Research Review™
PRODUCT REVIEW

Secukinumab (Cosentyx®) in Moderate-to-Severe Plaque Psoriasis

Making Education Easy 2016

Independent commentary by Rodney Sinclair

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Abbreviations used in this review:
AE = adverse event;
DLQI = Dermatology Life Quality Index;
EQ-5D = European quality of life scale (5 dimensions);
HRQoL = health-related quality of life;
IGA = investigators' global assessment;
IL= interleukin; **IV** = intravenous;
PASI = Psoriasis Area and Severity Index;
PBS = Pharmaceutical Benefits Scheme;
PK = pharmacokinetic(s); **SC** = subcutaneous(ly);
TNF-α = tumour necrosis factor-α;
TNFi = tumour necrosis factor-α inhibitor(s).

Expert's summary

Psoriasis is a chronic, immune-mediated disease that affects the skin, nails and joints. Skin lesions of psoriasis can form anywhere on the skin, but are most common on the elbows, knees and scalp. Patients experience varying levels of symptom severity; however, moderate-to-severe psoriasis has a profound impact on health-related quality of life. Patients with moderate-to-severe psoriasis generally have lesions covering 10–70% of the skin surface. Psoriasis severity is evaluated using the Psoriasis Area and Severity Index (PASI), which multiplies the skin surface area affected by the degree of erythema, scale and thickness of individual lesions. Biologic therapies are chimeric monoclonal antibodies that generally target an inflammatory cytokine or its receptor. The introduction of biologic therapies for psoriasis has provided patients with refractory disease with highly effective treatments and also helped scientists understand the pathogenesis of this complex immune-mediated condition. Interleukin (IL)-17 has emerged from these studies as the 'master' cytokine in the pathogenesis of psoriasis. Secukinumab is a fully human monoclonal antibody that selectively targets IL-17A. It has been shown in phase 3 studies to be highly effective in the treatment of moderate-to-severe plaque psoriasis, starting at early time points, and with a sustained effect and favourable safety profile. It has proven to be so effective in the management of psoriasis that it has shifted the goalposts with respect to how we assess a satisfactory treatment response. Where once the goal was to reduce the PASI score by 75%, the target has now become PASI 90, a reduction of PASI by 90%. Patients who achieve a PASI 75 generally continue to use topical, oral or phototherapy for troublesome, resistant lesions, while a PASI 90 generally allows patients to stop all adjuvant therapy. Approximately 80% of patients started on secukinumab achieve a PASI 90 at 16 weeks.

Secukinumab was approved by the Therapeutic Goods Administration in January 2015 for the treatment of moderate-to-severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. Secukinumab monotherapy became available on the Pharmaceutical Benefits Scheme (PBS; authority required) on 1st September 2015 for the treatment of severe chronic plaque psoriasis.

In large-scale, phase III studies, secukinumab, an interleukin (IL)-17A inhibitor, demonstrated significantly greater efficacy than placebo (ERASURE) and etanercept (FIXTURE) over 52 weeks in patients with moderate-to-severe plaque psoriasis.[1] This was evident from high PASI 75 responses (the proportion of patients with a ≥75% PASI score decrease from baseline) in secukinumab-treated patients (~70–80% of patients; $p<0.001$ vs comparators) relative to etanercept (44%) and placebo recipients (~5%). Corresponding PASI 90 response rates at 12 weeks in these trials were ~50–60%, ~20%, and 1–2% ($p<0.001$ for secukinumab versus comparators). Recently, PASI 90 has become more widely used for establishing treatment success.[2] In the CLEAR study, secukinumab showed significantly greater efficacy than the IL-12/23 antagonist ustekinumab: at week 16, PASI 90 response rates were 79.0% and 57.6%, respectively ($p<0.0001$).

Such studies *'… provide dermatologists important head-to-head comparison information for consideration when choosing an appropriate therapy …'* and make secukinumab *'… the new reference standard treatment for patients with moderate to severe plaque psoriasis.'*[2]

Introduction

Psoriasis vulgaris, or plaque psoriasis, is the most common form of psoriasis. Principal features of the condition comprise chronicity, dermal inflammation, and the presence of red, scaly patches that are shed from the skin surface; the disorder is not contagious.[3–5] The most frequently affected regions are the elbows, knees and scalp, but the condition can occur anywhere on the body.[3,5,6] Patches of affected skin vary in size, but are usually well defined.[5] Itching and increased dermal susceptibility to chemical and physical irritation may also be key aspects of the disorder, although these symptoms typically manifest in only a minority of patients.[3] In some patients, dermal plaques may progress into uncomfortable fissures and cracks.[4]

Several genes are associated with a predisposition to psoriasis, and various 'triggers' are present in genetically susceptible individuals. Such triggers include: alcohol ingestion; cigarette smoke; dietary deficiencies; drug treatments (e.g. β-blockers, lithium, nonsteroidal anti-inflammatory drugs); general illness; lack of exercise; and stress.[3,7–9]

Psoriasis: prevalence

Up to 4% of the population has psoriasis,[8–12] and the condition is distributed evenly between men and women.[8,9] Globally, approximately 125 million people have psoriasis,[13] although this statistic is probably an underestimate because it is founded largely on patient self-reporting.[12] Psoriasis typically manifests as the plaque form of the disorder (psoriasis vulgaris; ~80–90% of patients). Most cases (~70–80%) are mild and can be treated successfully with topical therapy and phototherapy; however, about 20–30% of patients have moderate-to-severe disease that warrants systemic therapy.[10,11]

Anywhere from 10–40% of patients may have psoriatic nail involvement, and up to one-third of patients will have concurrent psoriatic arthritis. Nail and scalp involvement are prognostic indicators of psoriatic arthritis, which may be linked with negligible skin disease; conversely, severe forms of psoriatic arthritis are usually accompanied by severe skin disease.[3,4,10–12]

