Secukinumab for the Treatment of Plaque Psoriasis: A Review of Phase III Testing

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Abstract

IL-17 is the newest cytokine implicated in the pathogenesis of psoriasis. Preclinical and phase II testing to pharmaceutically block this cytokine has proved promising. The results of phase III clinical trials using secukinumab were reviewed to evaluate safety and efficacy profiles for this medication. By week 12, the percentages of patients achieving 75% improvement in Psoriasis Area and Severity Index (PASI 75) and the investigator's global assessment scores of 0 or 1 were superior with doses of secukinumab 300 mg and 150 mg over placebo. In a head-to-head study, secukinumab also performed superiorly compared to ustekinumab, an anti-interleukin-12/23 agent. The safety profile of secukinumab was favorable, with nasopharyngitis, upper respiratory tract infection, headache, and diarrhea being the most common adverse events. Infections, to include especially mild candida infections, were more prevalent over placebo, and few patients experienced asymptomatic neutropenia. Overall, secukinumab exhibited a strong efficacy clinically, with a good safety profile.

Introduction

Secukinumab is the most recent biologic medication to gained U.S. Food and Drug Administration (FDA) approval for the treatment of moderate-to-severe plaque psoriasis.[1] Psoriasis patients, especially those with moderate-to-severe disease, are substantially undertreated, leading to a severe impairment of social and occupational wellbeing.[2] The advent of biologic agents significantly increased the dermatologist's ability to treat moderate-to-severe psoriasis.[3]

Secukinumab is currently the only FDA approved biologic that acts by inhibiting the interleukin (IL)-17 cytokine.[1] IL-17 is a proinflammatory cytokine that has been detected in psoriatic lesions and is strongly implicated in psoriasis pathogenesis.[4-10] It is a downstream product of interleukin-23, which is targeted by another currently approved biologic, ustekinumab.[9,11,12] In particular, IL-17A, one of the six homodimers of IL-17, is considered the most important in this family for psoriasis development.[13-15] Secukinumab is a fully human monoclonal IgG1 antibody that specifically binds to and inhibits IL-17A, which normally acts on keratinocytes to promote changes culminating in the clinical manifestation of psoriasis.[16,17] Additionally, IL-17 plays a role in the recruitment and activation of neutrophils, the blockade of neutrophil apoptosis, and the stimulation of psoriasis angiogenesis.[14,18-21]

In addition to treating psoriasis, secukinumab is currently under investigation for the treatment of psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, multiple sclerosis, Crohn's disease, and non-infectious uveitis.[22-27]

The purpose of this article is to review the five phase III studies for secukinumab. Two clinical trials assessed the clinical response to secukinumab, with co-primary end points of at least 75% reduction in Psoriasis Area and Severity Index (PASI 75) and scores of 0 (clear) or 1 (almost-clear) based on a five-point investigator's global assessment (IGA) by week 12 of treatment. IGA is a tool used by clinicians to document their impression of disease severity, with scores ranging from 0 (clear) to 4 (severe disease).[28-30] An additional phase III trial compared secukinumab to ustekinumab in a head-to-head study, with a primary end point of PASI 90 at week 16.[31]

Methods

We reviewed the published phase III clinical trial results involving the clinical efficacy of secukinumab. An English language literature search was carried out on PubMed with the following word combinations: "secukinumab" and "psoriasis" or "IL-17" and "psoriasis." Citations within these publications were also reviewed for pertinent data. Additionally, information on these topics was collected from oral presentations from the 73rd Annual Meeting of the American Academy of Dermatology.

Results

Two major clinical trials were conducted to investigate efficacy and safety of different doses of secukinumab. The first study compared secukinumab against placebo, and the other against placebo and etanercept. In addition, two minor studies evaluated the efficacy of two different delivery methods of the medication. Another study directly compared secukinumab to ustekinumab with a head-to-head design.

ERASURE

Study design. In this clinical trial, a total of 737 patients were randomized 1:1:1 to either secukinumab 300 mg, secukinumab 150 mg, or placebo. The two co-primary endpoints were achievement of PASI 75 and IGA 0 or 1 at week 12. Patients who received secukinumab 300 mg and 150 mg were followed for another 40 weeks of maintenance. Those assigned to secukinumab received dosages at baseline, and then weekly for four weeks, followed by every four weeks for the remainder of the study.

