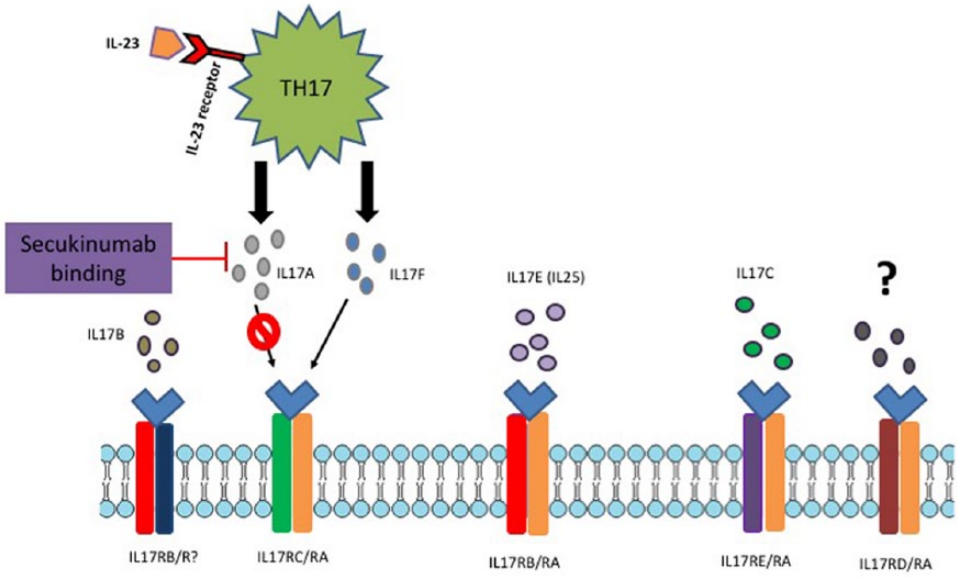

Figure 1. The five interleukin-17 receptor (IL-17R) complexes and their corresponding ligands. IL-17B binds to the receptor complex composed of the IL-17RB subunit and an unknown subunit. IL-17A and IL-17F are stimulated by T-helper-17 (TH17) cells and bind to the IL-17RC and IL-17RA receptor complex (not shown: IL-17A/IL-17F heterodimers also bind to this receptor complex). IL-17E (IL-25) binds to the IL-17RB and IL-17RA receptor complex. IL-17C binds to the IL-17RE and IL-17RA receptor complex. The ligand for the IL-17RD and IL-17RA receptor complex is currently unknown.[16] Secukinumab inhibits IL-17A and prevents it from binding to its receptor.

in the treatment of moderate to severe psoriasis. Multiple clinical trials have supported the significant virtue of these anti-IL-17 biologic agents.[29–31]

Secukinumab anti-IL-17A

Secukinumab (Cosentyx; Novartis International AG, Basel, Switzerland) is a recombinant human monoclonal immunoglobulin G1 (IgG1)/κ antibody that selectively targets IL-17A and blocks its interaction with the IL-17 receptor. Inhibition of the downstream effects of this proinflammatory cytokine thereby interferes with key psoriasis disease pathways while promoting normalization of immune function and skin histology. At therapeutic doses used in psoriasis, secukinumab fully neutralizes IL-17A without neutralizing IL-17F, or directly affecting other Th17 functions or the Th1 pathway. This target specificity offers the potential for fewer adverse effects compared with other currently available therapies. Secukinumab has been developed by Novartis Pharmaceutical Corporation in Switzerland, and was approved by the US Food and Drug Administration (FDA) for the treatment of moderate to severe plaque psoriasis (January 2015), PsA (January 2016), and ankylosing spondylitis (January 2016). The recommended dosage for plaque psoriasis is two 150 mg (300 mg) subcutaneous injections at weeks 0, 1, 2, 3, and 4 followed by 300 mg every 4 weeks. The same dosing regimen is also approved in the treatment of PsA.[32,33]

Pharmacokinetics

Secukinumab's pharmacokinetics were initially evaluated with both intravenous and subcutaneous dosing in healthy volunteers. After a single subcutaneous dose (150 mg or 300 mg), peak drug concentrations were achieved between 5 and 6 days post injection. After repeated monthly dosing, there was a twofold increase in peak concentrations, with steady state reached after 20 weeks. Similar to other IgG1 human monoclonal antibodies, the average bioavailability of subcutaneous secukinumab is 73%. The volume of distribution after a single intravenous dose indicates limited distribution to the peripheral compartments. Consistent with any endogenous immunoglobulin γ, secukinumab is metabolized *via* intracellular catabolism and degraded into small peptides and amino acids. This main route of elimination limits the potential for drug interactions, in addition to cytochrome P450 inhibitors and inducers, as hepatic metabolizing enzymes are not involved with monoclonal

antibody elimination. In healthy volunteers and patients with psoriasis, the mean elimination half life is approximately 27 days. Clearance of drug is dose and time dependent, and unaffected by sex, race, and disease severity after adjusting for bodyweight. Secukinumab metabolism and excretion are not expected to be influenced by various factors, including age (⩾65 years of age), renal and hepatic impairment.[33]

Clinical efficacy

Secukinumab has demonstrated excellent clinical efficacy in clinical trials for the treatment of moderate to severe plaque psoriasis. In general, disease severity for most clinical trials was based on: PASI ⩾ 12, Investigator's Global Assessment (IGA) score ⩾ 3, and BSA ⩾ 10%. Please refer to Table 1 for key results from the phase II and III clinical trials for secukinumab.

Phase II clinical trials for plaque psoriasis. Secukinumab demonstrated clinical superiority to placebo in phase II randomized, double-blind, placebo-controlled clinical trials.[29,34] In one trial, patients were randomized to receive subcutaneous secukinumab 1 × 25 mg (baseline only), 3 × 25 mg, 3 × 75 mg, 3 × 150 mg, or placebo (1:1:1:1:1) at weeks 0, 4, and 8.[29] A statistically significant difference in PASI 75 at week 12 (primary endpoint) was achieved by the secukinumab 3 × 150 mg and 3 × 75 mg groups compared with placebo (82% and 57% *versus* 9%; $p < 0.001$ and $p = 0.002$, respectively), and maintained through week 36 (26% and 19% *versus* 4%, respectively). Notably, patients weighing less than 90 kg had better PASI 75 responses in all treatment groups by week 12 compared with heavier patients (>90 kg) (94% *versus* 64%), suggesting that weight-based dosing could be relevant considering the increased rate of obesity in patients with moderate to severe psoriasis. Previous exposure to biologic or systemic psoriasis therapies did not reveal a significant impact on clinical response.[29]

The second phase II study randomized 404 adult patients to placebo or one of three secukinumab 150 mg induction regimens (1:1:2:2) (single: week 0; early: weeks 0, 1, 2, and 4; and monthly: weeks 0, 4, and 8).[34] PASI 75 responders from active treatment groups were rerandomized at week 12 to either a fixed interval (secukinumab 150 mg at weeks 12 and 24) or treatment at start of relapse maintenance regimen (loss of >50% of the maximum PASI improvement compared with baseline) for 20 weeks. A statistically significant primary endpoint was achieved by early and monthly induction treatment arms compared with placebo (54.5% and 42.0 % *versus* 1.5%, respectively; $p < 0.001$). Fixed-interval dosing in the maintenance period was superior to start of relapse treatment (PASI 75: 85% *versus* 67%; $p = 0.020$; PASI 90: 58% *versus* 21%).[34] A subanalysis of this study observed improved health-related QoL measures with all secukinumab dosing regimens compared with placebo ($p < 0.001$).[42] Moreover, the early secukinumab regimen was associated with a significant improvement in non-pustular hand and/or foot psoriasis compared with placebo at week 12 (IGA 0/1: 54.3% *versus* 19.2%; $p = 0.005$). Both early and monthly dosing regimens had improved composite fingernail scores than placebo [mean change from baseline: −19.1% and −10.6% *versus* 14.4%; $p = 0.010$ (early), $p = 0.027$ (monthly)].[43]

