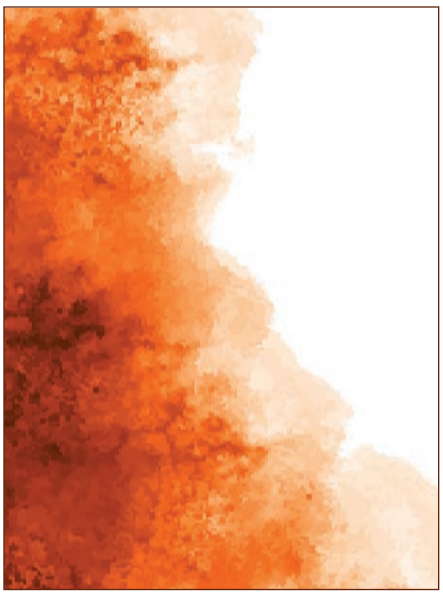

ORIGINAL RESEARCH

Early Onset of Clinical Improvement with Ixekizumab in a Randomized, Open-label Study of Patients with Moderate-to-severe Plaque Psoriasis

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ABSTRACT

Objective: The purpose of this study was to evaluate the speed of onset of clinical response to ixekizumab (IXE) and assess the progression of visible improvement in patients with moderate-to-severe plaque psoriasis. **Design:** This was an interventional, randomized, open-label, Phase IIIb clinical trial. **Setting:** This was a single center study at the Mount Sinai School of Medicine. **Participants:** Twelve patients were randomized at a ratio of 1:1 to receive 80mg of ixekizumab every two (IXE Q2W) or four (IXE Q4W) weeks following a starting dose of 160mg of ixekizumab. After Week 12, all patients received 80mg IXE Q4W through Week 44. **Measurements:** Clinical response was measured using the Patient's Global Assessment (PatGA), the Psoriasis Area and Severity Index (PASI), the static Physician's Global Assessment (sPGA), and the Itch Numeric Rating Scale (Itch NRS). Sequential patient photographs were taken at regular intervals during the study to evaluate visible improvement in plaque psoriasis. **Results:** The median time to an improvement of at least 1 point or 2 points from baseline in PatGA score was 5.0 and 10.0 days for patients randomized to IXE Q2W and 6.0 and 13.5 days for patients randomized to IXE Q4W. All patients achieved at least a 50- or 75-percent improvement in PASI from baseline by Weeks 2 and 4, respectively. At least half of the patients achieved at least a 4-point improvement from baseline in Itch NRS by Day 14. Improvement in disease was visibly evident within one week of treatment in patient photographs. **Conclusion:** Ixekizumab results in a rapid and visible improvement in plaque psoriasis in as early as one week of treatment.

KEYWORDS: Plaque psoriasis, ixekizumab, early onset, randomized, Phase IIIb, photographs

Plaque psoriasis is a common immune-mediated skin condition propagated by interleukin (IL)-17A and other pro-inflammatory cytokines.[1] Ixekizumab, a high-affinity monoclonal antibody that selectively targets IL-17A, has been shown to result in a significant improvement in psoriasis following 12 and 60 weeks of treatment.[2,3,4] Although the long-term efficacy of ixekizumab has been evaluated, the time to meaningful clinical improvement has not been fully assessed. In addition, the relationship between ixekizumab treatment and a visual improvement in skin over time has not been reported.

The primary objective of this study was to determine the time to improvement in disease as measured by a 1-point or greater improvement from baseline in the 6-point Patient's Global Assessment (PatGA) scale. Secondary objectives included evaluation of the time course of clinical response to ixekizumab, which was measured by the percent improvement from baseline in the Psoriasis Area and Severity Index (PASI), the change from baseline in the Itch Numeric Rating Scale (NRS), and the time to a 2-point or greater improvement from baseline in the PatGA. Efficacy was also measured by the percentage of patients achieving a static Physician's Global Assessment (sPGA) score of 0 or 1 or an sPGA score of 0. Standardized, sequential photographs were taken of each patient as visual evidence of improvement.