Efficacy. By week 12, significantly higher percentages of those in both secukinumab 300 mg and secukinumab 150 mg groups achieved PASI 75 (81.6% and 71.6%, respectively) and IGA 0 or 1 (65.3% and 51.2%, respectively) than those who took placebo, of whom 4.5% reached PASI 75 and 2.4% reached IGA 0 or 1 (P<0.001). Additionally, greater efficacy was demonstrated with 300 mg than with 150 mg. Similar patterns were also noted for PASI 90 during the maintenance period and improvements of QoL, as assessed by the Dermatology Life Quality Index (P<0.001) (**Table 1**).

Adverse events. There was an overall higher incidence of adverse events with the secukinumab 300 mg and 150 mg groups than with placebo (55.1%, 60.4%, and 47.0%, respectively). Infections were more prevalent with the secukinumab 300 mg and 150 mg groups versus placebo (29.4%, 26.9%, and 16.2%, respectively). The most common adverse events were nasopharyngitis, headache, and upper respiratory tract infection. The clinical presentations and rates of serious adverse events were similar with secukinumab 300 mg, 150 mg, and placebo (6.3/100, 6.4/100 and 7.4/100, respectively, in patient-years).

FIXTURE

Study design. A total of 1,305 patients were randomized 1:1:1:1 to either secukinumab 300 mg, secukinumab 150 mg, etanercept 50 mg, or placebo. This clinical trial evaluated secukinumab against placebo with co-primary endpoints of PASI 75 and IGA 0 or 1 at week 12. Those assigned to secukinumab received dosages at baseline, and then weekly for four weeks, followed by every four weeks for the remainder of the study; etanercept was

Table 1. Primary and secondary end points in ERASURE, FIXTURE, FEATURE, and JUNCTURE*

End Point (category)	STUDY	Secukinumab 300 mg	Secukinumab 150 mg	Placebo	Etanercept 50 mg**
PASI 75 Week 12 (1°)	ERASURE	81.6% (200/245)	71.6% (174/243)	4.5% (11/246)	--
	FIXTURE	77.1% (249/323)	67.0% (219/327)	4.9% (16/324)	44.0% (142/323)
	FEATURE	75.9% (44/58)	69.5% (41/59)	0% (0/59)	--
	JUNCTURE	86.7% (52/60)	71.7% (43/60)	3.3% (2/61)	--
IGA 0 or 1 Week 12 (1°)	ERASURE	65.3% (160/245)	51.2% (125/244)	2.4% (6/246)	--
	FIXTURE	62.5% (202/323)	51.1% (167/327)	2.8% (9/324)	27.2% (88/323)
	FEATURE	69.0% (40/58)	52.5% (31/59)	0% (0/59)	--
	JUNCTURE	73.3% (44/60)	53.3% (32/60)	0% (0/61)	--
PASI 90 Week 12 (2°)	ERASURE	59.2% (145/245)	39.1% (95/243)	1.2% (3/246)	--
	FIXTURE	54.2% (175/323)	41.9% (137/327)	1.5% (5/324)	20.7% (67/323)
	FEATURE	60.3% (35/58)	45.8% (27/59)	0% (0/59)	--
	JUNCTURE	55% (33/60)	40% (24/60)	0% (0/61)	--
PASI 75 Weeks 12-52 (2°)	ERASURE	80.5% (161/200)	72.4% (126/174)	--	--
	FIXTURE	84.3% (210/249)	82.2% (180/219)	--	72.5% (103/142)
	FEATURE	--	--	--	--
	JUNCTURE	--	--	--	--
DLQI Absolute Change (2°)	ERASURE	-11.4	-10.1	-1.1	--
	FIXTURE	-10.4	-9.7	-1.9	-7.9
	FEATURE	--	--	--	--
	JUNCTURE	--	--	--	--

*These studies were not conducted head-to-head. Studies had P<0.001 for ERASURE and FIXTURE and P<0.0001 for FEATURE and JUNCTURE.
**PASI 75 and IGA data for etanercept are considered secondary end points but are included for comparison.

