Ixekizumab Pharmacokinetics, Anti-Drug Antibodies, and Efficacy through 60 Weeks of Treatment of Moderate to Severe Plaque Psoriasis

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Kristian Reich[1], Kimberley Jackson[2], Susan Ball[3], Sandra Garces[3], Lisa Kerr[3], Laiyi Chua[4], Talia M. Muram[3] and Andrew Blauvelt[5]

Ixekizumab, a high-affinity monoclonal antibody that selectively targets IL-17A, is efficacious for moderate to severe plaque psoriasis. We examined relationships between serum ixekizumab concentrations, treatment-emergent anti-drug antibodies (TE-ADAs), and efficacy during 60 weeks of treatment in a randomized, controlled, phase 3 study. Steady-state ixekizumab serum trough concentrations were rapidly achieved and associated with high clinical responses at week 12 with a starting dose of 160 mg followed by 80 mg every 2 weeks. During the long-term extension period dosage of 80 mg every 4 weeks, stable serum trough concentrations maintained high clinical responses through week 60. Most (82.6%, 308/373) patients never developed TE-ADA. In TE-ADA−positive patients (17.4%, n = 65), variations in ADA titers, neutralizing capacity, and persistence were observed. Fifty-six patients (15%) developed low or moderate maximum titers, with serum concentrations and efficacy comparable to those of TE-ADA−negative patients. Nine patients (2.4%) developed high titers, with variable individual clinical responses; four of these nine patients achieved at least PASI 75 at week 60. Median serum concentrations in the TE-ADA-high titer group were generally comparable to the median serum concentrations in the lower titer groups. For most patients, TE-ADA had a negligible impact on ixekizumab serum concentrations and efficacy. Clinicaltrials.gov: NCT01646177

Journal of Investigative Dermatology (2018) ■, ■−■; doi:10.1016/j.jid.2018.04.019

INTRODUCTION

The efficacy of biologic therapies can be influenced by multiple factors, including the binding affinity to target, drug dose, dosing regimen, drug serum levels, and the development of anti-drug antibodies (ADAs), among others. Although not all ADAs may affect the efficacy of biologic therapy, associations between ADA, drug serum concentrations, and/or efficacy have been reported for biologics commonly used for moderate to severe psoriasis, such as adalimumab, infliximab, and ustekinumab (Chiu et al., 2015; Menter et al., 2007; 2008; Papp et al., 2008, 2011; Reich et al., 2005; Takahashi et al., 2013; Tsai et al., 2011). The clinical impact of ADAs is dependent on multiple interrelated factors, including the serum titer of ADAs, the persistence of ADAs over time, and their drug neutralizing capacity. Hence, ADAs (and neutralizing anti-drug antibodies [nADAs]) may have no clinically meaningful impact on efficacy unless they are present in sufficient concentrations to inhibit drug bioavailability or activity (Shankar et al., 2014).

Ixekizumab, a high-affinity monoclonal antibody that selectively targets IL-17A, is an efficacious treatment for moderate to severe plaque psoriasis (Blauvelt, 2016; Gordon et al., 2016; Griffiths et al., 2015; Liu et al., 2016). In this article, we describe the time course of ixekizumab serum drug levels; the incidence of treatment-emergent ADAs (TE-ADAs); and the relationship between TE-ADA, serum drug levels, and efficacy through 60 weeks of treatment in a randomized, phase 3 clinical trial of patients with moderate to severe psoriasis.

