Safety and Efficacy of Open-label Subcutaneous Ixekizumab Treatment for 48 Weeks in a Phase II Study in Biologic-naive and TNF-IR Patients with Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To evaluate ixekizumab, an anti-interleukin 17A monoclonal antibody, for safety and effectiveness through 64 weeks in biologic-naive and tumor necrosis factor–inadequate responder (TNF-IR) patients with rheumatoid arthritis.

Methods. Patients completing the 16-week double-blind period of a phase II study were eligible to enter the open-label extension (OLE) for an additional 48 weeks of ixekizumab treatment. After a treatment hiatus between weeks 10 to 16, 232 biologic-naive and 158 TNF-IR patients entered the OLE with all patients receiving 160 mg ixekizumab at weeks 16, 18, and 20, and then every 4 weeks through Week 64.

Results. A total of 201 (87%) biologic-naive and 99 (62%) TNF-IR patients completed the OLE. Treatment-emergent adverse events (AE) occurred in 168 (72%) biologic-naive and 115 (73%) TNF-IR patients during the OLE. Most AE were mild to moderate in severity and did not lead to study discontinuation. Serious AE (SAE) occurred in 17 (7%) biologic-naive patients, including 5 (2%) serious infections and 2 (1%) deaths. SAE occurred in 18 (11%) TNF-IR patients, including 4 (3%) serious infections and 1 (1%) death. No mycobacterial or invasive fungal infections were reported. Clinical responses [American College of Rheumatology (ACR) 20, ACR50, ACR70, and 28-joint Disease Activity Score with C-reactive protein] observed at Week 16 were maintained or improved through Week 64.

Conclusion. Ixekizumab was well tolerated, and safety findings in the OLE were consistent overall with those in the double-blind period of this study. Clinical improvements observed with ixekizumab through Week 16 were maintained or improved in patients participating in the OLE through Week 64. Trial registration number: NCT00966875. (First Release December 15 2015; J Rheumatol 2016;43:289–97; doi:10.3899/jrheum.140831)

Keyword Indexing Terms:
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Several proinflammatory cytokines, including interleukin (IL)-17, are known to contribute to the pathogenesis of rheumatoid arthritis (RA). IL-17 activates synovial fibroblasts, chondrocytes, and osteoclasts, leading to inflammation, bone erosions, and joint damage in RA[1]. In animal models of RA, IL-17 neutralization decreases inflammation, disease severity, and structural damage[2,3].

Ixekizumab (LY2439821) is a humanized monoclonal antibody that neutralizes IL-17A with high affinity and specificity, and with no reactivity to other IL-17 family members. In a phase I study of patients with RA who were naive to biologic therapies, ixekizumab significantly improved the signs and symptoms of RA with no significant safety findings[4]. A phase II dose-ranging study was conducted to confirm the efficacy of ixekizumab in a larger population of biologic-naive patients with moderate to severe RA and to evaluate the effectiveness of IL-17 neutralization in tumor

necrosis factor–inadequate responder (TNF-IR) patients. In the randomized, double-blind period of our study, the primary objective of a dose-response relationship of ixekizumab treatment on American College of Rheumatology 20% response rate (ACR20) in biologic-naive patients at Week 12 was achieved, and ixekizumab treatment rapidly improved signs and symptoms of RA in both biologic-naive (ACR20 response rates of 70%, 51%, and 54% in the 30 mg, 80 mg, and 180 mg dose groups, respectively, $p < 0.05$ vs placebo) and TNF-IR subpopulations (ACR20 response rates of 40% and 39% in the 80 mg and 180 mg dose groups, respectively, $p < 0.05$ vs placebo)[5]. Further, no unexpected safety findings were observed through Week 12 of the main study. Patients completing the double-blind period of the study had the option of participating in an open-label extension (OLE) of this phase II study. Here we report the safety and effectiveness findings through 48 weeks of open-label ixekizumab treatment in biologic-naive and TNF-IR patients with moderate to severe RA.

MATERIALS AND METHODS

Patients. Eligible patients met the inclusion criteria for the phase II randomized, double-blind, placebo-controlled study NCT00966875 as previously described[5]. Patients in the OLE participated from the following countries (percentages in parentheses): Argentina (7.2%), Chile (2.8%), Germany (1.3%), India (10.2%), Peru (7.2%), Poland (19.7%), Romania (5.6%), Russia (3.1%), South Korea (3.8%), Taiwan (6.1%), and the United States (33.0%).