PASI: Psoriasis Area and Severity Index; values indicate percentage improvement of cutaneous symptoms.
IGA: Investigator's global assessment.
DLQI: Dermatology Life Quality Index; an absolute decrease notes an improved individual assessment of a disease's impact on life.

administered twice at baseline, twice a week until week 12, and then weekly through week 51.

Efficacy. By week 12, the percentages of patients taking secukinumab 300 mg and 150 mg that achieved PASI 75 (77.1% and 67.0%, respectively) and IGA 0 or 1 (62.5% and 51.1%, respectively) were greater than with placebo (4.9% reached PASI 75 and 2.8% reached IGA 0 or 1) (P<0.001). Secukinumab at 300 mg produced superior results compared to 150 mg (P<0.001). Additionally, secukinumab 300 mg showed superiority over etanercept for the percentage of patients achieving PASI 75 (77.1% and 44.0%, respectively) and PASI 90 (54.2% and 20.7%, respectively) (**Figure 1**).

Adverse events. Overall, the incidence of adverse events was similar among secukinumab 300 mg and 150 mg and etanercept during induction (55.5%, 58.4%, and 57.6%, respectively), and was higher than placebo (49.8%). However, statistical analysis for significance was not performed. The most common adverse events with secukinumab were nasopharyngitis, headache and diarrhea. Infections were noted for secukinumab 300 mg and 150 mg, etanercept and placebo as follows: 26.7%, 30.9%, 24.5% and 19.3%, respectively. While more patients with secukinumab (33 out

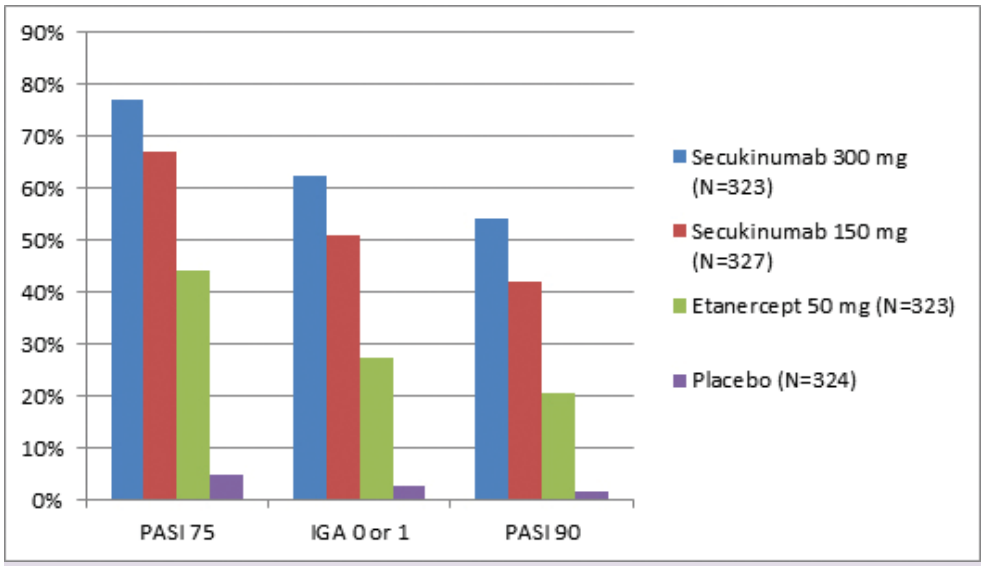

Figure 1. Percentages of patients achieving PASI 75, IGA 0 or 1, and PASI 90 at week 12. P<0.001 for all comparisons. Studies were not conducted in a head-to-head manner.

Table 2. Primary and secondary end points of secukinumab vs. ustekinumab phase III head-to-head study*

End Point (category)	Secukinumab	Ustekinumab
PASI 90 at Week 16 (1°)	79.0% (264/334)	57.6% (193/335)
PASI 100 at Week 16 (2°)	44.3% (148/334)	28.4% (95/335)
PASI 75 at Week 4 (2°)	50.0% (167/334)	20.6% (69/335)

*P<0.0001 for all comparisons.
PASI values indicate percent improvement of cutaneous lesions.