[1]*Dermatologikum Berlin and SCIderm Research Institute, Hamburg, Germany;* [2]*Eli Lilly and Company, Windlesham, UK;* [3]*Eli Lilly and Company, Indianapolis, Indiana, USA;* [4]*Lilly-NUS Centre for Clinical Pharmacology, Singapore, Singapore; and* [5]*Oregon Medical Research Center, Portland, Oregon, USA*

Correspondence: Kristian Reich, Dermatologikum Berlin, Friedrichstrasse 89, Berlin 10117, Germany. E-mail: reich@dermatologikum-berlin.de

Abbreviations: ADA, anti-drug antibody; nADA, neutralizing anti-drug antibody; PASI, Psoriasis Area and Severity Index; PK, pharmacokinetics; Q2W, every 2 weeks; Q4W, every 4 weeks; TE-ADA, treatment-emergent anti-drug antibody

Received 21 March 2018; revised 19 April 2018; accepted 22 April 2018; accepted manuscript published online 8 May 2018; corrected proof published online XXX

RESULTS

Patient characteristics

Baseline characteristics and patient disposition through 60 weeks of treatment in the UNCOVER-3 study were previously published (Gordon et al., 2016). Of 385 patients randomized to receive ixekizumab every 2 weeks (Q2W) during the 12-week induction dosing period, 363 (93.4%) completed week 12, and 325 (84.4%) were receiving ongoing treatment at the time of the 60-week database lock. Discontinuation rates were low for both the induction (5.7%) and long-term extension populations (10.2%). Baseline patient characteristics are provided in Table 1.

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Table 1. Baseline demographics and disease characteristics for patients receiving ixekizumab dosing Q2W/Q4W in the intent-to-treat population[1]

Variable	IXE Q2W/IXE Q4W (N = 385)
Age in years, mean (SD)	45.6 (13.1)
Male, n (%)	254 (66.0)
Caucasian, n (%)	361 (93.8)
Weight in kg, mean (SD)	90.4 (23.4)
<100, n (%)	275 (71.6)
≥100, n (%)	109 (28.4)
Duration of psoriasis in years, mean (SD)	17.8 (12.2)
% BSA involvement, mean (SD)	28.0 (17.3)
PASI, mean (SD)	20.7 (8.2)
sPGA ≥ 4, n (%)	178 (46.2)
Previous biologic therapy, n (%)	58 (15.1)

Abbreviations: BSA, body surface area; IXE, ixekizumab; PASI, Psoriasis Area and Severity Index; Q2W, every 2 weeks; Q4W, every 4 weeks; SD, standard deviation; sPGA, Static Physician's Global Assessment.
[1]Data in this table have been previously published by Gordon et al. (2016).

Ixekizumab pharmacokinetics (PK) and efficacy

With induction dosing (160-mg starting dose, then 80 mg ixekizumab Q2W through week 12), steady-state ixekizumab serum trough concentrations were quickly achieved, with a week 12 median concentration of 8.84 μg/ml. These concentrations were associated with a rapid attainment of high clinical response rates. During long-term extension dosing of 80 mg every 4 weeks (Q4W) dosing, median ixekizumab serum trough concentrations reached a new steady-state level by the week 24 assessment and remained stable to week 60, with median concentrations ranging from a minimum of 3.03 μg/ml to a maximum of 3.31 μg/ml during this period. These concentrations were associated with maintenance of high responses that persisted through week 60 (Figure 1). In addition, clinical response stratified by serum trough concentration quartiles was evaluated at week 60. PASI 75 and Static Physician's Global Assessment 0/1 response rates for each quartile are provided in Table 2. High clinical response was achieved across all concentration quartiles. The lowest quartile was associated with numerically lower rates of response.