When psoriasis occurs, patients are typically affected for most of their lives.[4] The peak ages at which the condition manifests are 30–39 and 60–69 years, but the disorder can first appear at any age.[8] Individuals living at higher latitudes rather than equatorial regions, and Caucasians relative to other races, have a greater prevalence of psoriasis.[9,12] Indigenous Australians are rarely affected by the disorder.[14]

Psoriasis: disease burden

Comorbidities are common in patients with psoriasis and may include cardiovascular disease, diabetes, elevated lipid levels, infections, inflammatory bowel disease, liver disease, lymphoma, and stroke. Such concurrent conditions seem to be unrelated to lifestyle alone, but rather are additional aspects of psoriasis itself. In a UK cross-sectional study, more than 9,000 individuals with psoriasis, and aged 25–64 years, were compared with more than 90,000 controls without psoriasis and who were matched for age and medical practice. Adjustments were made for age, sex and duration of follow-up and, in patients with versus those without psoriasis, significantly increased risks were documented for the following concurrent conditions (**Figure 1**): chronic obstructive pulmonary disease (+8%; p=0.02); diabetes (+22%; p<0.001); peptic ulcer disease (+27%; p=0.04); renal disease (+28%; p=0.005); diabetes with complications (+34%; p=0.006); myocardial infarction (+34%; p=0.03); peripheral vascular disease (+38%; p=0.02); mild liver disease (+41%; p=0.008); and rheumatological disease (+104%; p<0.001).[15]

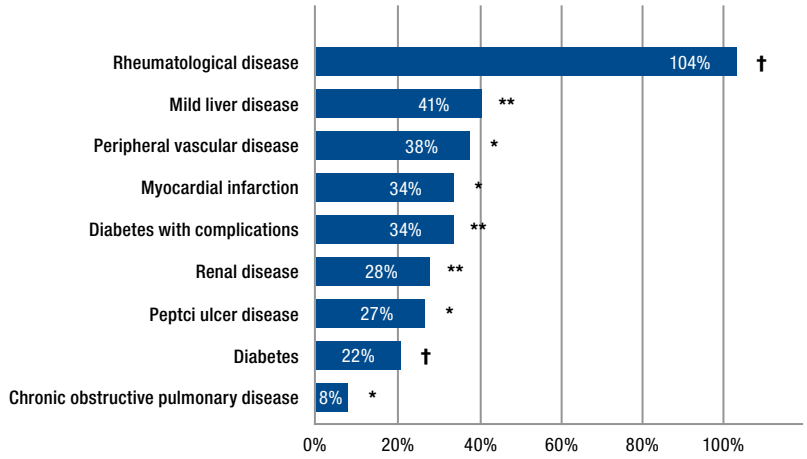

Figure 1. **Increased risk of comorbidities in patients with psoriasis**[15]
*p<0.05, **p≤0.01, †p<0.001 for patients with versus those without psoriasis.

As psoriasis is a chronic and considerably noticeable condition, it is often associated with psychiatric comorbidities such as depression.[4,6–8,11] Personal interactions, such as those necessitating skin contact, activities of daily living, and work ability and performance can all be adversely affected.[4,11,16] The costs to patients, healthcare systems and society are therefore enormous.[9]

Interventions for psoriasis (e.g. secukinumab) are becoming far more effective at managing dermal and systemic components of the disorder. The simultaneous, long-term management of concurrent conditions therefore takes on additional significance, since it is associated with marked increases in total healthcare costs. Results from the US in 2005 revealed that more than 3 million people had psoriasis, and annual disease-management costs were estimated at US$687 million (direct costs), US$121 million (indirect costs; lost productivity), and US$2.3 billion (indefinable costs due to quality of life impact).[17] In Australia, large cross-sectional studies endorsed the enormous burden posed by psoriasis: substantial proportions of patients admitted to energetically concealing their condition from the public (83%), friends (58%), family (40%), or a partner (20%). A major detrimental effect on health-related quality of life (HRQoL) was also evident from a mean EQ-5D scale score of only 0.73. In the three-quarters of patients with concurrent conditions, the EQ-5D score was further reduced to a mean of only 0.64.[18]

Psoriasis: treatment trends

Psoriasis cannot be cured, but it can be controlled with appropriate intervention. In cases of mild psoriasis, topical formulations such as corticosteroids, calcipotriol and coal tar are frontline treatments.[3,7] In moderate-to-severe disease, traditional treatments comprise acitretin, phototherapy with narrow-band ultraviolet B, cyclosporin, and methotrexate.

Acitretin, an oral retinoid, has limited efficacy as monotherapy and is typically used in conjunction with phototherapy. However, it can be associated with considerable mucocutaneous toxicity: dry lips, fragile skin, hair loss, and peeling of skin from the palms and soles. In women, hair loss, which also occurs frequently during methotrexate administration, is a common cause of treatment withdrawal. Acitretin is also contraindicated in women of childbearing potential, as it remains in the system for ≥2 years.

Phototherapy requires patients to attend a dermatology clinic with a phototherapy machine 3 times per week. This is a slow, protracted intervention, and responses often take 6–8 weeks to manifest. For long-term maintenance therapy, patients must visit the dermatology clinic once every week or fortnight, and problems with overdosing include erythema (sunburn) and pruritus.[4]

Methotrexate is used frequently, especially in patients with concurrent psoriatic arthritis. However, problems with methotrexate use are common in the elderly and in patients with renal impairment. Folic acid should be taken by all methotrexate-treated patients, as this has the potential to reduce nausea; the management of methotrexate-induced nausea may, however, remain challenging. Other frequent clinical problems during methotrexate therapy include mouth ulceration, photosensitivity and drug-drug interactions. Although long-term, methotrexate-related hepatotoxicity is rare, clinical monitoring for this adverse event (AE) is needed, especially in patients with diabetes, fatty liver or obesity, and in those who ingest large quantities of alcohol (≥2 units per day).[4]

Because of the potential for dermal malignancy, hypertension, renal toxicity and drug-drug interactions, the duration of maintenance cyclosporin treatment is restricted to 1 year in the US, and to 2 years in Europe; however, no treatment duration limit exists in Australia. Cyclosporin has also been frequently linked with excessive hair production in women; this may occur as early as 3 months into treatment and is a common cause of cyclosporin withdrawal.

