A 52-week, open-label study of the efficacy and safety of ixekizumab, an anti-interleukin-17A monoclonal antibody, in patients with chronic plaque psoriasis

Kenneth B. Gordon, MD,[a] Craig L. Leonardi, MD,[b] Mark Lebwohl, MD,[c] Andrew Blauvelt, MD, MBA,[d] Gregory S. Cameron, PhD,[e] Daniel Braun, MD, PhD,[e] Janelle Erickson, PhD,[e] and Michael Heffernan, MD[e]
Chicago, Illinois; St Louis, Missouri; New York, New York; Portland, Oregon; and Indianapolis, Indiana

Background: Patients with moderate to severe plaque psoriasis demonstrated positive responses to ixekizumab, an anti-interleukin-17A monoclonal antibody, in a phase-II, randomized, placebo-controlled trial.

Objective: We sought to evaluate long-term efficacy and safety of ixekizumab.

Methods: After receiving 10, 25, 75, or 150 mg of ixekizumab or placebo during randomized, placebo-controlled trial, patients with less than 75% improvement from baseline on the Psoriasis Area and Severity Index (PASI) score (PASI75) entered open-label extension (OLE); patients with PASI75 or higher entered a treatment-free period (weeks 20-32), then entered OLE after meeting response criteria. During OLE, patients received 120 mg of subcutaneous ixekizumab every 4 weeks.

Results: In all, 120 patients entered OLE; 103 completed 52 weeks or more of treatment. Overall, 77% of patients achieved PASI75 at week 52 (nonresponder imputation). Patients who responded to treatment in the randomized, placebo-controlled trial maintained a high-level response by week 52 of OLE (PASI75 = 95%; 90% improvement from baseline on the PASI score = 94%; 100% improvement from baseline on the PASI score = 82%). Irrespective of dose in the randomized, placebo-controlled trial, each group had similar response rates at week 52 of OLE. The exposure-adjusted incidence rate for adverse events was 0.47 and for serious adverse events was 0.06 per patient-year during OLE.

Limitations: No control group, small sample sizes, and bias toward retention of patients with positive responses limit interpretation.

Conclusion: A high proportion of patients responded to ixekizumab therapy and maintained clinical responses over 1 year of treatment with no unexpected safety signals. (J Am Acad Dermatol 2014;71:1176-82.)

Key words: interleukin 17; ixekizumab; long-term; monoclonal antibodies; open label; psoriasis; 1 year.

From Northwestern University, Feinberg School of Medicine, Chicago[a]; Saint Louis University School of Medicine[b]; Icahn School of Medicine at Mount Sinai, New York[c]; Oregon Medical Research Center[d]; and Eli Lilly and Company, Indianapolis.[e]

Supported by Eli Lilly and Company.

Disclosure: Dr Gordon is a consultant and/or investigator for AbbVie Inc, Amgen Inc, Centocor, Merck, Eli Lilly and Company, Novartis, and Pfizer. Dr Leonardi is a consultant and/or investigator for AbbVie Inc, Amgen Inc, Celgene Corp, Centocor, Eli Lilly and Company, Galderma, Genentech, Genzyme, GlaxoSmithKline, Incyte, Novartis, Novo Nordisk, Pfizer, Schering-Plough, Sirtris, Stiefel, Vascular Biogenics, and Wyeth, and is a speaker for AbbVie Inc. Dr Lebwohl has been a consultant and/or investigator for Inbios, Coronado Biosciences, AbbVie Inc, Valeant, Taro, Pfizer, UCB Pharma, Forward Pharma, DermiPsor, Galderma, Ranbaxy, Novartis, Dermira, Merz, Merck, LEO Pharma Inc, Janssen-Biotech, GlaxoSmithKline, Eli Lilly and Company, Celgene Corp, Can-Fite Biopharma Ltd, Anacor Pharmaceuticals Inc, and Amgen Inc. Dr Blauvelt is a consultant and/or investigator for AbbVie Inc, Amgen Inc, Boehringer Ingelheim, Celgene Corp, Janssen Biotech, Merck, Novartis, Pfizer, and Eli Lilly and Company. Drs Cameron, Braun, Erickson, and Heffernan are employees and shareholders of Eli Lilly and Company.

Data from this manuscript were presented at the 22nd Congress of the European Academy of Dermatology and Venereology, Istanbul, Turkey, October 2-6, 2013; and at the 72nd Annual Meeting of the American Academy of Dermatology, Denver, Colorado, March 21-25, 2014.

Accepted for publication July 27, 2014.

Reprint requests: Kenneth B. Gordon, MD, Department of Dermatology, Northwestern University, NMH/Galter Room 19-150, 675 N Saint Clair, Chicago, IL 60611. E-mail: kenneth-gordon@northwestern.edu.