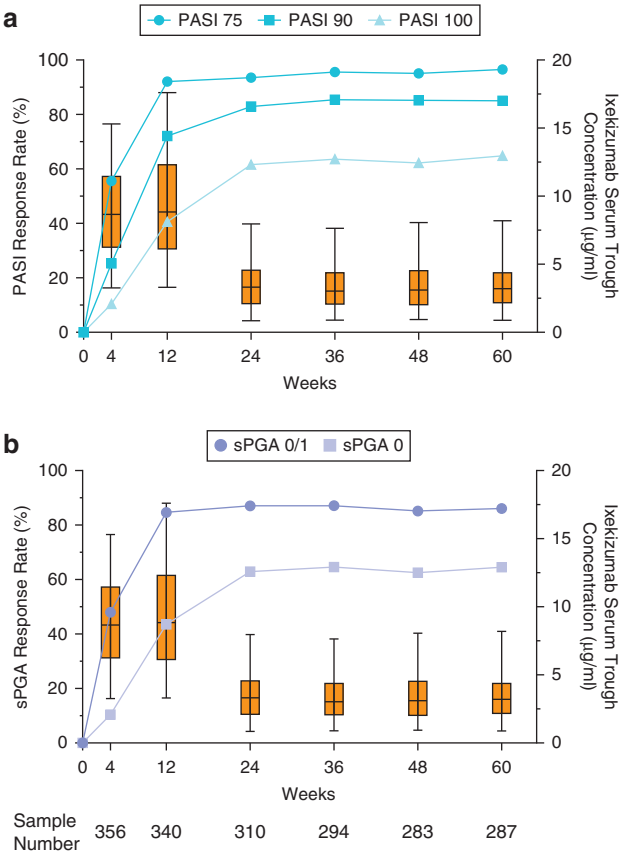

Figure 1. Time course of ixekizumab serum trough concentrations and clinical response rates for patients receiving ixekizumab Q2W/Q4W. Patients received an initial dose of 160 mg ixekizumab, then 80 mg ixekizumab every 2 weeks (Q2W) through week 12, followed by 80 mg every 4 weeks (Q4W) through week 60. Observed clinical response rates (left y-axis) are shown as the percentage of patients achieving (**a**) PASI 75, 90, and 100 and (**b**) Static Physician's Global Assessment 0/1 and 0. Serum trough concentration (μg/ml, right y-axis) is shown at each PK visit as box-and-whisker plots, providing 5th, 25th, median, 75th, and 95th percentiles. Analysis includes all patients in the PK population with one or more samples qualifying as a serum trough sample (N = 372). (**b**) The number of serum trough samples at each PK visit are provided below the x-axis of the panel. PASI, Psoriasis Area and Severity Index; PK, pharmacokinetics; Q2W, every 2 weeks; Q4W, every 4 weeks; sPGA, Static Physician's Global Assessment.

Anti-drug antibodies

Incidence of ADAs. Subjects were divided into four TE-ADA analysis populations depending on their maximum TE-ADA titer reached during 60 weeks of treatment. Titer subgroups included TE-ADA negative, TE-ADA low (maximum titer < 1:160), TE-ADA moderate (maximum titer ≥ 1:160 and < 1:1,280), and TE-ADA high (maximum titer ≥ 1:1,280). If TE-ADA titer observations were within the range of their TE-ADA titer subgroup at more than one visit (regardless of whether these were consecutive visits or not), their maximum titer was conservatively defined as "persistent."

The incidence of TE-ADAs and nADAs through week 60 is summarized in Table 3. Briefly, most (82.6%) patients were TE-ADA negative through week 60. With increasing TE-ADA

Table 2. Clinical response rates at week 60 stratified by ixekizumab serum trough concentration quartiles for patients receiving ixekizumab Q2W/Q4W[1]

	Q1 N = 69	Q2 N = 73	Q3 N = 71	Q4 N = 72
PASI 75	62 (89.9) 82.0–97.7	72 (98.6) 95.3–100.0	69 (97.2) 92.6–100.0	72 (100.0) 99.3–100.0
sPGA 0/1	47 (68.1) 56.4–79.8	65 (89.0) 81.2–96.9	63 (88.7) 80.7–96.8	70 (97.2) 92.7–100.0

Abbreviations: PASI, Psoriasis Area and Severity Index; Q1, quartile 1 (<2.18 μg/ml); Q2, quartile 2 (≥2.18 to <3.20 μg/ml); Q2W, every 2 weeks; Q3, quartile 3 (≥3.20 to <4.35 μg/ml); Q4, quartile 4 (≥4.35 μg/ml); Q4W, every 4 weeks; sPGA, Static Physician's Global Assessment.
[1]Values are provided as n (%) and 95% confidence interval.

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