METHODS

Patients were at least 18 years old with a history of moderate-to-severe plaque

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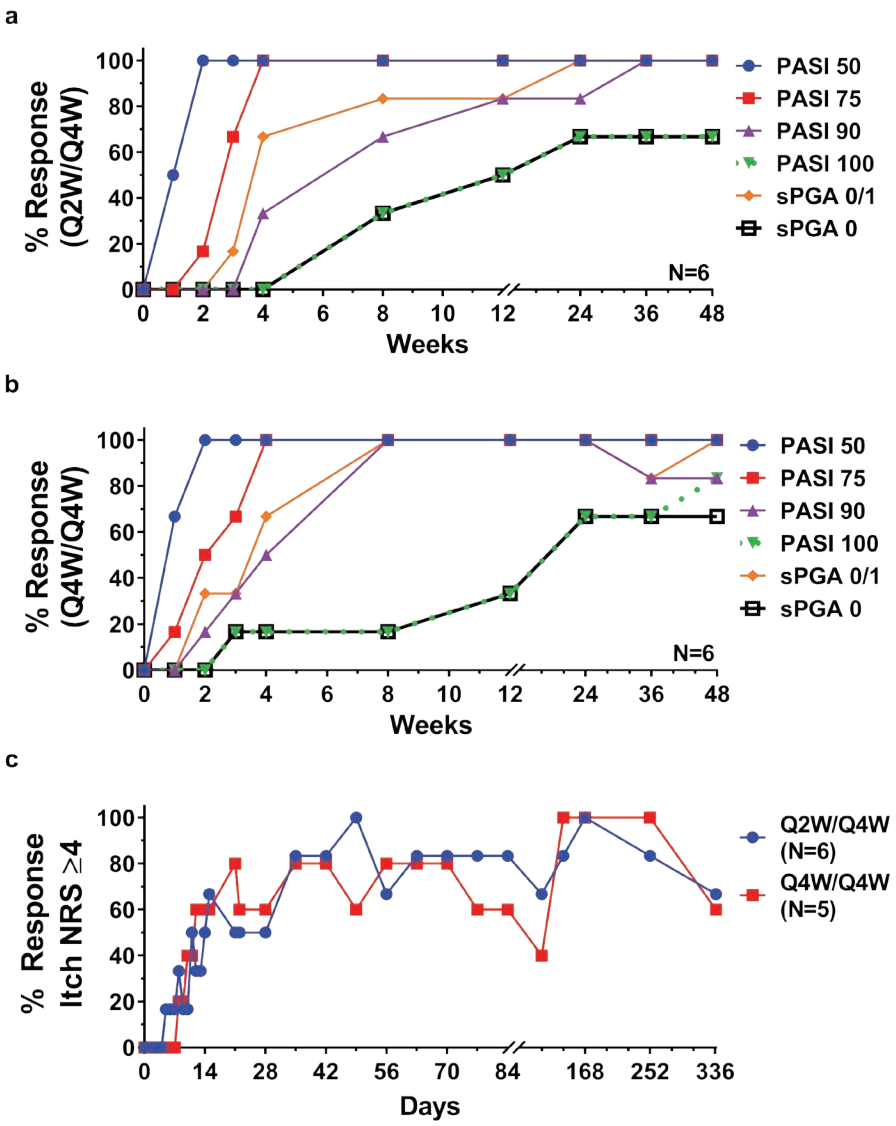

FIGURE 1. Rapid onset of clinical response to ixekizumab—Response rates are presented as the percentage of patients achieving the indicated treatment outcomes at each visit. PASI 50 (blue circles), PASI 75 (red squares), PASI 90 (purple triangles), PASI 100 (inverted green triangles, dotted line), sPGA 0/1 (orange diamonds), and sPGA 0 (open black squares) response rates are shown for patients receiving A) 80mg IXE Q2W/Q4W (N=6) or B) 80mg IXE Q4W/Q4W (N=6) treatment regimens; C) Response rates for patients achieving an itch NRS improvement of at least 4 points from baseline (for patients with a baseline score of ≥4) are shown for both the IXE Q2W/Q4W (N=6, blue circles) and IXE Q4W/Q4W (N=5, red squares) treatment regimens. Because of a decreased frequency of patient visits between Weeks 12 and 48, the x-axis scale is condensed after Week 12. Missing values were imputed as nonresponse. All patients achieved PASI 50 and 75 by Weeks 2 and 4, respectively.

