ORIGINAL ARTICLE

Secukinumab long-term safety experience: A pooled analysis of 10 phase II and III clinical studies in patients with moderate to severe plaque psoriasis

Peter C. M. van de Kerkhof, MD, PhD,[a] Christopher E. M. Griffiths, MD,[b] Kristian Reich, MD, PhD,[c] Craig L. Leonardi, MD,[d] Andrew Blauvelt, MD, MBA,[e] Tsen-Fang Tsai, MD,[f] Yankun Gong, PhD,[g] Jiaqing Huang, MD, PhD,[h] Charis Papavassilis, MD, PhD,[i] and Todd Fox, RPh, PharmB, ACPR[i]

Nijmegen, The Netherlands; Manchester, United Kingdom; Göttingen, Germany; Saint Louis, Missouri; Portland, Oregon; Bethesda, Maryland; Taipei, Taiwan; Shanghai, China; East Hanover, New Jersey; and Basel, Switzerland

Background: Secukinumab, a fully human anti−interleukin-17A monoclonal antibody, has demonstrated efficacy and safety in patients with moderate to severe plaque psoriasis.

Objective: We reviewed safety data from the secukinumab psoriasis phase II/III program.

Methods: Data were pooled from 10 phase II/III secukinumab psoriasis studies.

Results: Analysis included 3993 subjects; 3430 received secukinumab, representing 2725 subject-years (SYs) of exposure. Over 52 weeks, for secukinumab 300 mg, 150 mg, and etanercept, respectively, exposure-adjusted incidence rates (IRs) per 100 SYs were comparable across treatments for total adverse events (AEs; 236.1, 239.9, and 243.4, respectively); infections (91.1, 85.3, and 93.7, respectively); serious AEs (7.4, 6.8, and 7.0, respectively); serious infections (1.4, 1.1, and 1.4, respectively); malignant or unspecified tumors (0.77, 0.97, and 0.68, respectively); and adjudicated major adverse cardiovascular events (0.42, 0.35, and 0.34, respectively). AEs were not dose-related except for nonserious, mild/moderate, skin/mucosal candidiasis (IRs 3.55, 1.85, and 1.37 for secukinumab 300 mg, 150 mg, and etanercept, respectively).

Limitations: There was a limited number of patients in comparator groups and the exposure to placebo was short.

From the Department of Dermatology,[a] Radboud University Nijmegen Medical Centre, Nijmegen; Dermatology Centre,[b] Salford Royal Hospital, University of Manchester, Manchester Academic Health Science Centre, Manchester, United Kingdom; Dermatologikum Hamburg and Georg-August-University,[c] Göttingen, Germany; Saint Louis University Health Sciences Center[d]; Oregon Medical Research Center,[e] Portland; National Taiwan University Hospital,[f] National Taiwan University College of Medicine, Taipei; Beijing Novartis Pharma Co Ltd,[g] Shanghai; Novartis Pharmaceuticals Corporation,[h] East Hanover; and Novartis Pharma AG,[i] Basel, Switzerland.

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Dr van de Kerkhof has carried out clinical trials or provided consultancies and/or acted as a speaker for AbbVie, Almirall, Amgen, Celgene, Centocor, Eli Lilly, Galderma, Janssen-Cilag, Leo Pharma, Mitsubishi, Novartis, Pfizer, Philips, and Sandoz. Dr Griffiths has received honoraria or research grants from AbbVie, Amgen, Bristol-Meyers Squibb, Celgene, Eli Lilly, GSK, Janssen-Cilag, Leo, MSD, Novartis, Pfizer, Sandoz, Trident, and UCB. Dr Reich has served as a consultant or paid speaker for or participated in clinical trials sponsored by AbbVie, Amgen, Biogen-Idec, Celgene, Centocor, Covagen, Eli Lilly, Forward Pharma, GSK, Janssen-Cilag, Leo, Medac, MSD, Novartis, Pfizer, Takeda, and Vertex. Dr Leonardi has served as consultant or investigator or participated in a speakers' bureau for AbbVie, Amgen, Celgene, Dermira, Eli Lilly, Galderma, Janssen, Leo Pharma, Merck, Novartis, Pfizer, Sandoz, Stiefel, and UCB. Dr Blauvelt has served as a scientific consultant and clinical study investigator for AbbVie, Amgen, Boehringer Ingelheim, Celgene, Demira, Eli Lilly, Genentech, Janssen, Merck, Novartis, Pfizer, Regeneron, and Sandoz. Dr Tsai has carried out clinical trials or provided consultancies or acted as a speaker for AbbVie, Allergan, Celgene, Eli Lilly, Galderma, Janssen-Cilag, Leo Pharma, Novartis, and Pfizer. Drs Gong, Huang, and Papavassilis and Mr Fox are full-time employees of or own stock in Novartis.