Several treatment schedules (e.g. combination, intermittent, rotational and sequential) have been evaluated and advocated for their potential to limit toxicities associated with traditional antipsoriatic therapies. However, Australian patients with psoriasis generally appear reticent about a change of treatment schedule, especially if they consider treatment efficacy to be satisfactory.

In recent years, biological agents have dramatically altered the treatment landscape for both dermal and arthritic aspects of psoriasis.[3,10] The Australian PBS subsidizes several such agents: the earlier compounds adalimumab, etanercept and infliximab; and the recent additions secukinumab, a first-in-class IL-17A inhibitor, and ustekinumab, an IL-12/23 antagonist. The earlier compounds were associated with serious infections such as tuberculosis and reactivation of hepatitis B, and with non-melanoma skin cancer.[10] However, uncertainty exists about whether increased risks of the latter event, and potentially also melanoma, are a class effect or the result of excessive sun exposure in patients with psoriasis.

In the large-scale, 1-year FIXTURE trial, the incidences of AEs were generally similar in secukinumab-treated patients versus etanercept recipients: for example, all AEs (236.4–252.0 vs 243.4 events per 100 patient-years); infections or infestations (91.9–105.4 vs 91.4 events per 100 patient-years); and upper respiratory tract infections (6.6 vs 6.4 events per 100 patient-years). Secukinumab was significantly ($p<0.001$) more effective than etanercept regarding co-primary endpoints at week 12: PASI 75 response rate, and a response of 0 or 1 on the modified investigators' global assessment (IGA).[1] In another large-scale, 1-year study — CLEAR — secukinumab proved significantly ($p<0.0001$) more effective than ustekinumab regarding PASI 90 response rate at week 16. A significantly ($p<0.0001$) better HRQoL, as evident from a Dermatology Life Quality Index (DLQI) score of 0 or 1 at week 16, was also recorded in the secukinumab versus ustekinumab group.[2]

These results, together with demonstrated efficacy for secukinumab over 52 weeks in the placebo-controlled ERASURE trial, confirm IL-17A as a key therapeutic target in patients with moderate-to-severe plaque psoriasis.[1] Findings from FIXTURE and CLEAR provide definitive, head-to-head, comparative data, which are not available in many disease states, to facilitate decision-making for doctors when selecting appropriate treatment. The high PASI 90 response rates attained with secukinumab also indicate a key role for the compound in precision-medicine strategies for the management of moderate-to-severe plaque psoriasis.[2]

Secukinumab in Australia

Secukinumab is an IG1κ monoclonal antibody that selectively targets IL-17A, which has a key pathogenetic role in psoriasis by acting directly on keratinocytes to cause the release of inflammatory mediators.[2] In Australia, secukinumab is indicated for the treatment of moderate-to-severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.[19] Secukinumab monotherapy became available on the PBS (authority required) on 1st September 2015 for the treatment of severe chronic plaque psoriasis.

The efficacy and HRQoL benefits of secukinumab have already been emphasized, as has the clinical superiority of secukinumab over etanercept and ustekinumab. The safety and tolerability profiles of secukinumab are generally similar to those of etanercept and ustekinumab.[1,2] With secukinumab, continued watchfulness is warranted for any possible signs of increased risks of neutropenia or infections due to *Candida* spp.; indeed, IL-17A is important in host defence systems, and also has a key role in granulopoiesis and neutrophil transport.[1] However, pooled phase III data provide safety information for almost 2,000 patients (~3,600 patient-years of exposure) treated with secukinumab,[19] and confirm the compound's generally favourable safety profile.[20,21] In a meta-analysis of eight randomized controlled trials, and involving a total of more than 3,200 patients, there were no significant differences in the incidences of headache, pruritus or nasopharyngitis, or in the incidences of serious AEs (acute myocardial infarction, neoplasms, psoriatic arthropathy, transient ischaemic attacks, viral gastroenteritis) or infections, between secukinumab and placebo recipients.[21] Several studies of secukinumab are ongoing in various immune-mediated inflammatory diseases. In the currently considered condition of plaque psoriasis, continuing research (**Table 1**) is soon likely to provide additional clarity regarding the definitive place of secukinumab in precision-medicine antipsoriatic strategies. Extension studies of the longer-term efficacy and safety of secukinumab (up to 2 years of treatment) are ongoing, as are specific investigations of secukinumab in patients with psoriasis affecting the palms and soles (GESTURE), scalp (SCALP), and nails (TRANSFIGURE). Secukinumab is also being evaluated in patients with an inadequate response to tumour necrosis factor-α inhibitors (TNFi; SIGNATURE).

It has recently been reported that about 60% of patients with psoriasis have the presence of the genetic marker Cw6, and that the PASI 90 response to ustekinumab varies markedly between Cw6-positive and Cw6-negative patients.[22] In addition, the response to TNFi may be lower in Cw6-positive than Cw6-negative patients. Identification of a compound with equal efficacy, irrespective of the Cw6 status of patients, would facilitate precision antipsoriatic therapy, and would obviate the need for expensive Cw6 testing. An interesting Italian study, SUPREME, is therefore planned to determine the efficacy of secukinumab in Cw6-positive and Cw6-negative patients with moderate-to-severe plaque psoriasis. The study is due to be completed in September 2016.