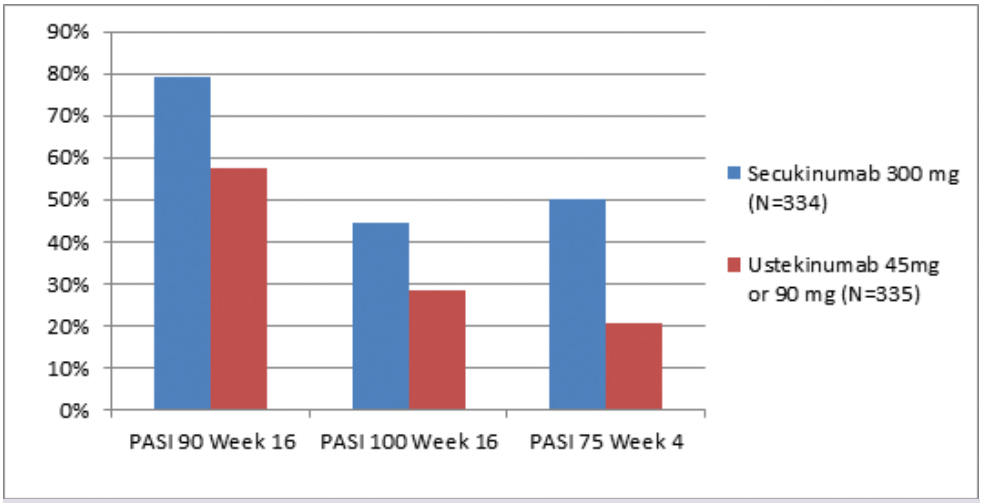

Figure 2. Percentages of patients achieving PASI 90 and 100 at week 16 and PASI 75 at week 4. P<0.0001 for all comparisons. Dosage of ustekinumab depended on a patient's body weight: Patients <100 kg (220 lbs) received 45 mg, whereas patients >100 kg (220 lbs) received 90 mg.

of 946) over etanercept (4 out of 333) developed candida infections, none of those associated with secukinumab were classified as "severe," while two cases associated with etanercept were classified as "severe." Nine patients in both secukinumab groups were determined to have Grade 3 neutropenia without associated infection, while one patient on etanercept was diagnosed with Grade 4 neutropenia. Serious adverse events were numerically lower with secukinumab 300 mg, secukinumab 150 mg and etanercept than with placebo (6.8/100, 6.0/100 7.0/100, and 8.3/100, respectively, in patient-years), though significance was not calculated. There was one suicide with placebo.

FEATURE and JUNCTURE

Study design. In the first study, 177 patients were randomized 1:1:1 to secukinumab 300 mg, secukinumab 150 mg or placebo. Medication administration was carried out using a pre-filled syringe (FEATURE). In a second study, 182 patients were randomized 1:1:1 to the same groups, but medication was administered by autoinjector/pen (JUNCTURE). Primary end points were again achievement of PASI 75 and IGA 0 or 1 among the three groups, whereas secondary end points included medication-administration dynamics.

Efficacy. Efficacies of the three treatment groups were similar to former studies, despite small sample sizes (**Table 1**). Both the pre-filled syringe and autoinjector/pen delivery methods were shown to be successfully learned and employed by the first week of use (**Table 1**).

Adverse events. Nasopharyngitis was a common adverse event. There were no new safety concerns of note that deviated from the former major studies.[28,30]

Head-to-head Against Ustekinumab

Study design. In this head-to-head phase III trial, 676 patients were randomized 1:1 to either secukinumab 300 mg or to either 45 mg or 90 mg of ustekinumab, depending on their weight. In line with FDA dosage guidelines, ustekinumab dosing was based on each patient's weight such that patients weighing <100 kg (220 lbs) received 45 mg, and patients weighing ≥100 kg (220 lbs) received 90 mg at each appropriate visit. Secukinumab was administered once at baseline and then weekly at weeks 1, 2, 3, and 4, and then every four weeks through week 48. Ustekinumab was also administered at baseline, then at weeks 4, 16, 28, and 40. The primary end point for this study was achievement of PASI 90 at week 16. Secondary end points included PASI 100 at week 16 and PASI 75 at week 4.

Efficacy. Of 334 secukinumab and 335 ustekinumab patients evaluated, 79.0% and 57.6%, respectively, reached PASI 90 at week 16. Secukinumab was shown to be superior to ustekinumab in all secondary end points, including: PASI 100 at week 16 (44.3% and 28.4%, respectively), PASI 75 at week 4 (50.0% and 20.6%, respectively), and PASI 75 and IGA 0 or 1 at week 16 (**Table 2**, **Figure 2**).