Two subpopulations of patients with active RA were evaluated in our study: biologic-naive and TNF-IR. Patients enrolled in the biologic-naive subpopulation had received no previous treatment with any biologic therapy. Patients enrolled in the TNF-IR subpopulation had an insufficient response, loss of response, or were intolerant of treatment with at least 1 biologic TNF inhibitor, with no record maintained to distinguish between these causes. Patients who completed the double-blind period of the study were eligible to enter the optional OLE.

Study design. In the double-blind period, both patient subpopulations were randomized to receive subcutaneous injections of placebo or ixekizumab at weeks 0, 1, 2, 4, 6, 8, and 10[5]. Biologic-naive patients received placebo or 3, 10, 30, 80, or 180 mg ixekizumab, and TNF-IR patients received placebo or 80 or 180 mg ixekizumab. After a treatment hiatus between weeks 10 to 16, all patients electing to participate in the OLE received 160 mg ixekizumab at weeks 16, 18, and 20 and every 4 weeks (Q4W) thereafter through Week 64.

Dose selection for the OLE (160 mg Q4W) was based on its expected pharmacokinetic equivalence to the 80 mg Q2W administration of ixekizumab tested in the double-blinded portion of the study. It was anticipated that both regimens would yield similar serum concentrations of the study drug.

The study protocol was approved by the investigational review board at each study center. All patients provided written informed consent. The study was designed jointly by representatives of the sponsor and the investigators, and was conducted in accordance with principles described in the Declaration of Helsinki and the applicable laws and regulations. Data were collected and analyzed by a contract research organization (Parexel Inc.), with oversight by the sponsor.

Safety assessments. Safety was monitored throughout the study. Assessments including treatment-emergent adverse events (TEAE) and serious adverse events (SAE; including deaths), discontinuations because of adverse events (AE), and clinical laboratory test abnormalities are reported here through Week 16 and Week 64. For safety assessments in the OLE, baseline was established as entry to the OLE. AE, SAE, and AE of special interest were identified and coded to Medical Dictionary for Regulatory Activities terms. Grading for neutropenia and liver function tests were coded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0.

Efficacy assessments. The primary endpoint of the double-blind period of the study was a dose-response relationship of ixekizumab at Week 12 in the biologic-naive subpopulation as measured by ACR20 response[5]. ACR20, ACR50, and ACR70 responses over time were measured throughout both the double-blind period of the study and the OLE, as was the Disease Activity Score in 28 joints with C-reactive protein (DAS28-CRP)[6,7]. Improvement in disease activity was also assessed using the European League Against Rheumatism (EULAR) 28 good/moderate responses[8] and DAS28-CRP ≤ 3.2 measure.

Statistical methods. Statistical analyses for the double-blind period of the study have been previously described[5]. Briefly, all analyses were conducted on a modified intent-to-treat basis and included data from all randomized patients who received at least 1 dose of study drug. Separate analyses were done within the biologic-naive and TNF-IR subpopulations. In the OLE, all efficacy and safety data were summarized without formal statistical analyses because all patients received 160 mg ixekizumab.

RESULTS

Patient baseline demographics and clinical characteristics. The demographics and baseline clinical characteristics for all patients in the biologic-naive and TNF-IR subpopulations were generally comparable between the 2 subpopulations at randomization at study entry, as well as at entry into the OLE (Table 1). Within each subpopulation, the clinical characteristics for all patients at entry into the OLE had improved compared with study entry (Table 1). During the OLE, 13 biologic-naive patients discontinued from the study by Week 40, and 12 additional patients discontinued by Week 64. In the TNF-IR group, 5 patients discontinued by Week 28, 19 discontinued between weeks 28 and 40, and an additional 23 patients discontinued by Week 64.

Patient disposition. Of the 260 biologic-naive patients who entered the study, 236 (91%) patients completed the double-blind period, and of these, 232 (98%) patients entered the OLE (Figure 1). A total of 201 (87%) biologic-naive patients completed the OLE. Of the 188 TNF-IR patients who entered the study, 161 (86%) patients completed the double-blind period, and of these, 158 (98%) patients entered the OLE. A total of 99 (63%) TNF-IR patients completed the OLE. For both subpopulations, the most common reason for discontinuation from the OLE was lack of efficacy [10 (4%) biologic-naive and 27 (17%) TNF-IR patients].