Published online September 20, 2014.
0190-9622/$36.00

http://dx.doi.org/10.1016/j.jaad.2014.07.048

Psoriasis is an immune-mediated disease in which several T-cell subsets, keratinocytes, and other cell types (eg, mast cells, dendritic cells) are activated and express elevated levels of cytokines that alter growth and differentiation of skin cells to produce psoriatic lesions. Interleukin-17A is a proinflammatory cytokine that is produced by a variety of cells (eg, T helper 17 [Th17], $CD8^+$ T cells, mast cells, neutrophils, and natural killer cells) and is thought to play a critical role in the pathogenesis of psoriasis.[1-5]

Ixekizumab is an anti-interleukin-17A monoclonal antibody that has been shown to provide a positive response in patients with moderate to severe chronic plaque psoriasis in a phase-II, randomized, placebo-controlled trial (RCT).[6] Here, we report the 52-week efficacy results and greater than or equal to 52-week safety results of ixekizumab treatment during the open-label extension (OLE) that followed the RCT.

CAPSULE SUMMARY

- Interleukin-17A appears to be involved in the pathogenesis of psoriasis.
- Long-term efficacy and safety of ixekizumab, an anti-interleukin-17A monoclonal antibody, was evaluated in moderate to severe plaque psoriasis.
- More than 75% of all patients responded to ixekizumab and maintained clinical responses over 1-year treatment; safety findings were overall consistent with 12-week blinded treatment.

METHODS

Study design and treatment

This was a multicenter, OLE study of a phase-II RCT designed to evaluate the long-term use of ixekizumab in patients with chronic (≥ 6 months) moderate to severe plaque psoriasis. Patients were administered ixekizumab (10, 25, 75, or 150 mg) or placebo subcutaneously at 0, 2, 4, 8, 12, and 16 weeks in the RCT, the results of which have been previously published.[6] Patients who completed 20 weeks of the RCT and who had not experienced a treatment-related adverse event (AE) or a serious AE (SAE) deemed to be detrimental with continued treatment were eligible to participate in this OLE study (Fig 1).

At week 20 of the RCT, patients without 75% improvement from baseline on the Psoriasis Area and Severity Index (PASI) (PASI75) were eligible to enter the OLE and initiate monthly ixekizumab treatment. All other patients entered a treatment-free period from weeks 20 to 32 and became eligible to enter the OLE at the study visit where they fell below PASI75 or at week 32 if PASI75 or higher was maintained throughout the treatment-free period. All patients were administered 120 mg of ixekizumab subcutaneously every 4 weeks once they entered the OLE. The OLE was designed to evaluate subcutaneous ixekizumab dosing for up to 240 weeks. Here we report interim data; efficacy analyses include all patients who completed or discontinued 52 weeks of open-label treatment and safety analyses include all patient data available during the OLE.

The protocol was approved by local institutional review boards in accordance with the Declaration of Helsinki and applicable laws and regulations (Clinical Trials.gov number: NCT01107457). All patients provided written informed consent.

Assessments

Improvement in disease activity during the OLE was assessed by the percent improvement from baseline score (collected at week 0 of the RCT) on the PASI and the static Physician Global Assessment (sPGA). Here we report the proportion of patients achieving PASI75 or higher, 90% improvement from baseline on the PASI (PASI90) or higher, and 100% improvement from baseline on the PASI (PASI100) along with sPGA (0,1 and 0) for the 52-week, open-label period. At each visit, AEs, SAEs, and vital signs were recorded. Laboratory test results were collected at regular intervals during the OLE.

Statistical analyses

All efficacy analyses were conducted on the enrolled patient population, defined as all subjects who completed the RCT and entered the OLE. Safety analyses included all enrolled patients who received at least 1 dose of ixekizumab in the open-label period. Baseline demographics, clinical characteristics, efficacy measures (PASI and sPGA), and safety assessments were summarized. Unless otherwise specified, missing data were imputed with the use of a nonresponder imputation (NRI), in which patients who discontinued early (ie, before week 52), regardless of the status of response at the time of discontinuation, had data imputed as a nonresponse at the week-52 time point.

The PASI75, PASI90, PASI100, and sPGA (0,1 and 0) response rates at week 52 (NRI) were summarized based on the enrolled patient population. In addition, the categorical PASI results at week 52 (observed) were calculated for patients based on ixekizumab dose taken during the RCT, for week-20 responders, and for patients initially assigned to placebo during the RCT. Week-20 responders were defined as ixekizumab-treated patients who achieved a PASI75 response at week 20 (NRI) of the RCT and who were