The approaching release of longer-term and economic data for secukinumab in psoriasis will be especially relevant, as will the emergence of data about potentially clinically useful secukinumab-containing combination schedules. Meanwhile, as stipulated by authors of the CLEAR study comparison of secukinumab with ustekinumab, secukinumab is *'… the new reference standard treatment for patients with moderate to severe plaque psoriasis.'*[2]

Table 1. **Key planned or ongoing studies of secukinumab in patients with psoriasis**

Study	Status	Region	Start date	Estimated completion	Number of patients	Primary study endpoint
GESTURE	Fully enrolled	Australia, Canada, Europe, Israel, Russia, USA	Jun 2013	Nov 2016	205	*Palmoplantar psoriasis:* ppIGA at wk 16
Phase III extension	Recruiting	Asia, Australia, Canada, Europe, South America, USA	Jun 2012	Jun 2017	1,144	*Long-term efficacy:* loss of PASI 75 response at wk 68
Phase III extension	Fully enrolled	Asia, Canada, Europe, USA	Sep 2012	Apr 2017	676	*Long term safety:* AEs up to wk 104
SCALP	Recruiting	USA	Sep 2014	Dec 2015	94	*Scalp psoriasis:* PSSI 90 at wk 12
SIGNATURE	Recruiting	Europe	Oct 2012	Jun 2016	288	*TNFi-IR:* PASI 75 at wk 16
SUPREME	Not yet recruiting	Italy	Mar 2015	Sep 2016	406	*Cw6-positive and Cw6-negative patients:* PASI 90 at wk 24
TRANSFIGURE	Fully enrolled	Australia, Europe, USA	Jun 2013	Jan 2017	198	*Nail psoriasis:* % change from BL to wk 16 in NAPSI

AE = adverse event; BL = baseline; IGA = Investigators' Global Assessment; NAPSI = Nail Psoriasis Severity Index; PASI = Psoriasis Area and Severity Index; ppIGA = palmoplantar Investigators' Global Assessment; PSSI = Psoriasis Scalp Severity Index; TNFi-IR = inadequate responder to tumour necrosis factor-α inhibitor; wk = week

Product 'In Brief': Secukinumab

Mechanism of action

Secukinumab is a fully human IgG1 antibody. It selectively binds to and neutralizes IL-17A, a pro-inflammatory cytokine involved in normal immune and inflammatory pathways. IL-17A has central functions in the provision of immune responses against infection, and in the pathogenesis of plaque psoriasis. The blood and affected skin of patients with psoriasis have increased numbers of natural immune cells and lymphocytes that produce IL-17A; and increased levels of IL-17A. This cytokine is upregulated in lesional, compared with non-lesional, skin in patients with psoriasis. It promotes tissue inflammation, neutrophil infiltration, bone and tissue destruction, and tissue remodelling (including angiogenesis and fibrosis).[3]

The mechanism of secukinumab action involves targeting of IL-17A through inhibition of the cytokine's interaction with IL-17A receptors, which are expressed on keratinocytes and several other cell types. Thus, secukinumab inhibits the cellular release of pro-inflammatory chemokines, cytokines, and mediators of tissue injury, and reduces the contribution of IL-17A to various immune-mediated inflammatory diseases. Secukinumab, at clinically significant levels, reaches the skin and reduces regional levels of markers of inflammation. In lesions of plaque psoriasis, secukinumab therefore reduces reddening, fibrosis and peeling.[3]

Pharmacodynamic properties

In pharmacodynamic studies, secukinumab has been shown to selectively 'collect' free IL-17A. Within 2–7 days of secukinumab administration to patients with psoriasis, plasma levels of total (i.e. free and secukinumab-bound) IL-17A are increased because of reduced clearance of secukinumab-bound IL-17A.[3]

After 1–2 weeks' administration of secukinumab, various biomarkers normally increased in the lesional skin of patients with plaque psoriasis were significantly reduced: these biomarkers included infiltrating epidermal neutrophils, and several neutrophil-related factors.[3]

Pharmacokinetic (PK) properties

Absorption

The mean absolute bioavailability of secukinumab is 73%. In patients with plaque psoriasis, a single subcutaneous (SC) dose of secukinumab 150 mg or 300 mg produced peak plasma concentrations of 13.7 or 27.3 µg/mL, respectively, 5–6 days after administration. The time to reach peak plasma concentration, after initial weekly administration during the first month of secukinumab treatment, was 31–34 days. With monthly SC doses of secukinumab 150 mg or 300 mg, peak plasma concentrations at steady-state were 27.6 or 55.2 µg/L, respectively. Steady-state was attained after 20 weeks. With repeated monthly secukinumab administration during maintenance therapy, peak plasma concentrations and area under the plasma concentration-time curve for secukinumab showed a 2-fold increase relative to single-dose administration.[3]

Exposure to secukinumab was dose-proportional in several studies in patients with psoriasis who received intravenous (IV) doses ranging from 1 x 0.3 mg/kg to 3 x 10 mg/kg, or SC doses ranging from a single 25 mg dose to multiple doses of 300 mg.[3]

Distribution

After administration of a single IV secukinumab dose to patients with psoriasis, the mean volume of distribution during the terminal phase was 7.10–8.60 L; this indicates that secukinumab is distributed minimally to peripheral compartments.[3]

After administration of a single SC dose of secukinumab 300 mg to patients with psoriasis, secukinumab concentrations in skin interstitial fluid were 28–39% of those in plasma, at 1–2 weeks postdose.[3]

Metabolism

Secukinumab's metabolic pathway has not been defined. However, as a fully human IgG1κ monoclonal antibody, the anticipated catabolic pathway for secukinumab is breakdown into small peptides and amino acids, in a fashion similar to that for endogenous IgG.[3]

Elimination

In patients with psoriasis, the mean systemic clearance of secukinumab was 0.19 L/day. Clearance was time- and dose-dependent, and mean elimination half-life was estimated at 27 days (range 17–41 days).[3]

PK in special populations

The PK of secukinumab have not been evaluated in paediatric patients, or in those with hepatic or renal impairment. However, based on data from the secukinumab clinical trial program, which included 230 patients with psoriasis aged ≥65 years, and 32 patients aged ≥75 years, population PK analysis suggests no difference in secukinumab clearance between elderly patients and those aged <65 years.[3]