Overall safety summary. During the double-blind period of the study, a similar frequency of TEAE was observed between the placebo and ixekizumab groups in both biologic-naive and TNF-IR subpopulations[5]. During the OLE, the exposure-adjusted incidence rate for TEAE was similar or lower than the exposure-adjusted incidence rate observed during the double-blind period for both subpopulations (Table 2). In addition, the types of TEAE observed in the OLE were mostly similar to those reported in the double-blind period, despite the longer exposure, and the majority were mild to

Table 1. Demographics and clinical characteristics of biologic-naive and TNF-IR subpopulations for all patients combined at study or OLE entry. Prednisone dose was ≤ 10 mg per day. Values are mean ± SD unless otherwise specified.

Characteristics	Biologic-naive		TNF-IR	
	Blinded, Weeks 0–16, n = 260	OLE, Weeks 16–64, n = 232	Blinded, Weeks 0–16, n = 188	OLE, Weeks 16–64, n = 158
Female, n (%)	220 (85)	194 (84)	163 (87)	139 (88)
Age, yrs	53 ± 11	53 ± 10	53 ± 11	53 ± 11
White, n (%)	143 (55)	126 (54)	162 (86)	136 (86)
BMI, kg/m^2	28 ± 6	28 ± 6	29 ± 8	29 ± 8
RA duration, yrs	7 ± 7	7 ± 7	11 ± 8	11 ± 7
ACPA+, %*	74	73	71	61
RF+, %*	72	71	74	72
MTX, mg/week	14 ± 5	15 ± 7	16 ± 5	13**
Prednisone use, n (%)	131 (50)	120 (52)	99 (53)	83 (53)
Tender joints count, 28 joints	16 ± 7	10 ± 8	15 ± 7	11 ± 9
Swollen joints count, 28 joints	13 ± 7	7 ± 7	12 ± 6	8 ± 7
Pain, 0–100	63 ± 21	43 ± 24	61 ± 23	50 ± 28
PtGA, 0–100	65 ± 21	43 ± 24	64 ± 23	50 ± 27
PGA, 0–100	60 ± 19	36 ± 22	59 ± 19	39 ± 24
HAQ-DI	1.5 ± 0.7	1.1 ± 0.7	1.6 ± 0.7	1.4 ± 0.7
DAS28-CRP	5.9 ± 1.0	4.5 ± 1.4	5.9 ± 1.0	4.7 ± 1.6
hsCRP, mg/l	18 ± 21	11 ± 15	21 ± 24	15 ± 19
ESR, mm/h	54 ± 27	39 ± 23	51 ± 26	43 ± 23

* RF status and ACPA status of patients at OLE entry were determined using patients' values at study entry. ** No SD reported for MTX use in TNF-IR subpopulation at OLE entry because only 1 patient reported. TNF-IR: tumor necrosis factor–inadequate responder; OLE: open-label extension; BMI: body mass index; RA: rheumatoid arthritis; ACPA: anticitrullinated peptide antibody; RF: rheumatoid factor; MTX: methotrexate; PtGA: patient's global assessment; PGA: physician's global assessment; HAQ-DI: Health Assessment Questionnaire–Disability Index; DAS28-CRP: 28-joint Disease Activity Score with C-reactive protein; hsCRP: high-sensitivity CRP; ESR: erythrocyte sedimentation rate.

moderate in severity. The exposure-adjusted incidence rate for SAE in the OLE was also similar to or lower than the exposure-adjusted incidence rate observed during the double-blind period for both the biologic-naive and TNF-IR subpopulations (Table 2). A total of 3 (1%) biologic-naive and 9 (6%) TNF-IR patients discontinued the OLE because of AE. There were 3 deaths (< 1% of all patients) during the OLE. In the biologic-naive subpopulation, 1 patient treated with 10 mg ixekizumab in the double-blind period discontinued from the OLE after 10 treatments (32 weeks in OLE) because of increased levels of transaminases. This patient was hospitalized with a severe urinary tract infection about 5 months after receiving her last dose of ixekizumab in the OLE and died nearly 3 weeks later from an unknown cause (26 weeks after discontinuation). A second biologic-naive patient randomized to 180 mg ixekizumab in the double-blind period discontinued from the OLE after 2 treatments because of the lack of efficacy and died of complications stemming from meningitis more than 9 months after his last dose of ixekizumab in the OLE; a brain biopsy demonstrated non-caseating granulomatous meningitis. One death occurred in the TNF-IR subpopulation. This patient had been treated with 80 mg ixekizumab in the double-blind period and had received 4 treatments of ixekizumab during the OLE. She died 5 weeks after the last treatment because of metastatic lung adenocarcinoma; the patient had smoked one-half to 1 full pack of cigarettes per day for many years.