Phase III clinical trials for plaque psoriasis

Fixed-interval versus as-needed secukinumab maintenance treatment. The phase III SCULPTURE study evaluated maintenance treatment with fixed-interval monthly subcutaneous secukinumab therapy (150 mg and 300 mg) compared to as-needed treatment (⩾20% loss of maximum PASI score improvement compared to baseline, or loss of PASI 75).[41] The primary endpoint was maintaining PASI 75 through week 52 after a 12-week induction period (secukinumab 150 mg or 300 mg at weeks 0, 1, 2, 3, 4, and 8). Fixed-dosing maintenance therapy (300 mg: 78.2%; 150 mg: 62.1%) was superior to as needed treatment (67.7%; 52.4%) in achieving the primary endpoint. Fixed-dosing consistently achieved higher PASI 75/90/100 and IGA 0/1 scores compared to retreatment as needed. The majority of patients in the 300 mg (85.2%) and 150 mg (85.4%) as needed groups experienced relapse at least once, with median time to relapse of 24 weeks and 20 weeks, respectively. 69.2% (300 mg) and 55.1% (150 mg) of patients regained PASI 75 within 8–12 weeks.[41] A double-blind extension of the SCULPTURE trial demonstrated sustained treatment responses for secukinumab 300 mg fixed-monthly dosing through 3 years of treatment (PASI 90: 63.8%; PASI 100: 42.6%). In contrast, PASI 90 and 100 scores at 3 years were 14.8% and 5.3%, respectively, for the as needed treatment regimen.[44]

Self-administered secukinumab. Two clinical trials, FEATURE and JUNCTURE, evaluated the efficacy, safety, and usability of self-administered

Table 1. Key phase II and III clinical trial results for secukinumab in psoriasis.

Trial	*n*	Total duration (including follow up)	Study arms	Dosage regimen	Primary outcomes
Phase II, randomized, double-blind, placebo-controlled, dose-ranging study[29]	125	36 weeks	(1:1:1:1) subcutaneous secukinumab 1 × 25 mg; 3 × 25 mg; 3 × 75 mg; 3 × 150 mg; placebo	Baseline only (25 mg); or weeks 0, 4, and 8 (25, 75, and 150 mg)	Week 12 PASI 75: 3 × 150 mg: 82%; 3 × 75 mg: 57%; placebo: 9.0%; $p < 0.001$ and $p = 0.002$, respectively Week 36 PASI 75: 26% and 19% *versus* 4%
Phase II randomized, double-blind, placebo-controlled, multi-dose, regimen-finding study[34]	404	36 weeks	Induction: (1:1:2:2) subcutaneous placebo or secukinumab 150 mg at one of three dosing regimens (single, early, monthly) Maintenance: PASI 75 responders at week 12 rerandomized (1:1) to FI or RAN*	Single: week 0; Early: weeks 0, 1, 2, and 4; Monthly: weeks 0, 4, and 8 Maintenance: FI: (weeks 12 and 24); or RAN* for PASI 75 responders at week 12	Week 12 PASI 75: early: 54.5%; monthly: 42.0%; placebo: 1.5%; $p < 0.001$ for both Week 36 PASI 75: FI: 55%; RAN: 31%
Phase III, placebo-controlled, safety and efficacy of self-administered prefilled syringe, (FEATURE)[35,36]	177	52 weeks	(1:1:1) subcutaneous secukinumab 300 mg, 150 mg, placebo	Weeks 0, 1, 2, 3, 4 followed by monthly dosing through week 48	Week 12 PASI 75: 300 mg: 75.9%; 150 mg: 69.5%; placebo: 0%; $p < 0.0001$) Week 52 PASI 75: 83.5% and 63.5% for 300 mg and 150 mg, respectively
Phase III, placebo-controlled, safety and efficacy of self-administered autoinjector/pen (JUNCTURE)[37]	182	52 weeks	(1:1:1) subcutaneous secukinumab 300 mg, 150 mg, placebo	Weeks 0, 1, 2, 3, 4 followed by monthly dosing through week 48	Week 12 PASI 75: 300 mg: 86.7%; 150 mg: 71.7%; placebo: 3.3%; $p < 0.0001$ Week 52 PASI 75: 81.4% and 75.2% for 300 and 150 mg, respectively
Phase III placebo-controlled safety and efficacy study of two fixed-dose regimens in target population (ERASURE)[38]	738	52 weeks	(1:1:1) subcutaneous secukinumab 300 mg, 150 mg, or placebo	Weeks 0, 1, 2, 3, 4, and then every 4 weeks through week 48	Week 12 PASI 75: 300 mg: 81.6%; 150 mg: 71.6%; placebo: 4.5%; $p < 0.001$ for both Week 52 PASI 90/100: 60.0%/39.2% and 36.2%/20.2% for 300 mg and 150 mg, respectively
Phase III placebo and active comparator-controlled safety and efficacy study (FIXTURE)[38]	1306	52 weeks	(1:1:1:1) subcutaneous secukinumab 300 mg, 150 mg, etanercept 50 mg, placebo	Weeks 0, 1, 2, 3, 4, and then every 4 weeks through week 48	Week 12 PASI 75: 300 mg: 77.1%; 150 mg: 67.0%; etanercept: 44.0%; placebo: 1.9% ($p < 0.001$ for secukinumab doses *versus* placebo)
Phase III randomized controlled, safety and efficacy study in partial responders (STATURE)[39]	43	52 weeks (SCULPTURE 12-week induction plus 40 weeks)	Induction: (1:1) secukinumab 10 mg/kg intravenously or 300 mg subcutaneously Maintenance: subcutaneous secukinumab 300 mg	Induction: intravenous dosing: weeks 0, 2, and 4; subcutaneous dosing: weeks 0 and 4 Maintenance: monthly through week 36	Week 8 PASI 75: intravenous: 90.5%; subcutaneous: 66.7%; $p = 0.06$ Week 40 PASI 75: intravenous: 62%, subcutaneous: 48%

(Continued)

Table 1. (Continued)

Trial	*n*	Total duration (including follow up)	Study arms	Dosage regimen	Primary outcomes
Phase IIIb randomized, double-blind, study of safety and efficacy of secukinumab *versus* ustekinumab (CLEAR)[40]	676	52 weeks	(1:1) subcutaneous secukinumab 300 mg and ustekinumab (dosed per recommendations)[$]	Weeks 0, 1, 2, 3, and 4, followed by monthly dosing through week 48	Week 16 PASI 90/100: secukinumab: 79.0%/44.3%; ustekinumab: 57.6%/28.4%; $p < 0.0001$ for all comparisons) Week 52 PASI 90/100: secukinumab: 76%/46%, ustekinumab: 61%/36%; $p < 0.001$ and $p = 0.0103$, respectively
Phase III RAN *versus* FI maintenance regimen (SCULPTURE)[41]	966	52 weeks	Induction: (1:1) subcutaneous secukinumab 300 mg or 150 mg Maintenance: PASI 75 responders at week 12: FI (300 or 150 mg); or RAN[‡] (300 or 150 mg)	Induction: weeks 0, 1, 2, 3, 4, and 8 Maintenance: FI: monthly through week 48; RAN: at loss of response/relapse[‡]	Week 12 PASI 75: 300 mg: 90.1%; 150 mg: 84.4% Week 52 PASI 75: 300 mg RAN: 67.7%; 150 mg RAN: 52.4%; 300 mg FI: 78.2%; 150 mg FI: 62.1%

FI, fixed interval; PASI, Psoriasis Area and Severity Index; RAN, retreatment as needed.
*Loss of over 50% of the maximum PASI improvement compared with baseline.
[$]45 mg ⩽ 100 kg bodyweight; 90 mg > 100 kg bodyweight.
[‡]At least 20% loss of maximum PASI score improvement compared with baseline, or loss of PASI 75.

secukinumab.[35,45] Both studies randomized patients (1:1:1) to subcutaneous secukinumab 300 mg, 150 mg, or placebo given once weekly for 4 weeks followed by monthly dosing. In the FEATURE trial, each dose of secukinumab was superior to placebo at week 12 in terms of PASI 75 (75.9% and 69.5% *versus* 0%; $p < 0.0001$) and modified IGA 0/1 (69.0% and 52.5% *versus* 0%; $p < 0.0001$).[35] Superiority was maintained through week 52 with PASI 75/90/100 responses of 83.5%/68.0%/47.5% and 63.5%/50.3%/31.3% for subcutaneous secukinumab 300 mg and 150 mg, respectively.[36] Superiority of each secukinumab dose was also demonstrated in the JUNCTURE study.[37,45] Overall, patient acceptability was high throughout the duration of both studies. Thus, self-administered secukinumab is both efficacious and associated with significant patient acceptance.