IXE: ixekizumab; NRS: numeric rating scale; PASI: Psoriasis Area and Severity Index; Q2W: every 2 weeks; Q2W/Q4W, 80mg IXE Q2W during the induction dosing period and Q4W during the maintenance dosing period; Q4W: every 4 weeks; Q4W/Q4W, 80mg IXE Q4W during both the induction and maintenance dosing periods; sPGA: static Physician's Global Assessment

psoriasis spanning six months or longer. Patients were candidates for phototherapy and/or systemic therapy. Inclusion criteria also required that patients had at least a 10-percent body surface area (BSA) involvement, a PASI score of at least 12, a sPGA score of at least 3 (6-point scale), and a PatGA score of at least 3 at baseline. Patients were excluded if they were unwilling or unable to commit to the photography schedule for the study duration, if they had a form of psoriasis other than plaque psoriasis, if they had a serious disorder or illness other than psoriasis, if they had a serious infection within three months prior to baseline, if there was evidence or suspicion of active or latent tuberculosis, or if they were women who were pregnant or lactating. Patients were also excluded if they had previously received IL-17 or IL-23 antagonists, as both agents affect similar cytokines and signaling pathways and prior exposure could potentially confound interpretation of study results. All enrolled patients provided written informed consent prior to undergoing study related procedures.

For this 48-week, randomized, single-center, open-label study, patients were randomized at a ratio of 1:1 to receive 80mg of ixekizumab either every two (Q2W) or four (Q4W) weeks during the induction dosing period (0–12 weeks) following an initial 160mg dose of ixekizumab. All patients received 80mg ixekizumab Q4W during the maintenance dosing period (12–48 weeks), with the final dose of ixekizumab administered at Week 44. PatGA and Itch NRS were reported daily by patients using an electronic diary between Weeks 0 and 2, then twice a week from Weeks 2 to 4, once a week from Weeks 4 to 12, once per month from Weeks 12 to 24, and once every three months from Weeks 24 to 48. Clinicians assessed sPGA and PASI during each visit at Weeks 0, 1, 2, 3, 4, 8, 12, 24, 36, and 48. The study protocol was approved by the site's institutional review board and the study was performed in accordance with the ethical standards of the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study prior to undergoing study related procedures. Clinicaltrials.gov identifier: NCT02387801.

Anterior and posterior photographs were taken of the torso, upper extremities, groin, buttocks, and lower extremities of each patient under similar lighting and magnification conditions by a professional photographer. Photographs were taken twice-weekly (Weeks 0–3), once-weekly (Weeks 4–8), every two weeks (Weeks 8–12), then every 12 weeks (Weeks 12–48) with a two-day minimum between photos.

Time-to-event analysis was used to assess the time to a 1-point or greater improvement or a 2-point or greater improvement from baseline in the PatGA using the Kaplan-Meier product limit method. Response rates were summarized using nonresponder imputation to account for missing data. Safety data were summarized by frequency of adverse events occurring during the induction dosing period and the maintenance dosing period.

RESULTS

Twelve patients were randomized to receive either IXE Q2W (6 patients) or IXE Q4W (6 patients) through Week 12. The baseline demographics and disease characteristics for each treatment regimen are provided in Table 1.

For patients randomized to IXE Q2W, the median time to a 1-point or greater improvement and a 2-point or greater improvement in the PatGA from baseline was 5.0 and 10.0 days, respectively. The median time to a 1-point or greater improvement and a 2-point or greater improvement from baseline in PatGA was 6.0 and 13.5 days for patients randomized to IXE Q4W, respectively. By Weeks 2 and 4, all patients achieved at least 50- or 75-percent PASI improvement from baseline, respectively (Figure 1). Of 11 patients with a baseline Itch NRS score of at least 4 (1 patient had a baseline Itch NRS score of 1), at least half (Q2W: 3 patients, 50.0%; Q4W: 3 patients, 60.0%) achieved at least a 4-point Itch NRS improvement from baseline by Day 14 (Figure 1C). Patient photographs demonstrated visible improvement in disease within one week of treatment (Figures 2–4 and Supplemental Video [click HERE to access video (in e-edition) or visit http://jcadonline.com/wp-content/uploads/Supplemental-Video.mp4).