Infections and allergic/hypersensitivity events. During the double-blind period of the study, a slightly higher frequency of infections was observed in the biologic-naive patients treated with higher doses of ixekizumab compared with placebo[5]. For both the biologic-naive and TNF-IR subpopulations, the exposure-adjusted incidence rate of serious infections in the OLE was similar to or lower than the exposure-adjusted incidence rate observed in the double-blind period of the study (Table 2). Serious infections in the biologic-naive subpopulation in the OLE included meningitis, pneumonia, acute pyelonephritis, and urinary tract infection. Serious infections in the TNF-IR subpopulation included bronchitis, staphylococcal bacteremia, upper respiratory tract infection, and urosepsis. No patients in the biologic-naive subpopulation discontinued the study during the OLE because of an infection, while 4 patients in the TNF-IR subpopulation with infections (furuncle, staphylococcal infection, staphylococcal bacteremia, and upper respiratory tract infection) discontinued from the study during the OLE. No mycobacterial or invasive fungal infections were reported during the OLE in either subpopulation. AE categorized as systemic allergic/hypersensitivity events occurred in 19 (8%) biologic-naive and 9 (6%) TNF-IR patients during

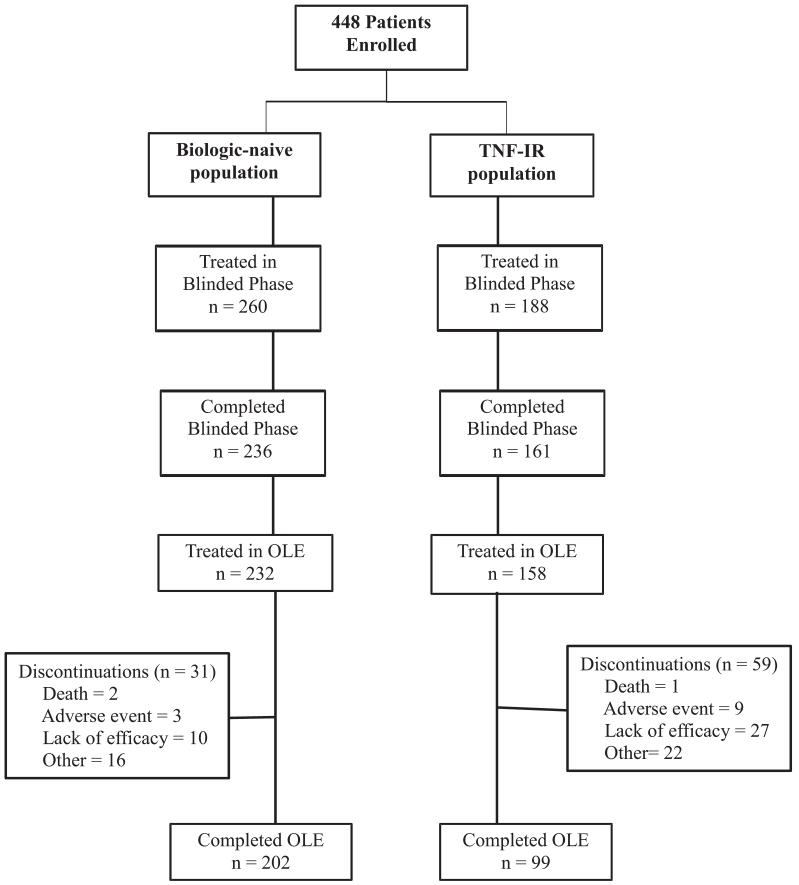

Figure 1. Patient disposition through Week 64 in the OLE. Other reasons for discontinuations include entry criteria, lost to followup, and physician, sponsor, or subject decision. OLE: open-label extension; TNF-IR: tumor necrosis factor–inadequate responder.

the OLE compared with 12 (5%) biologic-naive and 8 (4%) TNF-IR patients in the double-blind period. All such events in the OLE were mild or moderate in severity with none leading to discontinuation.