Secukinumab reinitiation after withdrawal. Data from a phase III randomized withdrawal trial of secukinumab were analyzed to evaluate the effects of secukinumab reinitiation on clinical response.[46] After a 52-week maintenance period of monthly subcutaneous secukinumab 300 mg or 150 mg, subjects with at least a PASI 75 response were rerandomized (2:1) to either continue monthly secukinumab, or placebo until relapse (loss of >50% of the maximum PASI improvement compared with baseline). Of the 181 patients randomized to placebo (withdrawal), 16.0% maintained their PASI response over 52 weeks of placebo administration, 8.8% withdrew from the study for various reasons, and 75.1% met the relapse criterion. By weeks 12–16, more than 90% of patients retreated after relapse regained PASI 75 response. Median time needed to regain PASI 90 and PASI 100 responses for secukinumab 300 mg was 4.0 and 8.1 weeks, respectively. Similar to SCULPTURE, this analysis demonstrated the benefit of maintaining fixed-interval rather than as-needed dosing. Nonetheless, secukinumab reinitiation can regain clinical responses in the majority of patients.[46]

Secukinumab and partial responders. The STATURE trial randomized partial responders (PASI ⩾ 50% but <75%) from the induction phase of the SCULPTURE trial to (1:1) secukinumab 10 mg/kg intravenous (baseline, weeks 2, and 4) or subcutaneous secukinumab 300 mg (baseline, week 4), followed by monthly subcutaneous secukinumab 300 mg dosing.[39] Intravenous secukinumab achieved significantly higher IGA 0/1 responses (66.7% *versus* 33.3%; $p = 0.03$) as well as higher, but insignificant, PASI 75 scores

at week 8 compared with subcutaneous dosing (90.5% *versus* 66.7%; $p = 0.06$). Of note, the subcutaneous cohort had a higher baseline mean body mass index (BMI) and IGA scores, likely a result of the small sample size ($n = 43$). While the primary endpoint was not achieved, the results suggest a benefit of prolonged dosing with 300 mg subcutaneous secukinumab, or higher doses with intravenous therapy for partial responders after 12 weeks.[39]

Fixed-dose regimens. The ERASURE and FIXTURE phase III, double-blind, multicenter, randomized, placebo-controlled, 52-week trials evaluated two fixed regimens of secukinumab.[38] Each study consisted of a 12-week induction period and a 40-week maintenance period. Patients in the ERASURE study were randomized to receive subcutaneous secukinumab 300 mg, 150 mg, or placebo (1:1:1), whereas the FIXTURE trial had an additional comparative arm of etanercept 50 mg dosed twice weekly (1:1:1:1). At week 12, patients in the placebo group who did not achieve PASI 75 were rerandomized to either subcutaneous secukinumab 300 mg or 150 mg. For both studies, the primary end point of PASI 75 and modified IGA score of 0/1 at week 12 was achieved by a significantly greater proportion of patients in each secukinumab dose group compared with placebo and etanercept ($p < 0.001$ for each secukinumab dose *versus* comparators). Clinical efficacy across all end points was greater for 300 mg than 150 mg.[38]

In the ERASURE study, PASI 90/100 at week 12 was observed in a significantly greater proportion of patients on secukinumab 300 mg (PASI 90: 59.2%; PASI 100: 28.6%) and 150 mg (39.1% and 12.8%, respectively) doses compared with placebo (1.2% and 0.8%, respectively; $p < 0.001$ for all comparisons). Superior patient-reported improvements in itch, pain, and scaling, as well as health-related QoL measures at week 12 were observed for each secukinumab dose group ($p < 0.001$ for all comparisons). Furthermore, each secukinumab dose group demonstrated superiority to etanercept in the FIXTURE trial as assessed by the endpoints of week 12 PASI 75/90/100, modified IGA 0/1, and Dermatology Life Quality Index (DLQI) 0/1, as well as maintenance of modified IGA 0/1 and PASI 75 to week 52. The median time to PASI 50 from baseline was significantly shorter for secukinumab 300 mg and 150 mg compared with etanercept (3.0 weeks and 3.9 weeks, respectively *versus* 7.0 weeks; $p < 0.001$ for both comparisons). Notably, patients who were biologic naïve demonstrated superior clinical responses than patients with previous exposure to biologic therapy (PASI 90: 300 mg: 58.1% *versus* 50.7%; 150 mg: 44.6% *versus* 29.4%).[38] This is consistent with a subanalysis of four phase III clinical trials: ERASURE, FIXTURE, FEATURE, and JUNCTURE, which also revealed higher PASI 90 response rates in patients who were biologic naïve. Nonetheless, this subanalysis reported superiority of secukinumab to placebo, regardless of prior exposure or response to biologic therapy.[47]

A subanalysis of the ERASURE study evaluating secukinumab in 87 Japanese patients with moderate to severe plaque psoriasis demonstrated consistent findings.[48] Secukinumab (300 mg and 150 mg) achieved significantly rapid PASI 75 responses by week 4 compared with placebo ($p < 0.01$), with superiority continued through week 12 (PASI 75: 82.8% and 86.2% *versus* 6.9%; $p < 0.0001$; modified IGA 0/1: 55.2% and 55.2% *versus* 3.4%; $p < 0.0001$), and maintained through week 52. Additionally, rapid improvement in DLQI scores was observed for both secukinumab dose cohorts by week 4, and were sustained throughout the study duration.[48] Overall, secukinumab is associated with a rapid clinical response, which is sustained over a long treatment duration; an important finding for a chronic, life-long disease

Secukinumab versus active-comparator. A head-to-head safety and efficacy comparison of secukinumab (300 mg) and ustekinumab (45 mg $\leqslant$ 100 kg bodyweight; 90 mg $>$ 100 kg bodyweight) (1:1) was performed in the CLEAR phase IIIb randomized, double-blind clinical trial over 52 weeks.[40] Among 676 randomized patients with moderate to severe plaque psoriasis, secukinumab demonstrated superiority to ustekinumab in PASI 90 response at week 16 (79.0% *versus* 57.6%; $p < 0.001$), PASI 90 at week 52 (76.2% *versus* 60.6%; $p < 0.0001$), and PASI 100 at week 52 (45.9% *versus* 35.8%; $p = 0.0103$); this was independent of ustekinumab dose and previous exposure to psoriasis systemic therapy. Patient-reported itch (77.6% *versus* 68.3%), pain (80.1% *versus* 58.8%), and scaling (82.6% *versus* 71.8%) were significantly decreased with secukinumab compared with ustekinumab. Secukinumab was associated with a greater mean percentage improvement in DLQI at all assessed time points.[40]

Another head-to-head trial (PRIME) compared secukinumab with oral fumaric acid ester (FAE) systemic therapy in patients with moderate to severe psoriasis naïve to systemic therapy.[49] Two hundred and two patients were randomized (1:1)

to subcutaneous secukinumab 300 mg or oral FAE. Compared with FAE, a significantly greater proportion of patients on secukinumab experienced PASI 75 (89.5% *versus* 33.7%; $p < 0.001$), PASI 90 (81.0% *versus* 28.4%; $p < 0.001$), and DLQI 0/1 (71.4% *versus* 25.3%; $p < 0.001$) at week 24.[49]

Secukinumab and health-related QoL. Strober and colleagues assessed the effect of secukinumab on health-related QoL outcomes for the 2042 patients enrolled in the ERASURE and FIXTURE studies as measured by the DLQI.[50] The DLQI measures the impact of a skin disease (i.e. psoriasis) on domains such as activities of daily living, personal relationships, work/school, and treatment. A DLQI score of 0/1 indicates no negative impact of a skin condition on quality of life. Secukinumab (300 mg and 150 mg) was associated with a more rapid achievement of DLQI scores of 0/1 compared with etanercept (median time to DLQI 0/1: 12 *versus* 24 weeks, respectively; $p < 0.01$), and improvement was maintained through week 52: DLQI score 0/1 in secukinumab 300 mg: 79.9%; 150 mg: 70.8%; etanercept: 59.4%.[50] Korman and colleagues reported consistent results in their analysis of the same pooled data, highlighting greater improvements in daily activity and personal relationship subscale scores for secukinumab compared with etanercept.[51]