Dosage

The recommended dosage of secukinumab is 300 mg given by SC injection, with initial doses at weeks 0, 1, 2, and 3, then monthly maintenance doses of 300 mg from week 4 onwards. Each 300 mg dose is administered as 2 x 150 mg SC injections of secukinumab. No dosage recommendations can be made for paediatric or adolescent patients, or patients with hepatic or renal impairment; however, no secukinumab dosage adjustments are needed in elderly patients.[3]

Contraindications

Secukinumab should not be administered to any patients who have experienced severe hypersensitivity reactions to the active constituent or to any of the formulation excipients.[3]

Interactions with other medicines

Live vaccines should not be administered concomitantly with secukinumab. Interaction studies have not been conducted in humans. However, as part of the secukinumab clinical trial program, the compound was administered concurrently with methotrexate in patients with arthritis. No interaction was noted between secukinumab and methotrexate.[3]

Adverse events

Pooled data about the safety profile of secukinumab are available from four, 12-week, phase III, placebo-controlled trials (ERASURE, FIXTURE, FEATURE and JUNCTURE) involving a total of more than 2,000 patients with psoriasis. The most common AEs were upper respiratory tract infections (primarily nasopharyngitis and rhinitis; **Table 2**), which were usually mild or moderate in severity. Uncommon AEs (incidence >1 in 1,000 to ≤1 in 100) comprised sinusitis, tinea pedis, tonsillitis, oral candidiasis, conjunctivitis, and neutropenia. In these trials, the proportion of patients who discontinued secukinumab due to AEs (1.2%) was the same as the percentage who discontinued placebo (1.2%).[3]

Table 2. **AEs (% patients) occurring with a frequency of ≥1% in phase III clinical trials[3]**

AE	Secukinumab 150 mg (N=692)	Secukinumab 300 mg (N=690)	Placebo (N=694)
Infections and infestations:			
Nasopharyngitis	12.3	11.4	8.6
Upper respiratory tract infection	3.2	2.5	0.7
Rhinitis	1.4	1.4	0.7
Oral herpes	0.1	1.3	0.3
Pharyngitis	1.0	1.2	0.0
Gastrointestinal disorders:			
Diarrhoea	2.6	4.1	1.4
Skin and SC tissue disorders:			
Urticaria	1.2	0.6	0.1
Respiratory, thoracic and mediastinal disorders:			
Rhinorrhoea	0.3	1.2	0.1

During 12-week clinical trials, the incidence of infections was 28.7% in secukinumab-treated patients, compared with 18.9% in placebo recipients. Most infections were mild or moderate, but serious infections occurred in 0.14% versus 0.3% of patients. During follow-up for up to 1 year, 47.5% of secukinumab-treated patients had infections (0.9 events per patient-year); and 1.2% of secukinumab recipients had serious infections (0.015 events per patient-year). An increased incidence of mucosal or cutaneous candidiasis was noted in secukinumab-treated patients because of the mechanism of secukinumab action. These cases of candidiasis were mild or moderate, non-serious, and responded to standard therapy; they did not require cessation of secukinumab therapy. During the 12-week induction period, the overall incidence of candidiasis was 1.2% with secukinumab 300 mg, 0.3% with etanercept, and 0.3% with placebo.[3]

In the secukinumab clinical trial program, one case of urticaria and one of anaphylaxis was reported. The incidence of antibody development to secukinumab was <1% during 1 year of treatment. Up to 50% of the treatment-emergent anti-secukinumab antibodies were neutralizing; however, these were not associated with loss of secukinumab efficacy or PK alterations. During the 12-week induction phase of clinical trials, mild-to-moderate reproductive system AEs were reported in women treated with secukinumab 300 mg: dysmenorrhoea (1.9%); metrorrhagia (including menometrorrhagia; 1.4%); and menorrhagia (0.9%).[3]

Clinical trials of secukinumab

Secukinumab in plaque psoriasis — results of two phase three trials

Authors: Langley RG, et al.

Background: IL-17A has a key role in the pathogenesis of psoriasis. Two studies — Efficacy of Response And Safety of two fixed secUkinumab REgimens in psoriasis (ERASURE) and Full year Investigative eXaminaTion of secUkinumab vs. etaneRcept using two dosing regimens to determine Efficacy in psoriasis (FIXTURE) — were therefore conducted to determine the efficacy and safety of secukinumab, a fully human IL-17A antagonist, in patients with moderate-to-severe plaque psoriasis.

Methods: These were double-blind, 1-year studies. In ERASURE, 738 patients were randomized to SC secukinumab 150 mg or 300 mg, once weekly for 5 weeks, then once every 4 weeks, or placebo. FIXTURE was the same as ERASURE, but with inclusion of etanercept 50 mg twice weekly for 12 weeks, then once every week, as an additional comparator schedule; a total of 1,306 patients were randomized in FIXTURE. Co-primary endpoints at week 12 in these trials were PASI 75 response rate, and the proportion of patients with a score of 0 (clear) or 1 (almost clear) on the modified IGA.

Results: For both secukinumab dosages, PASI 75 response rate at week 12 (67.0–81.6%) was significantly (p<0.001) greater than in etanercept-treated patients (44.0%) and placebo recipients (4.5–4.9%). The same was true for IGA response (51.1–65.3% vs 27.2% vs 2.4–2.8%; p<0.001 for secukinumab vs both comparators; **Figures 2 & 3**). The incidence of AEs, including infections, during the induction period was greater in both secukinumab groups than in placebo recipients. However, during the induction period and overall 1-year treatment phase, the incidence of AEs was similar in the secukinumab and etanercept groups. Injection-site reactions occurred less frequently in patients treated with secukinumab than etanercept (0.7% vs 11.1% of patients), but this difference was not evaluated for statistical significance.