Malignancy. One biologic-naive patient treated with 3 mg ixekizumab presented with breast cancer 5 months after discontinuing from the double-blind period. A total of 5 malignant neoplasms were reported in 3 TNF-IR patients in the OLE of the study. During the OLE, metastatic lung adenocarcinoma was reported in 1 TNF-IR patient who had received 80 mg ixekizumab in the double-blind period. A second TNF-IR patient treated with 80 mg ixekizumab in the double-blind period presented with basal cell carcinomas at weeks 32 and 42. Endometrial and ovarian cancer was reported in a third TNF-IR patient who received 180 mg ixekizumab in the double-blind period. This patient received the last dose of study drug 48 weeks after randomization and subsequently discontinued the study at Week 55 because of the cancer diagnoses.

Laboratory results. At Week 64, biologic-naive patients showed a decrease of 9% overall in mean absolute neutrophil counts from values collected at study entry. Patients in the TNF-IR subpopulation showed a decrease of 5% overall in mean absolute neutrophil counts at Week 64 from values measured at study entry. During the OLE, 8 biologic-naive and 2 TNF-IR patients experienced a CTCAE Grade 2 neutrophil count decrease, defined as $< 1.5 – 1.0 \times 10^9$ cells/l, and 1 biologic-naive patient experienced a Grade 3 neutrophil count decrease, defined as $< 1.0 – 0.5 \times 10^9$ cells/l, with spontaneous recovery to a Grade 2 neutropenia. There were no Grade 4 neutrophil counts in either the biologic-naive or TNF-IR subpopulations. Changes in mean white blood cell counts in the OLE were similar to those seen in mean absolute neutrophil counts in both subpopulations. One patient who had a Grade 1 alanine aminotransferase (ALT) at the double-blind period baseline and a normal level at the OLE baseline experienced an increase in ALT to Grade 3 that normalized with continued study drug treatment during the OLE. No other patients in either subpopulation had changes in mean serum ALT or aspartate aminotransferase levels of Grade 3 or above during the OLE compared with values at study entry.

ACR response. In the double-blind period of our study, the primary endpoint of a dose-response relationship of ixekizumab was met at Week 12 as measured by ACR20 response in the biologic-naive subpopulation[5]. For patients originally randomized to ixekizumab in the double-blind period of the study, maintenance of or improvement in the

Table 2. Summary of adverse events.

Adverse Events	Biologic-naive							
	Blinded, Weeks 0–16						OLE, Weeks 16–64	
	Placebo		Combined Dose Groups		All Patients		All Patients	
	n = 54	PY = 15.8	n = 206	PY = 61.9	n = 260	PY = 77.7	n = 232	PY = 235.6
	%	IR	%	IR	%	IR	%	IR
SAE	1.9	0.06	3.4	0.11	3.1	0.10	7.3	0.07
Serious infections	0	0	0.5	0.02	0.4	0.01	2.2	0.02
Neoplasms, benign, and malignant*	1.9	0.06	0	0	0.4	0.01	0.3	0.01
Deaths	0	NA	0	NA	0	NA	0.9	NA
TEAE	55.6	1.90	59.2	1.97	58.5	1.96	72.4	0.71
Discontinuations because of TEAE	3.7	NA	1.5	NA	1.9	NA	1.3	NA
Infections	20.4	0.70	28.6	0.95	26.9	0.90	40.5	0.40

Adverse Events	TNF-IR							
	Blinded, Weeks 0–16						OLE, Weeks 16–64	
	Placebo		Combined Dose Groups		All Patients		All Patients	
	n = 64	PY = 18.4	n = 124	PY = 37.0	n = 188	PY = 55.4	n = 158	PY = 140.1
	%	IR	%	IR	%	IR	%	IR
SAE	1.6	0.05	8.9	0.30	6.4	0.22	11.4	0.13
Serious infections	0	0	4.0	0.14	2.7	0.09	2.5	0.03
Neoplasms, benign, and malignant*	0	0	4.0	0.14	2.7	0.09	3.2	0.04
Deaths	0	NA	0	NA	0	NA	0.6	NA
TEAE	65.6	2.28	65.3	2.19	65.4	2.22	72.8	0.82
Discontinuations because of TEAE	0	NA	4.8	NA	3.2	NA	5.7	NA
Infections	29.7	1.03	31.5	1.05	30.9	1.05	40.5	0.46