Phase IV clinical trials for plaque psoriasis

Secukinumab following cyclosporine. A phase IV multicenter, open-label study conducted in Japan assessed the efficacy of secukinumab after direct switching from cyclosporine (CyA) therapy.[52] Patients were required to have undergone a minimum of 12 weeks of CyA treatment before baseline with inadequate treatment response (PASI $\geq$ 10, IGA $\geq$ 2). A total of 37 patients were administered subcutaneous secukinumab 300 mg per standard recommendations. Secukinumab demonstrated early response rates, with 41.2% of patients achieving PASI 50 by week 2. Four patients experienced an increase in PASI score from baseline at week 2, but an improvement was seen by week 3 in three of these patients. The primary endpoint of PASI 75 response at week 16 was observed in 82.4% patients. PASI 90/100 and IGA 0/1 were achieved by 64.7%, 29.4%, and 70.6%, respectively. Similar rates of improvements were seen when comparing the effects of varying doses and durations of CyA treatment. Of note, higher response rates were observed in biologic-naïve patients compared with those with previous biologic exposure. Results from this study reveal that immediate secukinumab treatment after abrupt discontinuation of CyA will permit early clinical improvement without CyA withdrawal early relapse as is seen in the majority of patients.[52]

Meta-analyses for plaque psoriasis

One meta-analysis of seven phase III clinical trials assessing the safety and efficacy of secukinumab compiled data on different treatment regimens, including secukinumab 150 mg or 300 mg, etanercept 50 mg, weight-based ustekinumab (45 mg if $\leq$100 kg, 90 mg if $\geq$100 kg), and placebo.[53] Of the four pivotal trials (FIXTURE, ERASURE, FEATURE, and JUNCTURE), secukinumab (150 mg and 300 mg) was superior to placebo in regard to the proportion of patients achieving at least a PASI 75 response and IGA score of 0/1 ($p < 0.0001$ for all comparisons). Furthermore, secukinumab demonstrated superiority to etanercept, with 77.1% and 67.0% of patients attaining at least PASI 75 responses in the 300 mg and 150 mg cohorts, respectively, compared with 44.0% for etanercept; more patients on secukinumab also achieved IGA scores of 0/1 ($p < 0.01$ for all comparisons). Overall, the odds ratios (OR) to achieve PASI 75 response and IGA score of 0/1 were 65.6 and 62.5 for the secukinumab regimens compared with placebo, and 3.7 compared with etanercept. Secukinumab 300 mg was superior to the 150 mg dose, demonstrating higher proportions of PASI 75 responders [absolute difference 10.2%, 95% confidence interval (CI) 5.6–14.8; $p < 0.01$) and IGA=0/1 responders (13.5%, 95% CI 8.4–18.7; $p < 0.01$). Moreover, more patients on secukinumab 300 mg maintained a PASI 90 response through week 52 ($p < 0.01$). Data on ustekinumab were only available for the CLEAR trial and discussed previously.[53]

Another meta-analysis of eight randomized, double-blind, placebo-controlled trials including 3213 psoriasis cases reported similar findings.[54] Secukinumab 150 mg and 300 mg were superior to placebo in terms of week 12 PASI 75, PASI 90, and IGA = 0/1 response rates ($p < 0.00001$ for all comparisons). Secukinumab 300 mg demonstrated more benefit than 150 mg in regard to these same endpoints ($p < 0.00001$ for all comparisons). Thus, higher doses of secukinumab are associated with superior clinical responses.[54]

Clinical efficacy in PsA

The efficacy of secukinumab in the treatment of PsA was assessed in a randomized, double-blind, placebo-controlled, proof-of-concept phase II clinical trial.[55] Forty-two patients with moderate to severe PsA (according to the Classification for Psoriatic Arthritis criteria) were randomly assigned (2:1) to receive two doses of either intravenous secukinumab 10 mg/kg or placebo (day 1 and day 22), and followed for up to 21 weeks. The primary endpoint of American College of Rheumatology 20 (ACR20) response rates at week 6 between secukinumab (39%) and placebo (23%; $p = 0.27$) was insignificant. Nonetheless, secukinumab was associated with a more rapid ACR20 response onset (by week 2) and consistently higher ACR20/50/70 response rates at all assessed time points compared with placebo. Statistically significant results were observed for improvements in QoL measures and decreases in acute phase reactant protein levels [C-reactive protein ($p = 0.039$); erythrocyte sedimentation rate ($p = 0.038$)] in secukinumab compared with placebo. Thus, while the primary clinical efficacy endpoint was not met, improvements in QoL and a clear trend towards positive clinical effects support a potential therapeutic benefit of secukinumab in the treatment of PsA.[55]

Further evaluation of efficacy in PsA was performed in the FUTURE 2 phase III clinical trial.[56] In this multicenter, double-blind, placebo-controlled study, 397 patients with active PsA were randomized (1:1:1:1) to subcutaneous placebo or secukinumab 300 mg, 150 mg, or 75 mg weekly for four weeks, followed by monthly dosing. At week 24, a significantly higher proportion of patients from each secukinumab dose group achieved an ACR20 response compared with placebo [300 mg: 54% *versus* placebo: 15.0% ($p < 0.0001$); 150 mg: 51.0% ($p < 0.0001$); 75 mg: 29% ($p = 0.0399$)]. Clinical responses were maintained at week 52 for secukinumab 300 mg and 150 mg dose groups. Additionally, these two higher dose groups demonstrated significant benefits in other secondary endpoints (i.e. PASI 75/90, ACR50, and QoL measures) at week 24 compared with placebo. Thus, the authors concluded that secukinumab 300 mg and 150 mg provide significant and sustained improvement in the signs and symptoms of PsA.[56]

In this same cohort, the effect of prior TNF inhibitor exposure on secukinumab efficacy was also examined.[57] Patients naïve to TNF treatment achieved significantly higher ACR20 response rates at week 24 compared with patients with prior TNF inhibitor therapy (TNF naïve *versus* TNF exposed, respectively: 300 mg: 58.2% *versus* 45.5%; 150 mg: 63.5% *versus* 29.7%; 75 mg: 36.9% *versus* 14.7%; placebo: 15.9% *versus* 14.3%). Clinical responses were sustained through weeks 52 and 104, with higher responses maintained in patients who were TNF naïve (week 104 ACR20 responses: 300 mg: 74.8% *versus* 58.4%; 150 mg: 79.3% *versus* 38.9%; 75 mg: 62.7% *versus* 26.3%). The substantially higher response rates for secukinumab 300 mg compared with the 150 mg and 75 mg doses among patients with prior TNF inhibitor exposure suggest a dose response in this patient cohort.[58]

The FUTURE 1 phase III clinical trial evaluated the effect of secukinumab on patient-reported outcomes (PROs) in relation to PsA.[59] A total of 606 patients were randomized (1:1:1) to receive intravenous secukinumab 10 mg/kg (weeks 0, 2, and 4) followed by subcutaneous secukinumab 150 mg or 75 mg every 4 weeks (up to 24 weeks), or matching placebo. Both secukinumab dose groups achieved statistically significant higher least square mean changes in baseline patient global assessment of disease activity and patient assessment of PsA pain by visual analog scale compared with placebo at all assessed time points through week 24 ($p < 0.0001$ for all comparisons). Further improvement was seen for both secukinumab dose groups at week 52. By 24 weeks, secukinumab dose groups achieved meaningful improvements in other PROs pertaining to work productivity, activities of daily living, social and emotional wellbeing, fatigue and physical function, and pain, with improvements sustained or further improved through week 52.[59] Two-year data obtained from 476 patients from FUTURE 1 demonstrated sustained improvements in PsA, with week 104 ACR20 responses of 66.8% and 58.6% for secukinumab 150 mg and 75 mg, respectively.[60] No radiographic disease progression was observed during 2 years of treatment in the majority of patients in both 150 mg and 75 mg dose groups (84.3% and 83.8%).[60]

Meta-analyses for PsA

A meta-analysis of 20 randomized control trials (RCTs) compared secukinumab with licensed biologic agents and apremilast in adults with active PsA whose condition failed to respond to traditional disease-modifying antirheumatic

drugs (DMARDs).[61] In patients who were biologic naïve, week 16 ACR20 responses were significantly higher for secukinumab 150 mg (61%) and 300 mg (58%) than for ustekinumab 45 mg [relative risk (RR) 150 mg: 1.95, 95% CI 1.29–2.85; 300 mg: 1.84, 95% CI 1.21–2.74) and apremilast (RR 2.51, 95% CI 1.52–4.29; RR 2.37, 95% CI 1.39–4.12, respectively). Both doses of secukinumab also demonstrated higher ACR50 and ACR70 responses. No statistical significance was noted for the use of secukinumab *versus* TNF inhibitors for these outcomes.[61]