Treatment emergent adverse events (TEAEs) were mild to moderate in severity except for one severe TEAE of arthralgia

TABLE 1. Baseline demographics and disease characteristics

DEMOGRAPHIC	IXE Q2W (N=6)	IXE Q4W (N=6)
Age, years	41.8 (12.5)	55.2 (7.4)
Male, n (%)	5 (83.3)	3 (50.0)
Caucasian, n (%)	4 (66.7)	5 (83.3)
Duration of psoriasis, years	17.4 (13.0)	22.2 (23.4)
Weight, kg	67.7 (15.7)	81.4 (20.9)
Percent BSA	25.5 (20.4)	32.5 (18.3)
PatGA	4.8 (0.4)	4.8 (0.4)
PASI score	21.0 (9.2)	25.2 (8.4)
Itch NRS score	8.2 (1.6)	7.2 (3.2)
sPGA score	3.8 (0.8)	4.0 (0.6)

Data are provided as mean (SD) unless otherwise indicated; BSA: Body Surface Area; NRS: Numeric Rating Scale; IXE: Ixekizumab; PASI: Psoriasis Area and Severity Index; PatGA: Patient's Global Assessment; Q2W: Every 2 weeks; Q4W: Every 4 weeks; SD: Standard deviation; sPGA: static Physician's Global Assessment

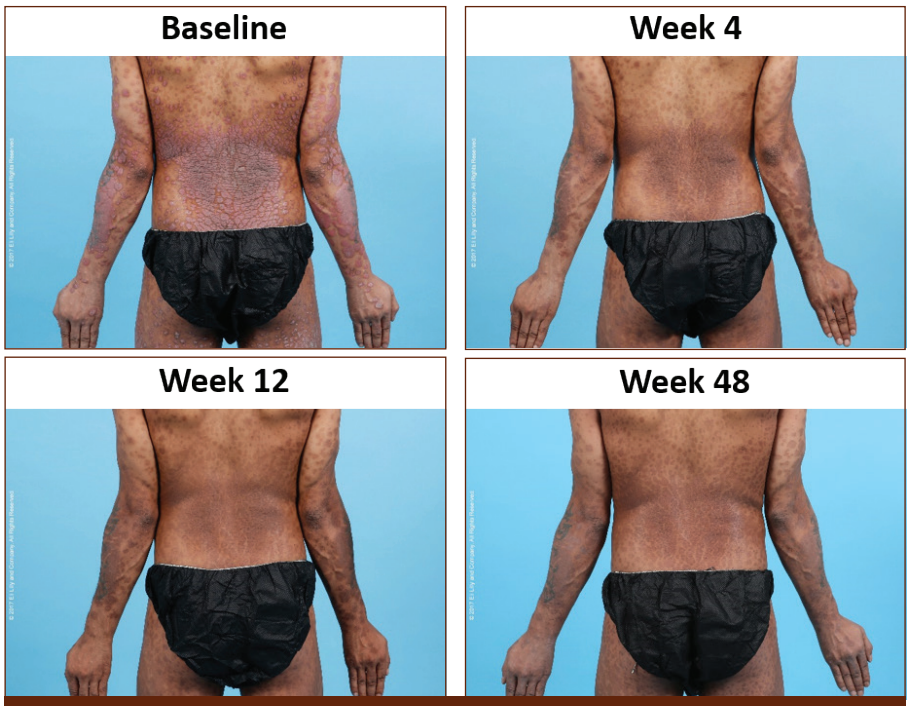

FIGURE 2. Visible clearance of psoriatic plaques over 48 weeks of treatment with IXE Q2W/Q4W—A 37-year-old man, with baseline PASI score of 32.5 and baseline BSA of 58%, achieved PASI 75 at Week 4 and PASI 90 at Week 12, which was maintained through Week 48.
BSA: body surface area; IXE: ixekizumab; PASI: Psoriasis Area and Severity Index; Q2W: every two weeks; Q2W/Q4W, 80mg IXE Q2W during the induction dosing period and Q4W during the maintenance dosing period; Q4W: every four weeks