* In the biologic-naive subpopulation, 1 malignancy (breast cancer) presented after the patient discontinued from the double-blind period of the study. In the TNF-IR subpopulation, 2 malignancies (bladder transitional cell carcinoma and breast cancer) occurred during the double-blind period, and 5 malignancies (2 basal cell carcinomas in the same patient, 1 metastatic lung adenocarcinoma, and 1 endometrial and 1 ovarian cancer in the same patient) occurred during the OLE. OLE: open-label extension; PY: patient year; IR: exposure-adjusted incidence rate; SAE: serious adverse event; TEAE: treatment-emergent adverse event; TNF-IR: tumor necrosis factor– inadequate responder; NA: IR not available for deaths and discontinuations due to TEAE.

ACR20, ACR50, and ACR70 responses were observed in both biologic-naive and TNF-IR subpopulations through the OLE portion of the study (Figure 2). For patients originally assigned to placebo in the double-blind period of the study, ACR20, ACR50, and ACR70 responses in the OLE were comparable with those observed in patients who received ixekizumab in the double-blind period (Figure 2).

Maintenance of ACR20, ACR50, and ACR70 responses was observed in 95/107 (89%), 30/39 (77%), and 9/13 (69%) biologic-naive patients, respectively, and in 31/41 (76%), 12/18 (67%), and 4/9 (44%) TNF-IR patients, respectively, after further treatment for 48 weeks in the OLE. Among patients who did not reach an ACR20, ACR50, or ACR70 response at Week 16, such response was observed at Week 64 in 53/94 (56%), 65/162 (40%), and 31/188 (17%) biologic-naive patients, respectively, and 25/65 (39%), 20/88 (23%), and 12/97 (12%) TNF-IR patients, respectively.

DAS28-CRP and EULAR responses. A significant reduction in disease activity as measured by DAS28-CRP scores was observed for both biologic-naive and TNF-IR subpopulations treated with ixekizumab in the double-blind period of our study[5]. The improvements in DAS28-CRP observed at Week 16 were maintained or improved after switching to 160 mg ixekizumab in both subpopulations during the OLE through Week 64 (Figure 3A and 3B). For biologic-naive and TNF-IR patients originally randomized to placebo at study entry, a rapid decline in DAS28-CRP scores was observed during the OLE, comparable to those seen for patients in the ixekizumab groups in the double-blind period (Figures 3A and 3B). DAS28-CRP ≤ 3.2 was observed in 41% of biologic-naive (n = 84) and 31% of TNF-IR (n = 33) patients after 64 weeks of ixekizumab treatment (Figures 3C and 3D). DAS28-CRP < 2.6 was observed in 23% of biologic-naive (n = 46) and 22% of TNF-IR (n = 23) patients after 64 weeks of ixekizumab treatment (Figure 3C and 3D). Of patients with a good/moderate EULAR response at Week 16 (biologic-naive n = 139, TNF-IR n = 58), this response was maintained through Week 64 in 128 biologic-naive (92%) and 52 TNF-IR (90%) patients (data not shown).