Another meta-analysis of 12 RCTs examined the efficacy of biologic agents in patients with PsA who experienced an inadequate response or intolerance of DMARDs or nonsteroidal anti-inflammatory drugs.[62] Patients on secukinumab (150 mg and 300 mg) were more likely to achieve ACR20 responses at weeks 12–24 compared with patients receiving apremilast, certolizumab, or ustekinumab. Limitations to this analysis included a possible uneven distribution of effect modifiers, short disease duration in ustekinumab trials, as well as the small number of studies.[62]

Clinical efficacy in palmoplantar psoriasis

Psoriasis involving the palms and soles is associated with significant disability and resistance to all modalities of treatment. The use of secukinumab for moderate to severe hyperkeratotic palmoplantar psoriasis (hPPP) (palmoplantar IGA score $\geqslant 3$) was evaluated in the multicenter phase IIIb, double-blind, GESTURE clinical trial, which randomized 205 patients (1:1:1) to subcutaneous secukinumab 300 mg, 150 mg, or placebo.[63] Doses were given weekly from baseline to week 4, followed by monthly dosing through week 16. Both secukinumab dose groups were superior to placebo as assessed by the primary endpoint of palmoplantar IGA 0/1 scores at week 16: 300 mg: 33.3% *versus* placebo: 1.5%; $p < 0.0001$; 150 mg: 22.1%; $p = 0.0002$). Secukinumab also demonstrated consistently greater reductions in palmoplantar PASI scores at all assessed time points *versus* placebo (week 16: 300 mg: –54.5%; 150 mg: –35.3%; placebo: –4.0; $p < 0.0001$ and $p = 0.0006$, respectively).[63]

Secukinumab in this study also resulted in significant improvements in patient-reported health-related QoL outcomes. At week 16, 26.6%, 16.9%, and 1.5% of patients receiving secukinumab 300 mg, 150 mg, and placebo, respectively, achieved DLQI scores of 0/1 ($p < 0.0001$ and $p < 0.005$, respectively). Moreover, the percentage of patients experiencing no difficulty due to involvement of both palms and soles as measured by the Palmoplantar Quality-of-Life Instrument (ppQLI) survey increased from 0% at baseline to 12.5% and 10.8% at week 16 for secukinumab 300 mg and 150 mg, respectively. There was no change in baseline for placebo. By the end of the study, secukinumab resulted in meaningful improvements in regard to extreme pain, inability to work and walk, and general health impairment. Overall, secukinumab 300 mg demonstrated greatest efficacy across all assessed measures. Results from this clinical trial support the efficacy of secukinumab in treating hPPP.[63]

Clinical efficacy in generalized pustular psoriasis

The use of secukinumab in the treatment of generalized pustular psoriasis (GPP) was evaluated in a phase III open-label Japanese study.[64] All patients ($n = 12$) received subcutaneous secukinumab 150 mg from baseline (weeks 0, 1, 2, 3, and 4), followed by monthly dosing from week 8 either maintained at 150 mg, or titrated up to 300 mg if there was insufficient improvement [based on Clinical Global Impression (CGI)]. By week 8, 10 patients were continued on 150 mg, one patient had increased to 300 mg, and one patient discontinued due to protocol deviation. GPP severity was assessed by the CGI, which delineates the following categories: 'very much improved', 'much improved', 'minimally improved', and 'no change'. At week 16, treatment success was achieved by 83.3% of subjects, as defined by CGI ratings of 'very much improved' ($n = 9$) and 'much improved' ($n = 1$), and improvements were maintained through week 52. Results from this small study support the potential benefit of secukinumab for the treatment of GPP.[64]

Safety and tolerability of secukinumab

Secukinumab is associated with a generally favorable safety profile in the treatment of moderate to severe plaque psoriasis. A pooled safety analysis of 10 phase II and III clinical studies was performed by van de Kerkhof and colleagues and included data from a total follow-up period of 52 weeks and 2725 subject years of exposure to secukinumab (Tables 2–4).[65] A total of 3993 patients were included, of whom 3430 received secukinumab (subcutaneous 300, 150, 75, or 25 mg; or intravenous 10 mg/kg), 323 received etanercept, and 793

Table 2. Adverse events from baseline through week 12 from pooled safety analysis.[65]

Baseline through week 12	Secukinumab 300 mg* (*n* = 1173)	Secukinumab 150 mg* (*n* = 1174)	Secukinumab all doses$ (*n* = 2877)	Etanercept 50 mg‡ (*n* = 323)	Placebo (*n* = 793)
Subjects with any AEs, *n* (%)	636 (54.2)	661 (56.3)	1620 (56.3)	186 (57.6)	400 (50.4)
Total SAEs	13	16	42	0	5
Deaths	0	0	0	0	0
Most common AEs (%)					
Nasopharyngitis (%)	10.6	11.3	11.8	11.1	9.1
Headache	5.3	5.1	5.4	7.1	4.9
URIs	3.0	3.3	3.3	2.2	1.4
Pruritus	2.9	3.4	2.9	2.5	2.6
Diarrhea	3.1	2.1	2.4	3.4	1.4
Hypertension	1.5	2.8	2.2	1.5	1.6
Arthralgia	1.5	2.5	2.0	3.7	2.1

*Subjects from phase III studies randomized to this particular secukinumab dose from the start of study.
$Subjects from phase II and III studies randomized to any secukinumab dose from the start of study.
‡Etanercept data from the phase III FIXTURE trial.
AE, adverse event; SAE, serious adverse event; URI, upper respiratory tract infection.

Table 3. Adverse events from baseline through week 52 from pooled safety analysis.[65]

Baseline through week 52	Secukinumab 300 mg* (*n* = 1410)	Secukinumab 150 mg* (*n* = 1395)	Secukinumab all doses$ (*n* = 3430)	Etanercept 50 mg‡ (*n* = 323)
Subjects with any AEs (%)	77.4	76.4	76.9	78.3
Total SAEs (*n*)	123	64	175	17
Deaths (*n*)	0	1	1	0
Most common AEs (%)				
Nasopharyngitis	19.9	19.1	20.0	26.6
Headache	8.16	7.96	8.16	12.4
URI	6.45	6.59	6.65	5.57
Arthralgia	4.82	4.95	5.07	7.12
Hypertension	4.75	4.87	4.81	4.33
Diarrhea	5.60	4.52	4.75	6.81
Back pain	4.40	3.73	4.26	8.05
Pruritus	3.83	4.73	3.94	4.95
Cough	4.96	3.15	3.88	3.72

*Subjects from phase III studies randomized to this particular secukinumab dose from the start of study or rerandomized from placebo at week 12 to secukinumab.
$Subjects from phase II and III studies rerandomized to any secukinumab dose from the start of study or rerandomized from placebo at week 12 to secukinumab.
‡Etanercept data from the phase III FIXTURE trial.
AE, adverse event; SAE, serious adverse event; URI, upper respiratory tract infection.

placebo. The majority of the studies (8/10) were placebo controlled and exclusion criteria were similar for all studies (i.e. active/untreated tuberculosis, active systemic infections, history of malignancy, unstable cardiac disease). Baseline characteristics were comparable across all groups except for

Table 4. Adverse events of special interest from baseline through week 12 from pooled safety analysis.[65]

AESI (%)	Secukinumab 300 mg* (n = 1173)	Secukinumab 150 mg* (n = 1174)	Secukinumab all doses$ (n = 2877)	Etanercept 50 mg‡ (n = 323)	Placebo (n = 793)
Infections	25.75	26.92	26.90	25.7	20.6
Neutropenia AE	0.68	0.60	0.56	0.6	0
NMSC	0.09	0.17	0.10	0	0.4
Malignancies	0.17	0.34	0.21	0	0.4
MACE	0.26	0	0.10	0	0.1
IBD	0.09	0.09	0.07	0.3	0
Crohn's disease	0	0.09	0.03	0	0
Ulcerative colitis	0.09	0	0.03	0.3	0