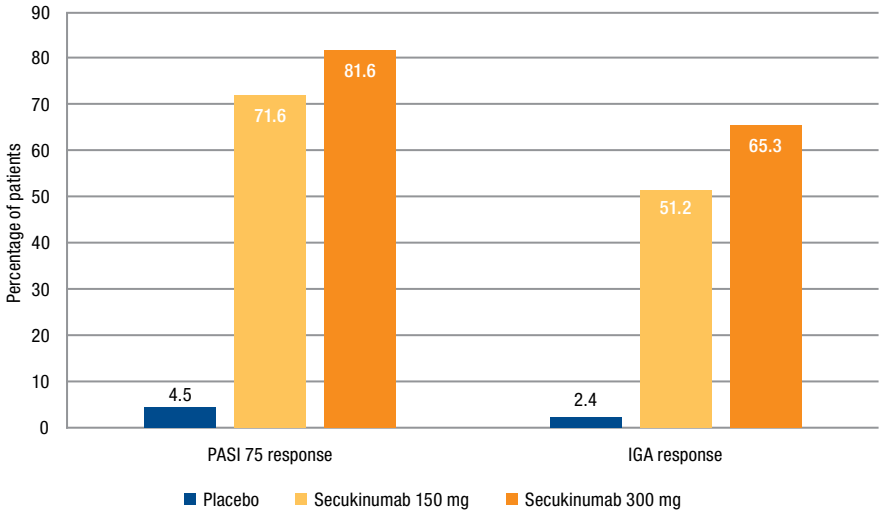

Figure 2. **Principal results from ERASURE at week 12.**
All differences p<0.001 vs placebo.

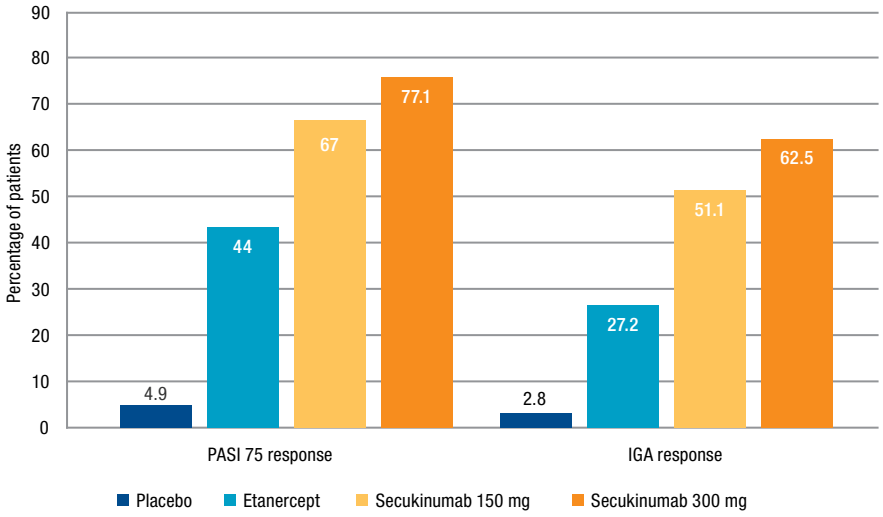

Figure 3. **Principal results from FIXTURE at week 12.**
For all secukinumab vs etanercept and placebo differences, p<0.001.

Conclusions: These studies confirm that IL-17A is a viable therapeutic target in patients with moderate-to-severe plaque psoriasis. They also confirm the significant efficacy of secukinumab for up to 52 weeks in this clinical setting.

Comment: These phase III studies, one of which included an active comparator (etanercept), demonstrate that secukinumab 300 mg SC every 4 weeks is superior to secukinumab 150 mg SC every 4 weeks, and that both doses are superior to etanercept SC twice every week. Etanercept is the market leading biologic therapy for psoriasis in many countries.

Reference: N Engl J Med 2014;371:326–38.
Full article

Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate to severe plaque psoriasis

Authors: Thaçi D, et al.

Background: In the FIXTURE trial, clinical superiority was demonstrated for secukinumab over etanercept in patients with moderate-to-severe plaque psoriasis. The current trial (CLEAR) was therefore conducted to compare secukinumab with a biological agent with a different mechanism of action: ustekinumab, which is an IL-12/23 antagonist. The CLEAR trial is ongoing and will obtain data over a 52-week treatment period. Results from week 16 are outlined here.

Methods: CLEAR is a randomized, double-blind study being conducted at 134 sites worldwide. A total of 676 patients with moderate-to-severe plaque psoriasis were randomized to SC secukinumab 300 mg (once weekly for 4 doses, then once every 4 weeks; n=337) or ustekinumab 45 mg or 90 mg (one dose at baseline and week 4, then one dose every 12 weeks; n=339).

Results: Secukinumab was significantly more effective than ustekinumab regarding the primary study endpoint of PASI 90 response rate at week 16 (79.0% vs 57.6%; p<0.0001; **Figure 4**). The same also applied for the following week-16 response rates: PASI 100 (44.3% vs 28.4%; p<0.0001), PASI 75 (93.1% vs 82.7%; p=0.0001), IGA (82.9% vs 67.5%; p<0.0001), and the proportion of patients with a DLQI score of 0 or 1 (71.9% vs 57.4%; p<0.0001). During the 16-week treatment period, no new or unanticipated safety signals were recognized for secukinumab. The safety profile for secukinumab was similar to that for ustekinumab and in line with that noted in the pivotal phase III studies of secukinumab.

Conclusions: *'Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate to severe plaque psoriasis with similar safety. Greater clinical efficacy with secukinumab is accompanied by significantly greater improvement in HRQoL, compared with ustekinumab.'*

Comment: This phase III, active-comparator study demonstrates that secukinumab has superior efficacy at 16 weeks compared to 12 weeks, and superior efficacy to ustekinumab at all time points. Ustekinumab was previously considered the most effective biologic therapy for psoriasis.