Adverse events. There were no new substantial safety findings that deviated from other major phase III clinical trials. Total incidents of adverse events were similar for secukinumab and ustekinumab, 64.2% and 58.3%, respectively, and infection rates were 29.3% and 25.3%, respectively. Both groups were notable for 3% serious adverse events. Headache, nasopharyngitis, diarrhea, arthralgia, and fatigue were the most common events for both groups.[31]

Discussion

The clinical efficacy of IL-17 inhibitors such as secukinumab in phase III clinical trials further supports the importance of IL-17 (particularly IL-17A) in the pathogenesis of plaque psoriasis. A significant portion of patients who received this anti-IL-17 medication achieved PASI 75 and IGA scores of 0 or 1 – far greater than the portion that received placebo. Secukinumab performed considerably better than etanercept and ustekinumab, which were used as active comparators in these studies. Within the confines of these studies, there was no substantial difference noted in the safety profiles of these three medications.

Two other biologic agents targeting IL-17 are currently in development. While IL-17A is thought to be the most important of the IL-17 homodimers involved with psoriasis, IL-17F is also thought to play at least a small part.[15,32] Brodalumab, a humanized antibody that blocks the receptor subunit (IL-17RA) to which both IL-17A and IL-17F bind, is thought to have a more powerful effect against psoriasis because of a wider blockage of IL-17 subsets. While there has been no head-to-head comparison, and dosages and schedules of administration were noted to be different, in phase II trials the percentage achieving PASI 90 was higher with brodalumab 210 mg (75%) than with secukinumab 150 mg (52%), while the PASI 75 was comparable (P<0.001).[34] Similar to the studies on secukinumab, the most common side effects in studies involving brodalumab were infectious in nature – though there was one case of serious neutropenia with brodalumab, leading to discontinuation of the medication in this patient.[34] One potential concern with brodalumab is that the broader blockage might prove to have negative clinical implications. For instance, in asthma studies, IL-17F deficiency (which would occur with brodalumab targeting the IL-17 receptor) led to higher expression of T helper type 2 (Th2) cytokine with more eosinophil function.[35] The clinical relevance of this information was not established.

Another drug in development is ixekizumab, a humanized IgG4 monoclonal antibody that also specifically targets 17A.[36] Secukinumab, on the other hand, is fully human. An increased humanness score is theoretically associated with a decreased extent of immunogenicity, as there is less deviation from the recipient species.[37] Therefore, the fully human secukinumab may pose less of an immunologic risk than the humanized ixekizumab. However, studies suggest that the fully human and high-scoring humanized antibodies share relatively similar

immunogenicity.[37,38] In the FIXTURE study, 7 of 19 patients who had anti-secukinumab antibodies at baseline continued to test positive for the antibodies. There were no associated decreases in efficacy or adverse events noted in these patients. Additionally, two patients on placebo and four patients on etanercept in the FIXTURE study, and two of 702 patients receiving secukinumab in the ERASURE study, tested positive for anti-secukinumab antibodies following the initiation of treatment.[29]

Likewise, there is a difference in the isotype used by the two medications. Ixekizumab uses the isotype IgG4, which has been shown to act as a bispecific molecule *in vivo*, with the ability to interact with two separate antigens. This bispecificity may potentially lead to unknown drug reactions. However, this isotype is thought to be functionally monovalent. IgG1, used for secukinumab, is the most common isotype that is selected for the manufacture of therapeutic antibodies. This isotype is of particular interest when an active antibody is necessary for complement activation and antibody-dependent effector-mediated cell killing, in the cases of certain cancer treatments. In contrast, IgG4 does not activate complement -- though when these criteria are not pertinent, as with these anti-psoriatic medications, studies have noted either choice (IgG1 and IgG4) may be considered acceptable theoretically, especially since the isotypes may be modified to improve function.[39] It would be prudent to follow long-term outcomes to see if these molecular design details convey any clinical difference.

Conclusions

The phase III trials of secukinumab have demonstrated positive results in the treatment of plaque psoriasis. While the drug has a satisfactory initial safety profile, long-term phase IV surveillance and registries are needed.

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