*Subjects from phase III studies randomized to this particular secukinumab dose from the start of study.
$Subjects from phase II and III studies randomized to any secukinumab dose from the start of study.
‡Etanercept data from the phase III FIXTURE trial.
AE, adverse event; AESI, adverse event of special interest; IBD, inflammatory bowel disease; MACE, major adverse cardiovascular event; NMSC, nonmelanoma skin cancer.

slightly higher rates of cardiovascular risk factors/disease for the secukinumab cohorts. Over the first 12 weeks, all groups had similar durations of study treatment exposure. In contrast, placebo exposure was significantly lower over the entire 52-week period, as many nonresponders were rerandomized to secukinumab per protocol. Thus, safety analysis over the entire 52 weeks did not include comparison with the placebo group.[65]

During the initial 12 weeks, overall incidences of adverse events (AEs) for both secukinumab dose groups (300 and 150 mg) were similar to etanercept, but slightly higher than placebo (300 mg: 54.2%; 150 mg: 56.3%; etanercept: 57.6%; placebo: 50.4%) (Table 2). Exposure-adjusted incidence rates (IRs) for total AEs remained comparable between all secukinumab dose groups and etanercept throughout 52 weeks (Table 3). Nasopharyngitis (11.8% and 29.3%, respectively), headache (5.4% and 11.0%), and upper respiratory tract infection (URI) (3.3% and 8.8%) were the most commonly reported AEs for secukinumab. Other more common AEs (⩾5/100 subject years) included arthralgia, hypertension, diarrhea, back pain, pruritus, and cough. Serious adverse events (SAEs) were rare and comparable across secukinumab 300 mg, 150 mg, and etanercept treatment groups through week 52 (SAE incidence rates per 100 subject years: 7.4, 6.8, and 7.0, respectively). There was one reported death due to hemorrhagic stroke on day 319 in a patient receiving secukinumab 150 mg as needed.[65]

In regard to AEs of special interest (AESIs), rates of infection requiring antimicrobial treatment during the first 12 weeks were comparable among the secukinumab 300 mg, 150 mg, and etanercept (11.1%, 9.0%, and 9.9%) groups, and numerically lower in placebo (7.4%) (Table 4). Exposure-adjusted rates remained comparable between secukinumab dose groups and etanercept through week 52. No incidents of disseminated herpes or reactivation of latent tuberculosis occurred in any cohort throughout the entire treatment period. Numerically higher IRs of nonserious candidiasis infections were reported for secukinumab than etanercept (300 mg: n = 41; 150 mg: n = 21; etanercept: n = 4); all infections were mucocutaneous in origin, mild to moderate severity, and responsive to standard treatment.[65]

A total of 443 cases of new, or worsening, neutropenia were reported in all cohorts during the 52-week period, with the majority (77%) rated as grade 1 (absolute neutrophil count < lower limit of normal to 1.5 × 10^9/liter) and not associated with serious infections. IRs of higher-grade neutropenia (⩾ 3) associated with secukinumab were low (grade 3 IRs: secukinumab: 0.5% *versus* placebo: 0.1%) and often transient. No grade 4 neutropenia cases were reported for secukinumab, whereas one case was observed for etanercept.[65]

IRs of malignancy in the first 12 weeks were similar among secukinumab 300 mg, 150 mg, and placebo groups; no incidents were reported for etanercept. By week 52, exposure-adjusted rates of malignancy were similar across secukinumab 300 mg, 150 mg, and etanercept (0.77, 0.97, and 0.68, respectively). Nonmelanoma skin cancers

(NMSCs) [i.e. basal cell carcinoma (BCC) and squamous cell carcinoma], particularly BCCs, were the most commonly reported malignancies for secukinumab, with no difference in exposure rates between the 300 mg and 150 mg dose groups. Of note, most cases of BCC occurred in patients with previous phototherapy exposure. Excluding NMSC, the most frequently reported malignancies for secukinumab (any dose) were melanoma ($n = 4$), bladder cancer ($n = 2$), and thyroid cancer ($n = 2$).[65]

Rates of adjudicated major adverse cardiovascular events (MACEs) during the initial 12 weeks were 0.26% for secukinumab 300 mg and 0.10% for placebo; no MACEs were reported for secukinumab 150 mg or etanercept. By week 52, exposure-adjusted IRs of adjudicated MACEs were similar between secukinumab (any dose) and etanercept (0.37 and 0.34, respectively). Notably, all MACEs occurred in subjects with documented cardiovascular disease or risk factors.

In this pooled safety analysis, secukinumab treatment was not associated with the occurrence or exacerbation of inflammatory bowel disease (IBD). The authors observed no clinically meaningful differences in the occurrence of Crohn's disease and ulcerative colitis during the first 12 weeks between all treatment groups. During the entire 52-week duration, exposure-adjusted IRs of IBD for any dose of secukinumab was 0.33, and comparable to rates for etanercept (0.34). IRs for Crohn's disease and ulcerative colitis in patients receiving any dose of secukinumab at week 52 were 0.11 ($n = 3/3430$) and 0.15 ($n = 4/3430$), respectively.[65] In contrast, a proof of concept study of secukinumab in 59 patients with moderate to severe Crohn's disease observed trends towards increased disease activity. As such, caution should be used when prescribing secukinumab in patients with a history of IBD.[32,66]

Three-year safety data from an extension study ($n = 682$) of the SCULPTURE core trial reported no new or unexpected AEs related to secukinukab.[44] The most common AEs were similar to all prior studies, that is, nasopharyngitis, headaches, and URIs. Rates of AESIs were similar to previous reports. In regard to immunogenicity, 4/682 patients (fixed dose: $n = 2$; as needed: $n = 2$) tested positive for anti-secukinumab antibodies, all occurring in the third year of treatment. This was not associated with a decrease in therapeutic response, AEs, or pharmacokinetic abnormalities.[44]

The CLEAR trial observed similar safety profiles between secukinumab and ustekinumab.[40] IRs of any AE between secukinumab (280.9) and ustekinumab (250.1) were comparable, with similar proportions of patients who then discontinued treatment ($n = 10$ *versus* 9). Consistent with other studies, the most frequent AEs for both groups included nasopharyngitis, headache, and URI. Secukinumab had numerically higher numbers of *Candida* infections (20) compared with ustekinumab (5), but this was not statistically significant. Additionally, IRs for SAEs were also comparable between the two groups, with the majority being single events. Each group had one reported MACE (secukinumab: stroke; ustekinumab: myocardial infarction) in patients with baseline cardiovascular risk factors, and there was one death in the secukinumab cohort due to an unknown cause.[40]

Overall, data from the pooled safety analysis observed similar safety profiles between secukinumab 300 mg and 150 mg doses, which are also comparable to etanercept over a 52-week period. Based on one phase IIIb clinical trial, secukinumab and ustekinumab have comparable safety profiles. The safety profile of secukinumab appears to remain consistent over a 3-year treatment period.[32]

Conclusion

Secukinumab is an efficacious anti-IL-17A biologic agent for the treatment of moderate to severe plaque psoriasis. It has demonstrated superiority to placebo in a number of phase II and III clinical trials, as well as superiority to etanercept and ustekinumab. Specifically, secukinumab is associated with a rapid rate of clinical response, with PASI 50/75 responses observed by 4 weeks, and maintained or improved responses documented through week 52.[38,48] Furthermore, a greater proportion of patients on secukinumab achieve higher clinical responses of PASI 90 and 100 compared with other biologics.[40] This correlates to greater improvements in health-related quality of life measures. Secukinumab has also shown efficacy for the treatment of other forms of psoriasis (i.e. GPP and hPPP) as well as psoriatic arthritis. Further evaluations will be needed to determine its full therapeutic potential for these conditions.

In regard to safety, secukinumab is generally well tolerated and has a safety profile comparable to other antipsoriatic biologic agents. Like many biologic agents, the most common AEs include URIs

and headache. Other AESIs that should be closely monitored include infections, neutropenia, candidiasis, and rare cases of new or worsening IBD.[65] Continued pharmacovigilance will provide further information on the long-term safety and efficacy of this important new biologic agent. In summary, secukinumab offers the potential for significant therapeutic response in both psoriasis and PsA, and has to be considered as an important and valuable addition to our psoriasis therapeutic armamentarium.