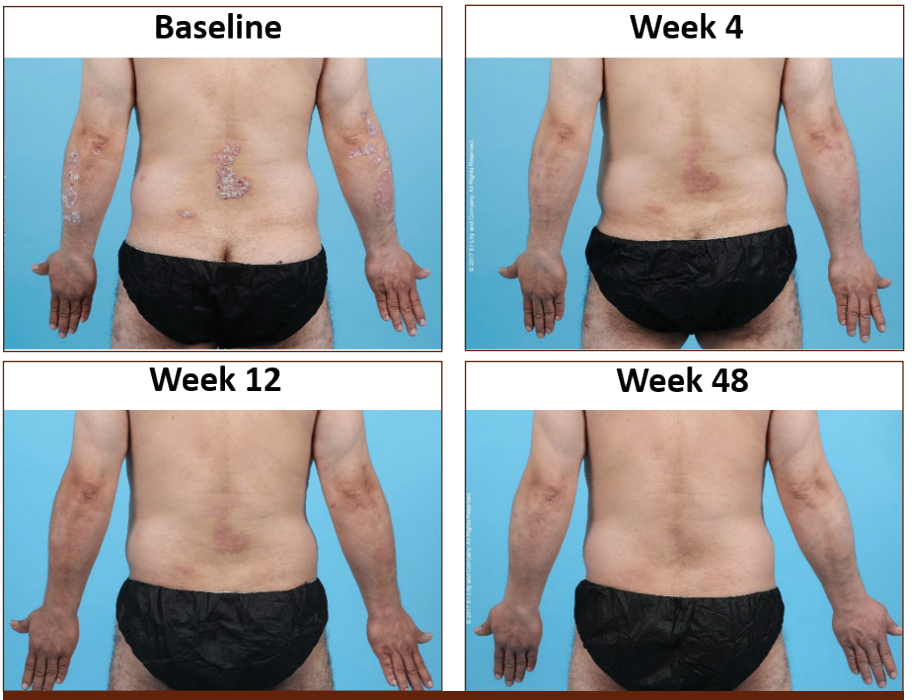

FIGURE 3. Visible clearance of psoriatic plaques over 48 weeks of treatment with IXE Q2W/Q4W—A 40-year-old man with a baseline PASI score of 13 and a 10% BSA achieved PASI 75 at Week 3, PASI 90 at Week 4, and PASI 100 at Week 8, which was maintained through Week 48.
BSA: body surface area; IXE: ixekizumab; PASI: Psoriasis Area and Severity Index; Q2W: every 2 weeks; Q2W/Q4W, 80mg IXE Q2W during the induction dosing period and Q4W during the maintenance dosing period; Q4W: every 4 weeks