Reference: J Am Acad Dermatol 2015;73:400–9.
Full article

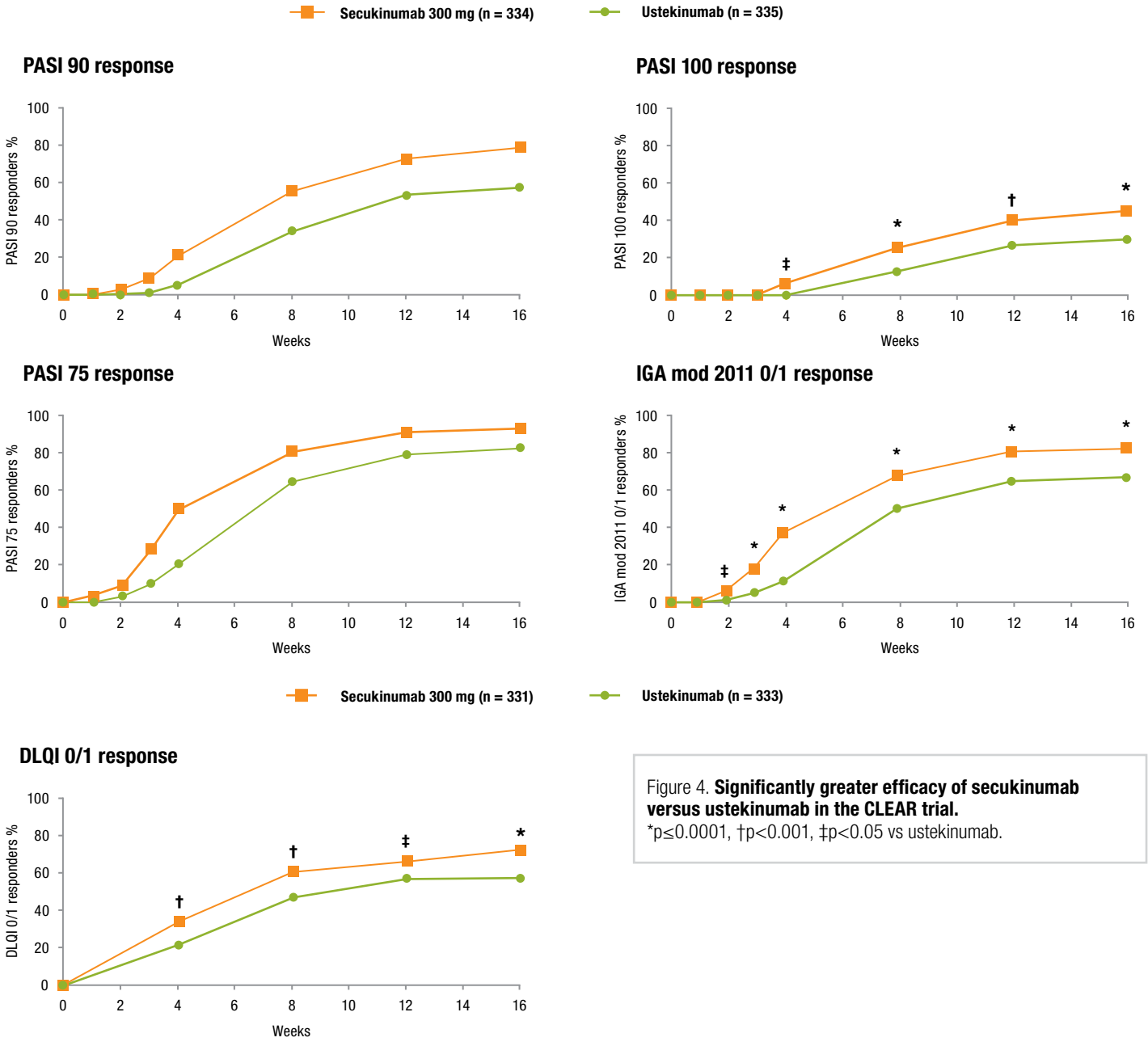

Figure 4. **Significantly greater efficacy of secukinumab versus ustekinumab in the CLEAR trial.**
*p≤0.0001, †p<0.001, ‡p<0.05 vs ustekinumab.

Efficacy, safety and usability of secukinumab administration by autoinjector/pen in psoriasis

Authors: Paul C, et al.

Background: Secukinumab is a fully human anti-IL-17A monoclonal antibody that has demonstrated marked efficacy in the management of moderate-to-severe plaque psoriasis. The current study, JUNCTURE, was designed to assess the efficacy, safety and usability of a secukinumab autoinjector/pen.

Methods: In this phase III trial, 182 patients with moderate-to-severe plaque psoriasis were randomized to self-injection of secukinumab 150 mg (n=61), 300 mg (60) or placebo (61), once every week for 4 weeks, then once every 4 weeks.

Results: At week 12, secukinumab was significantly more effective than placebo regarding the co-primary endpoints of PASI 75 response rate (71.7–86.7% vs 3.3%; p<0.0001), and the proportion of patients with an IGA score of 0/1 (53.3–73.3% vs 0.0%; p<0.0001). Self-administration of secukinumab was successfully achieved by all patients at week 1, with no major use-related problems. During the 12-week study period, patient acceptability of the autoinjector was high. The AE incidence was greater in secukinumab-treated patients than placebo recipients (63.9–70.0% vs 54.1%), primarily because of mild-to-moderate nasopharyngitis.

Conclusions: *'Secukinumab delivered by autoinjector/pen is efficacious, well-tolerated and associated with high usability in moderate to severe plaque psoriasis.'*

Comment: This study confirmed the safety and utility of a novel autoinjector pen for patient self-administration of secukinumab.

Reference: J Eur Acad Dermatol Venereol 2015;29:1082–90.
Abstract

Secukinumab retreatment-as-needed versus fixed-interval maintenance regimen for moderate to severe plaque psoriasis

Authors: Mrowietz U, et al.

Background: With a fixed-interval regimen, secukinumab has shown marked, sustained efficacy for up to 52 weeks in patients with psoriasis. The current study, SCULPTURE, was therefore conducted to compare a fixed-interval secukinumab schedule with a retreatment-as-needed regimen.