Conflict of interest statement

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr Frieder and Dr Kivelevitch have no conflicting interests to disclose. Dr Menter reports grants and honoraria from AbbVie, Allergan, Amgen, Boehringer Ingelheim, Janssen Biotech, Inc., LEO Pharma, Novartis, Pfizer, and Xenoport; grants from Anacor, Celgene, Dermira, Merck, Neothetics, Regeneron, and Symbio/Maruho; and honoraria from Eli-Lily, Galderma, and Vitae, all outside of the submitted work.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Korman NJ, Zhao Y, Pike J, *et al.* Relationship between psoriasis severity, clinical symptoms, quality of life and work productivity among patients in the USA. *Clin Exp Dermatol* 2016; 41: 514–521.
2. Kirby B, Richards HL, Mason DL, *et al.* Alcohol consumption and psychological distress in patients with psoriasis. *Br J Dermatol* 2008; 158: 138–140.
3. Abuabara K, Azfar RS, Shin DB, *et al.* Cause-specific mortality in patients with severe psoriasis: a population-based cohort study in the U.K. *Br J Dermatol* 2010; 163: 586–592.
4. Neimann AL, Shin DB, Wang X, *et al.* Prevalence of cardiovascular risk factors in patients with psoriasis. *J Am Acad Dermatol* 2006; 55: 829–835.
5. Najarian DJ and Gottlieb AB. Connections between psoriasis and Crohn's disease. *J Am Acad Dermatol* 2003; 48: 805–821; quiz 22–24.
6. Menter A, Gottlieb A, Feldman SR, *et al.* Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. *J Am Acad Dermatol* 2008; 58: 826–850.
7. Menter A, Korman NJ, Elmets CA, *et al.* Guidelines of care for the management of psoriasis and psoriatic arthritis: section 6. Guidelines of care for the treatment of psoriasis and psoriatic arthritis: case-based presentations and evidence-based conclusions. *J Am Acad Dermatol* 2011; 65: 137–174.
8. Gelfand JM, Troxel AB, Lewis JD, *et al.* The risk of mortality in patients with psoriasis: results from a population-based study. *Arch Dermatol* 2007; 143: 1493–1499.
9. Callis Duffin K, Yeung H, Takeshita J, *et al.* Patient satisfaction with treatments for moderate-to-severe plaque psoriasis in clinical practice. *Br J Dermatol* 2014; 170: 672–680.
10. Bewley A and Page B. Maximizing patient adherence for optimal outcomes in psoriasis. *J Eur Acad Dermatol Venereol* 2011; 25(Suppl. 4): 9–14.
11. Chan SA, Hussain F, Lawson LG, *et al.* Factors affecting adherence to treatment of psoriasis: comparing biologic therapy to other modalities. *J Dermatolog Treat* 2013; 24: 64–69.
12. Di Cesare A, Di Meglio P and Nestle FO. The IL-23/Th17 axis in the immunopathogenesis of psoriasis. *J Invest Dermatol* 2009; 129: 1339–1350.
13. Lowes MA, Kikuchi T, Fuentes-Duculan J, *et al.* Psoriasis vulgaris lesions contain discrete populations of Th1 and Th17 T cells. *J Invest Dermatol* 2008; 128: 1207–1211.
14. Kagami S, Rizzo HL, Lee JJ, *et al.* Circulating Th17, Th22, and Th1 cells are increased in psoriasis. *J Invest Dermatol* 2010; 130: 1373–1383.
15. Lynde CW, Poulin Y, Vender R, *et al.* Interleukin 17A: toward a new understanding of psoriasis pathogenesis. *J Am Acad Dermatol* 2014; 71: 141–150.
16. Res PC, Piskin G, de Boer OJ, *et al.* Overrepresentation of IL-17A and IL-22 producing CD8 T cells in lesional skin suggests their involvement in the pathogenesis of psoriasis. *PLoS One* 2010; 5: e14108.
17. de Boer OJ, van der Meer JJ, Teeling P, *et al.* Differential expression of interleukin-17 family cytokines in intact and complicated human atherosclerotic plaques. *J Pathol* 2010; 220: 499–508.
18. Lin AM, Rubin CJ, Khandpur R, *et al.* Mast cells and neutrophils release IL-17 through

extracellular trap formation in psoriasis. *J Immunol* 2011; 187: 490–500.

19. Gaffen SL. Structure and signalling in the IL-17 receptor family. *Nat Rev Immunol* 2009; 9: 556–567.
20. Kolls JK and Linden A. Interleukin-17 family members and inflammation. *Immunity* 2004; 21: 467–476.
21. Nograles KE, Zaba LC, Guttman-Yassky E, *et al.* Th17 cytokines interleukin (IL)-17 and IL-22 modulate distinct inflammatory and keratinocyte-response pathways. *Br J Dermatol* 2008; 159: 1092–1102.
22. Harper EG, Guo C, Rizzo H, *et al.* Th17 cytokines stimulate CCL20 expression in keratinocytes in vitro and in vivo: implications for psoriasis pathogenesis. *J Invest Dermatol* 2009; 129: 2175–2183.
23. Chiricozzi A, Guttman-Yassky E, Suarez-Farinas M, *et al.* Integrative responses to IL-17 and TNF-alpha in human keratinocytes account for key inflammatory pathogenic circuits in psoriasis. *J Invest Dermatol* 2011; 131: 677–687.
24. Li J, Chen X, Liu Z, *et al.* Expression of Th17 cytokines in skin lesions of patients with psoriasis. *J Huazhong Univ Sci Technolog Med Sci* 2007; 27: 330–332.
25. Arican O, Aral M, Sasmaz S, *et al.* Serum levels of TNF-alpha, IFN-gamma, IL-6, IL-8, IL-12, IL-17, and IL-18 in patients with active psoriasis and correlation with disease severity. *Mediators Inflamm* 2005; 2005: 273–279.
26. Takahashi H, Tsuji H, Hashimoto Y, *et al.* Serum cytokines and growth factor levels in Japanese patients with psoriasis. *Clin Exp Dermatol* 2010; 35: 645–649.
27. Yilmaz SB, Cicek N, Coskun M, *et al.* Serum and tissue levels of IL-17 in different clinical subtypes of psoriasis. *Arch Dermatol Res* 2012; 304: 465–469.
28. Krueger JG, Fretzin S, Suarez-Farinas M, *et al.* IL-17A is essential for cell activation and inflammatory gene circuits in subjects with psoriasis. *J Allergy Clin Immunol* 2012; 130: 145–154. e9.
29. Papp KA, Langley RG, Sigurgeirsson B, *et al.* Efficacy and safety of secukinumab in the treatment of moderate-to-severe plaque psoriasis: a randomized, double-blind, placebo-controlled phase II dose-ranging study. *Br J Dermatol* 2013; 168: 412–421.
30. Papp KA, Leonardi C, Menter A, *et al.* Brodalumab, an anti-interleukin-17-receptor antibody for psoriasis. *N Engl J Med* 2012; 366: 1181–1189.
31. Leonardi C, Matheson R, Zachariae C, *et al.* Anti-interleukin-17 monoclonal antibody ixekizumab in chronic plaque psoriasis. *N Engl J Med* 2012; 366: 1190–1199.
32. Cosentyx. *Prescribing information*. Switzerland: Novartis Pharmaceutical Corporation, https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/cosentyx.pdf (2016, accessed 28 Jun 2017).
33. Novartis Pharmaceuticals Corporation. *Advisory committee briefing material for Cosentyx* 2014. Switzerland: Novartis Pharmaceuticals Corporation, https://www.fda.gov/downloads/AdvisoryCommittees/UCM419023.pdf (accessed 28 Jun 2017).
34. Rich P, Sigurgeirsson B, Thaci D, *et al.* Secukinumab induction and maintenance therapy in moderate-to-severe plaque psoriasis: a randomized, double-blind, placebo-controlled, phase II regimen-finding study. *Br J Dermatol* 2013; 168: 402–411.
35. Blauvelt A, Prinz JC, Gottlieb AB, *et al.* Secukinumab administration by pre-filled syringe: efficacy, safety and usability results from a randomized controlled trial in psoriasis (FEATURE). *Br J Dermatol* 2015; 172: 484–493.
36. Gottlieb AB, Blauvelt A, Prinz JC, *et al.* Secukinumab self-administration by prefilled syringe maintains reduction of plaque psoriasis severity over 52 weeks: results of the FEATURE trial. *J Drugs Dermatol* 2016; 15: 1226–1234.
37. Lacour JP, Paul C, Jazayeri S, *et al.* Secukinumab administration by autoinjector maintains reduction of plaque psoriasis severity over 52 weeks: results of the randomized controlled JUNCTURE trial. *J Eur Acad Dermatol Venereol* 2017; 31: 847–856.
38. Langley RG, Elewski BE, Lebwohl M, *et al.* Secukinumab in plaque psoriasis – results of two phase 3 trials. *N Engl J Med* 2014; 371: 326–338.
39. Thaci D, Humeniuk J, Frambach Y, *et al.* Secukinumab in psoriasis: randomized, controlled phase 3 trial results assessing the potential to improve treatment response in partial responders (STATURE). *Br J Dermatol* 2015; 173: 777–787.
40. Blauvelt A, Reich K, Tsai TF, *et al.* Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate-to-severe plaque psoriasis up to 1 year: results from the CLEAR study. *J Am Acad Dermatol* 2017; 76: 60–69. e9.
41. Mrowietz U, Leonardi CL, Girolomoni G, *et al.* Secukinumab retreatment-as-needed versus fixed-interval maintenance regimen for moderate to severe plaque psoriasis: a randomized,

double-blind, noninferiority trial (SCULPTURE). *J Am Acad Dermatol* 2015; 73: 27–36. e1.