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Correspondence to: Peter C. M. van de Kerkhof, MD, PhD, Department of Dermatology, Radboud University Nijmegen Medical Centre, PO Box 9101, 6500 HB, Nijmegen, The Netherlands. E-mail: peter.vandeKerkhof@radboudumc.nl.

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Conclusion: Secukinumab had a favorable safety profile, had no meaningful difference between the 300- and 150-mg doses and, in terms of safety, was comparable to etanercept over 52 weeks in patients with moderate to severe plaque psoriasis. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2016.03.024.)

Key words: long-term safety; phase II studies; phase III studies; pooled analysis; psoriasis; secukinumab.

INTRODUCTION

Psoriasis is a chronic inflammatory disease affecting the skin that is associated with systemic comorbidities.[1,2] The long-term use of conventional systemic agents has the potential to cause cumulative organ toxicities.[3,4] Biologic medications (eg, tumor necrosis factor [TNF]—alfa inhibitors and anti—interleukin (IL)-12/23 antibodies) have improved efficacy in short-term studies but can be associated with diminished long-term efficacy.[2-4]

Secukinumab is a fully human anti—IL-17A monoclonal antibody.[5] Phase II and III studies in patients with moderate to severe plaque psoriasis have shown that secukinumab (in doses of 300 mg or 150 mg) provides strong and sustained efficacy with a favorable safety profile over 52 weeks.[6-10]

Patients with psoriasis are at increased risk for malignancy and cardiovascular disorders and might be at risk for infection.[11-17] While not broadly involved in systemic immune defense, IL-17A plays roles in granulopoiesis, neutrophil trafficking,[18] and mucocutaneous defense against certain extracellular fungi and bacteria (eg, *Candida albicans* or *Staphylococcus aureus*).[10,19-22] Neutropenia and certain mucocutaneous infections are therefore potential concerns with anti—IL-17A therapy.

This pooled analysis of 10 phase II or III studies provides a comprehensive review of secukinumab safety in 3993 patients with moderate to severe plaque psoriasis over 52 weeks.

CAPSULE SUMMARY

- Secukinumab, an interleukin-17A inhibitor, has demonstrated efficacy in patients with plaque psoriasis.
- In this pooled analysis, secukinumab had a favorable safety profile with no meaningful differences between dose groups over 52 weeks in patients with moderate to severe plaque psoriasis.
- This extensive review of secukinumab safety informs appropriate patient management decisions.

METHODS

Subjects and study treatment

This analysis included pooled data from 10 studies: 4 phase II and 6 phase III randomized, double-blind studies (Fig 1; Supplementary Table I, available online at www.jaad.org) in patients with moderate to severe plaque psoriasis (Supplementary Methods section).[6-10,23-26] All studies (except for 2 phase III studies) were placebo-controlled, including the phase III Safety and Efficacy of Secukinumab Compared to Etanercept in Subjects with Moderate to Severe, Chronic Plaque-type Psoriasis (FIXTURE) study with an active comparator (etanercept) over a 52-week treatment period. Patient eligibility criteria relevant to safety analysis are listed in Table I.

In this analysis, equal proportions of subjects received secukinumab in subcutaneous (SC) doses of 300 or 150 mg (41% each). The remainder received either other SC doses (ie, 75 or 25 mg), intravenous (IV) infusion, or etanercept 50 mg SC or placebo (Supplementary Methods section and Supplementary Table I).

Methodology for pooled analysis

Safety data were pooled at the individual subject level. Adverse event (AE) severity was graded as mild, moderate, or severe by study investigators (Supplementary Methods section). AEs of special interest, infections, major adverse cardiovascular events (MACEs), malignancies, Crohn's disease, and potential AEs related to inhibition of the IL-17 pathway, such as Candida infections and neutropenia, were evaluated (Supplementary Methods).

RESULTS

Baseline characteristics and exposure

The analysis included 3993 patients. Baseline characteristics (Table II) were comparable across treatments except for the secukinumab groups, which had slightly more subjects with cardiovascular risk factors/diseases (Supplementary Results section).

During the first 12 weeks, all groups had similar durations of study treatment exposure. Over the entire 52 weeks, the duration of placebo exposure was substantially lower compared with active treatments because of the (per protocol) high proportion of placebo nonresponders (>95%) who were rerandomized to secukinumab at week 12 (Table III). Because of this design feature, safety analysis over the entire 52 weeks did not include comparison with the placebo group. Total