Methods: This was a randomized, double-blind study in which 966 adults with moderate-to-severe plaque psoriasis received secukinumab 150 mg (n=482) or 300 mg (484), once each week from baseline to week 4, and then once at week 8. Patients with a PASI 75 response at week 12 were then randomized to secukinumab retreatment-as-needed with 150 mg (n=200) or 300 mg (217), or to fixed-interval therapy with secukinumab 150 mg (203) or 300 mg (217). The principal study endpoint was noninferiority regarding maintenance of the PASI 75 response to week 52 for retreatment-as-indeed versus fixed-interval secukinumab therapy.

Results: At week 12, the PASI 75 response to secukinumab was high: 84.4–91.1%. From week 12 to 52, fewer patients in the retreatment-as-needed versus fixed-interval group had a maintained PASI 75 response: secukinumab 150 mg (52.4% vs 62.1%); secukinumab 300 mg (67.7% vs 78.2%). However, statistical noninferiority was not demonstrated. The safety profile of secukinumab was similar between the two treatment regimens, including a low incidence (<0.5% of patients) of treatment-emergent anti-secukinumab antibody development.

Conclusions: The maintenance efficacy of a fixed-interval secukinumab schedule was greater than that of a retreatment-as-needed regimen, and both regimens displayed safety profiles in line with those from previous studies. The retreatment-as-needed secukinumab schedule now merits additional assessment.

Comment: This study determined that patients who continue with maintenance therapy once their psoriasis has cleared up achieve better long term control than patients who stop their treatment once their psoriasis is clear and only restart their treatment after relapse.

Reference: J Am Acad Dermatol 2015;73:27–36.
Abstract

Expert's comments: TNFi such as etanercept, infliximab and adalimumab represent the first-generation biologic therapies for psoriasis. Their introduction changed the lives of hundreds of thousands of people with psoriasis worldwide. Second-generation biologic therapies such as ustekinumab target the IL-12/23 pathway and represented a significant advance over first-generation biologics in terms of efficacy and convenience with 3-monthly dosing. Secukinumab represents the first of the third-generation of biologic therapies for psoriasis and targets the IL-17 pathway. It has redefined efficacy goals in that patients now aspire to complete clearance of their psoriasis rather than disease control.

References

1. Langley RG, Elewski BE, Lebwohl M, et al. Secukinumab in plaque psoriasis—results of two phase 3 trials. *N Engl J Med* 2014;371:326–38.
2. Thaçi D, Blauvelt A, Reich K, et al. Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate to severe plaque psoriasis: CLEAR, a randomized controlled trial. *J Am Acad Dermatol* 2015;73:400–9.
3. Better Health Channel. Psoriasis. State of Victoria. Available from: https://www.betterhealth.vic.gov.au/health/conditionsandtreatments/psoriasis?viewAsPdf=true [accessed 2 November 2015].
4. Sullivan JR, Preda VA. Treatments for severe psoriasis. *Australian Prescriber* 2009;2009:14–8.
5. Plaque psoriasis (psoriasis vulgaris). Psoriasis Rx. Available from: http://www.psoriasisrx.com/plaque_psoriasis.asp [accessed 2 November 2015].
6. Psoriasis. Healthdirect Australia. Available from: http://www.healthdirect.gov.au/psoriasis [accessed 2 November 2015].
7. Clarke P. Psoriasis. *Aust Fam Physician* 2011;40:468–73.
8. Chong HT, Kopecki Z, Cowin AJ. Lifting the silver flakes: the pathogenesis and management of chronic plaque psoriasis. *Biomed Res Int* 2013;2013:168321.
9. Parisi R, Symmons DP, Griffiths CE, Ashcroft DM. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. *J Invest Dermatol* 2013;133:377–85.
10. Kivelevitch D, Mansouri B, Menter A. Long term efficacy and safety of etanercept in the treatment of psoriasis and psoriatic arthritis. *Biologics* 2014;8:169–82.
11. Lonnberg AS, Zachariae C, Skov L. Targeting of interleukin-17 in the treatment of psoriasis. *Clin Cosmet Investig Dermatol* 2014;7:251–9.
12. Cimmino MA. Epidemiology of psoriasis and psoriatic arthritis. *Reumatismo* 2007;59 Suppl 1:19–24.
13. Cole GW. Psoriasis. MedicineNet, Inc. Available from: http://www.medicinenet.com/script/main/art.asp?articlekey=459 [accessed 2 November 2015].
14. Heyes C, Tait C, Toholka R, Gebauer K. Non-infectious skin disease in Indigenous Australians. *Australas J Dermatol* 2014;55:176–84.
15. Yeung H, Takeshita J, Mehta NN, et al. Psoriasis severity and the prevalence of major medical comorbidity: a population-based study. *JAMA Dermatol* 2013;149:1173–9.
16. Gooderham M, Posso-De Los Rios CJ, et al. Interleukin-17 (IL-17) inhibitors in the treatment of plaque psoriasis: a review. *Skin Therapy Lett* 2015;20:1–5.
17. The Society for Investigative Dermatology and The American Academy of Dermatology Association. The burden of skin diseases 2005. Available from: http://www.lewin.com/content/dam/Lewin/Resources/Site_Sections/Publications/april2005skindisease.pdf [accessed 3 November 2015].
18. Baker CS, Foley PA, Braue A. Psoriasis uncovered--measuring burden of disease impact in a survey of Australians with psoriasis. *Australas J Dermatol* 2013;54 Suppl 1:1–6.
19. Cosentyx® prescribing information. Novartis Pharmaceuticals Australia Pty Limited. Available from: https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2015-PI-01060-1 [accessed 4 November 2015].
20. Adami S, Cavani A, Rossi F, Girolomoni G. The role of interleukin-17A in psoriatic disease. *BioDrugs* 2014;28:487–97.
21. 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;8:3156–72.
22. Talamonti M, Botti E, Galluzzo M, et al. Pharmacogenetics of psoriasis: HLA-Cw6 but not LCE3B/3C deletion nor TNFAIP3 polymorphism predisposes to clinical response to interleukin 12/23 blocker ustekinumab. *Br J Dermatol* 2013;169:458–63.

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