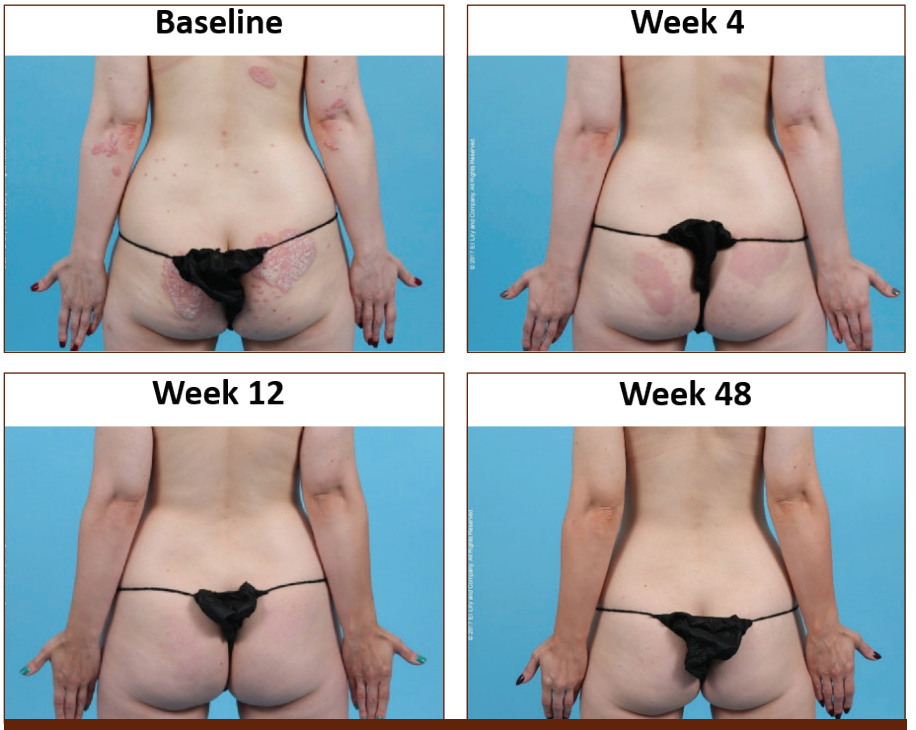

FIGURE 4. Visible clearance of psoriatic plaques over 48 weeks of treatment with IXE Q2W/Q4W—A 27-year-old woman with baseline PASI score of 19.2 and 12-percent BSA. Patient achieved PASI 75 at Week 4 and PASI 90 at Week 36, which was maintained through Week 48.
BSA: body surface area; IXE: ixekizumab; PASI: Psoriasis Area and Severity Index; Q2W: every two weeks; Q2W/Q4W, 80mg IXE Q2W during the induction dosing period and Q4W during the maintenance dosing period; Q4W: every four weeks

(Table 2). This single severe TEAE was adjudicated as unrelated to ixekizumab and resolved without changing treatment. There were no serious adverse events, deaths, or discontinuations during the trial.

DISCUSSION

Previous studies of the efficacy of ixekizumab in patients with moderate-to-severe plaque psoriasis established the efficacy and safety of ixekizumab over long-term treatment in patients with moderate-to-severe plaque psoriasis.[3,4] The current study was designed specifically to evaluate the early improvement in disease in response to ixekizumab and to determine the speed of onset of efficacy. In parallel to these quantitative assessments of efficacy, this study also assessed the qualitative visual improvement in psoriasis symptoms in response to ixekizumab treatment by obtaining sequential photographs of participants over time.

Although limited by a small patient population and lack of a placebo comparator, this study demonstrated that ixekizumab treatment resulted in a rapid and early onset of efficacy in as early as one week of treatment. In addition, the early clinical responses were maintained throughout the 48-week study, consistent with previously published results showing long-term maintenance of efficacy for patients receiving ixekizumab.[3,4] Sequential patient photographs also demonstrated a rapid improvement in plaque psoriasis. Visible improvement was evident within one week of treatment and continued to improve over time. At 48 weeks of treatment, photographs demonstrated the maintenance of visible improvement in psoriasis symptoms, consistent with a persistent clinical response.

CONCLUSION

Patients with moderate-to-severe plaque psoriasis exhibited a rapid clinical response and visible improvement in psoriasis in response to treatment with 80mg of ixekizumab every two or four weeks. Both clinical response and visible improvement in disease were evident within one week and persisted through 48 weeks of treatment. There were no unexpected safety concerns observed during the study.

TABLE 2. Summary of treatment emergent adverse events

DOSING PERIOD	DOSING REGIMEN	PATIENTS WITH ≥1 TEAE, n (%)	TEAE SEVERITY		
			MILD	MODERATE	SEVERE
INDUCTION DOSING PERIOD (WEEKS 0–12)	IXE Q2W[a] (N=6)	5 (83.3)	2 (33.3)	2 (33.3)	1 (16.7)
	IXE Q4W[a] (N=6)	5 (83.3)	3 (50.0)	2 (33.3)	0
MAINTENANCE DOSING PERIOD (WEEKS 12–48)	IXE Q2W/Q4W[a] (N=6)	3 (50.0)	2 (33.3)	1 (16.7)	0
	IXE Q4W/Q4W[a] (N=6)	6 (100.0)	3 (50.0)	3(50.0)	0

n=number; IXE=ixekizumab; Q2W=every 2 weeks; Q4W=every 4 weeks; TEAE=treatment-emergent adverse event
aPatients were randomized to receive 80 mg ixekizumab either every 2 or every 4 weeks during induction (weeks 0-12) following an initial dose of 160 mg ixekizumab. After week 12, all patients received 80 mg ixekizumab every 4 weeks.

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