42. Augustin M, Abeysinghe S, Mallya U, *et al.* Secukinumab treatment of plaque psoriasis shows early improvement in DLQI response - results of a phase II regimen-finding trial. *J Eur Acad Dermatol Venereol* 2016; 30: 645–649.

43. Paul C, Reich K, Gottlieb AB, *et al.* Secukinumab improves hand, foot and nail lesions in moderate-to-severe plaque psoriasis: subanalysis of a randomized, double-blind, placebo-controlled, regimen-finding phase 2 trial. *J Eur Acad Dermatol Venereol* 2014; 28: 1670–1675.

44. Bissonnette R, Luger T, Thaci D, *et al.* Secukinumab sustains good efficacy and favourable safety in moderate to severe psoriasis after up to 3 years of treatment: results from a double-blind extension study. *Br J Dermatol.* Epub ahead of print 5 June 2017. DOI: 10.1111/bjd.15706.

45. Paul C, Lacour JP, Tedremets L, *et al.* Efficacy, safety and usability of secukinumab administration by autoinjector/pen in psoriasis: a randomized, controlled trial (JUNCTURE). *J Eur Acad Dermatol Venereol* 2015; 29: 1082–1090.

46. Blauvelt A, Reich K, Warren RB, *et al.* Secukinumab re-initiation achieves regain of high response levels in patients who interrupt treatment for moderate to severe plaque psoriasis. *Br J Dermatol* 2017; 177: 879–881.

47. Griffiths C, Papp K, Zaldivar RE, *et al. Secukinumab shows efficacy in subjects regardless of previous exposure to biologic therapy: a pooled subanalysis from four phase 3 clinical trials in psoriasis*. *Paper presented at 73rd AAD Annual Meeting*, March 20–24, 2015, San Francisco, CA. Poster 1760.

48. Ohtsuki M, Morita A, Abe M, *et al.* Secukinumab efficacy and safety in Japanese patients with moderate-to-severe plaque psoriasis: subanalysis from ERASURE, a randomized, placebo-controlled, phase 3 study. *J Dermatol* 2014; 41: 1039–1046.

49. Sticherling M, Mrowietz U, Augustin M, *et al.* Secukinumab is superior to fumaric acid esters in treating subjects with moderate to severe plaque psoriasis who are naive to systemic treatments: results from the randomized controlled PRIME trial. *Br J Dermatol.* Epub ahead of print 5 June 2017. DOI: 10.1111/bjd.15707.

50. Strober B, Gottlieb AB, Sherif B, *et al.* Secukinumab sustains early patient-reported outcome benefits through 1 year: results from 2 phase III randomized placebo-controlled clinical trials comparing secukinumab with etanercept. *J Am Acad Dermatol* 2017; 76: 655–661.

51. Korman NJ, Sofen H, Fretzin S, *et al.* Secukinumab provides better relief from the impact of psoriasis on daily activities and personal relationships than etanercept: results of two phase 3 placebo-controlled randomized clinical trials in moderate-to-severe psoriasis. *J Dermatolog Treat* 2017; 28: 384–389.

52. Ohtsuki M, Morita A, Igarashi A, *et al.* Secukinumab improves psoriasis symptoms in patients with inadequate response to cyclosporine A: a prospective study to evaluate direct switch. *J Dermatol* 2017; 44: 1105–1111.

53. Ryoo JY, Yang HJ, Ji E, *et al.* Meta-analysis of the efficacy and safety of secukinumab for the treatment of plaque psoriasis. *Ann Pharmacother* 2016; 50: 341–351.

54. Xiong HZ, Gu JY, He ZG, *et al.* Efficacy and safety of secukinumab in the treatment of moderate to severe plaque psoriasis: a meta-analysis of randomized controlled trials. *Int J Clin Exp Med* 2015; 8: 3156–3172.

55. McInnes IB, Sieper J, Braun J, *et al.* Efficacy and safety of secukinumab, a fully human anti-interleukin-17A monoclonal antibody, in patients with moderate-to-severe psoriatic arthritis: a 24-week, randomised, double-blind, placebo-controlled, phase II proof-of-concept trial. *Ann Rheum Dis* 2014; 73: 349–356.

56. McInnes IB, Mease PJ, Kirkham B, *et al.* Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet.* 2015; 386: 1137–1146.

57. Kavanaugh A, McInnes IB, Mease PJ, *et al.* Efficacy of subcutaneous secukinumab in patients with active psoriatic arthritis stratified by prior tumor necrosis factor inhibitor use: results from the randomized placebo-controlled FUTURE 2 study. *J Rheumatol* 2016; 43: 1713–1717.

58. McInnes IB, Mease PJ, Ritchlin CT, *et al.* Secukinumab sustains improvement in signs and symptoms of psoriatic arthritis: 2 year results from the phase 3 FUTURE 2 study. *Rheumatol* 2017; 56: 1993–2003.

59. Strand V, Mease P, Gossec L, *et al.* Secukinumab improves patient-reported outcomes in subjects with active psoriatic arthritis: results from a randomised phase III trial (FUTURE 1). *Ann Rheum Dis* 2017; 76: 203–207.

60. Kavanaugh A, Mease PJ, Reimold AM, *et al.* Secukinumab for long-term treatment of psoriatic arthritis: a two-year followup from a phase III, randomized, double-blind placebo-controlled study. *Arthritis Care Res (Hoboken)* 2017; 69: 347–355.

61. McInnes IB, Nash P, Ritchlin C, *et al.* THU0437 secukinumab for the treatment of psoriatic arthritis: comparative effectiveness results versus licensed biologics and apremilast from a network meta-analysis [poster presentation]. *Ann Rheum Dis* 2016; 75: 348–349.

62. Ungprasert P, Thongprayoon C and Davis JM III. Indirect comparisons of the efficacy of biological agents in patients with psoriatic arthritis with an inadequate response to traditional disease-modifying anti-rheumatic drugs or to non-steroidal anti-inflammatory drugs: a meta-analysis. *Semin Arthritis Rheum* 2016; 45: 428–438.

63. Gottlieb A, Sullivan J, van Doorn M, *et al.* Secukinumab shows significant efficacy in palmoplantar psoriasis: results from GESTURE, a randomized controlled trial. *J Am Acad Dermatol* 2017; 76: 70–80.

64. Imafuku S, Honma M, Okubo Y, *et al.* Efficacy and safety of secukinumab in patients with generalized pustular psoriasis: a 52-week analysis from phase III open-label multicenter Japanese study. *J Dermatol* 2016; 43: 1011–1017.

65. van de Kerkhof PC, Griffiths CE, Reich K, *et al.* Secukinumab long-term safety experience: a pooled analysis of 10 phase II and III clinical studies in patients with moderate to severe plaque psoriasis. *J Am Acad Dermatol* 2016; 75: 83–98. e4.

66. Hueber W, Sands BE, Lewitzky S, *et al.* Secukinumab, a human anti-IL-17A monoclonal antibody, for moderate to severe Crohn's disease: unexpected results of a randomised, double-blind placebo-controlled trial. *Gut* 2012; 61: 1693–1700.

Visit SAGE journals online
journals.sagepub.com/
home/taj

SAGE journals