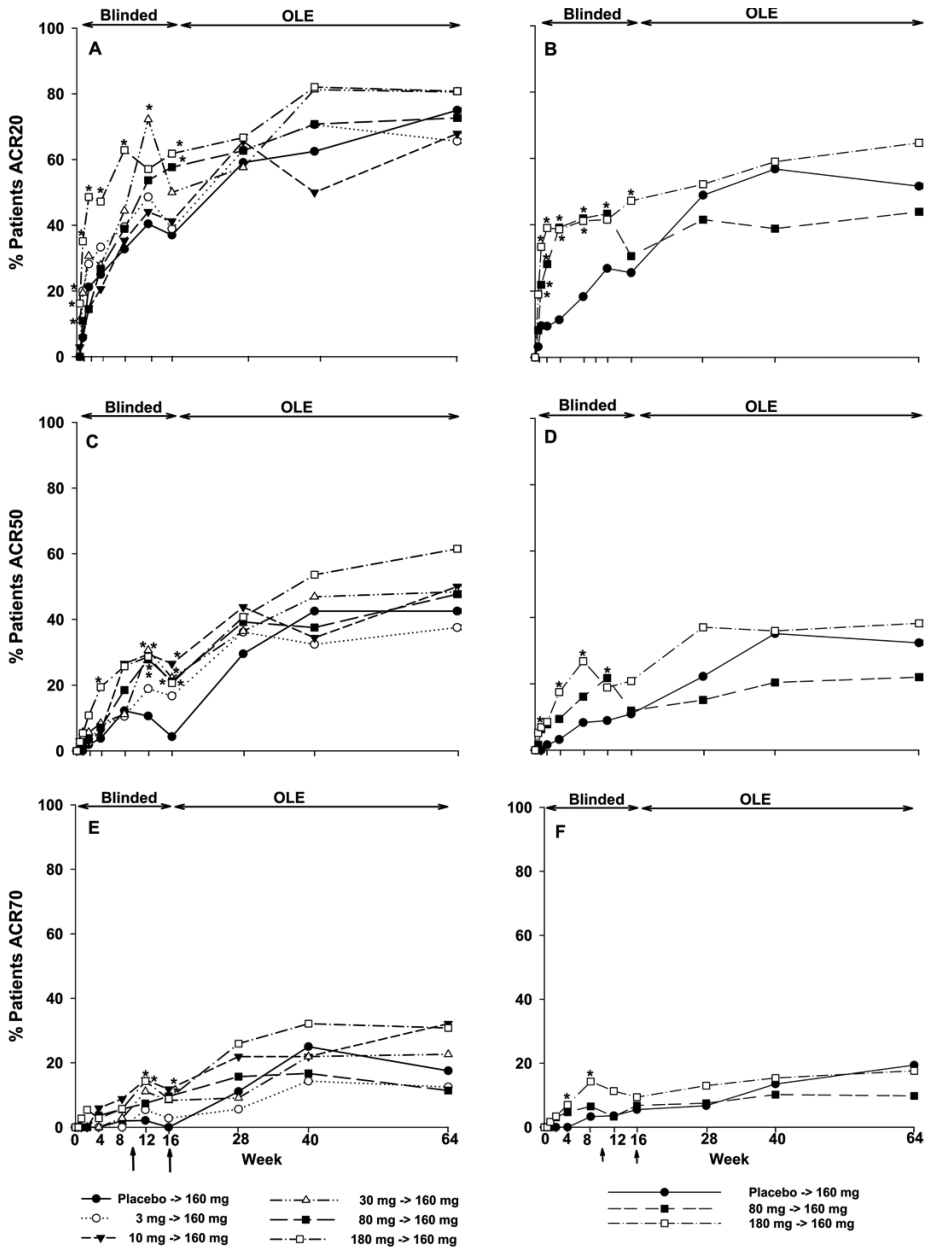

Figure 2. ACR20 (A and B), ACR50 (C and D), and ACR70 (E and F) response rates in biologic-naive (left) and TNF-IR (right) populations in the double-blind period (weeks 0–16) and the OLE (weeks 16–64). All data are reported as observed data. Arrows indicate last dose in the double-blind period at Week 10 and first dose in the OLE at Week 16. * $p \leq 0.05$. ACR: American College of Rheumatology; TNF-IR: tumor necrosis factor– inadequate responder; OLE: open-label extension.

DISCUSSION

Biologic agents that inhibit inflammatory cytokines have been used in the treatment of RA. Despite recent advances, a need for alternative therapies for RA still exists, particularly among patients who have failed treatment with previous therapies, including TNF inhibitors[9,10,11,12]. In a phase II dose-ranging study, we found that ixekizumab significantly improved the signs and symptoms of RA over 16 weeks in biologic-naive and TNF-IR patients[5]. Here we report the safety and efficacy results in an OLE of the phase II study through Week 64.

The safety profile of ixekizumab in the OLE through 64 weeks was comparable to that observed in the randomized, double-blind period through 16 weeks of the phase II study. The frequency of TEAE in the double-blind period of the study was similar across treatment arms in both biologic-naive and TNF-IR subpopulations, and the TEAE were generally mild to moderate in character. No major changes

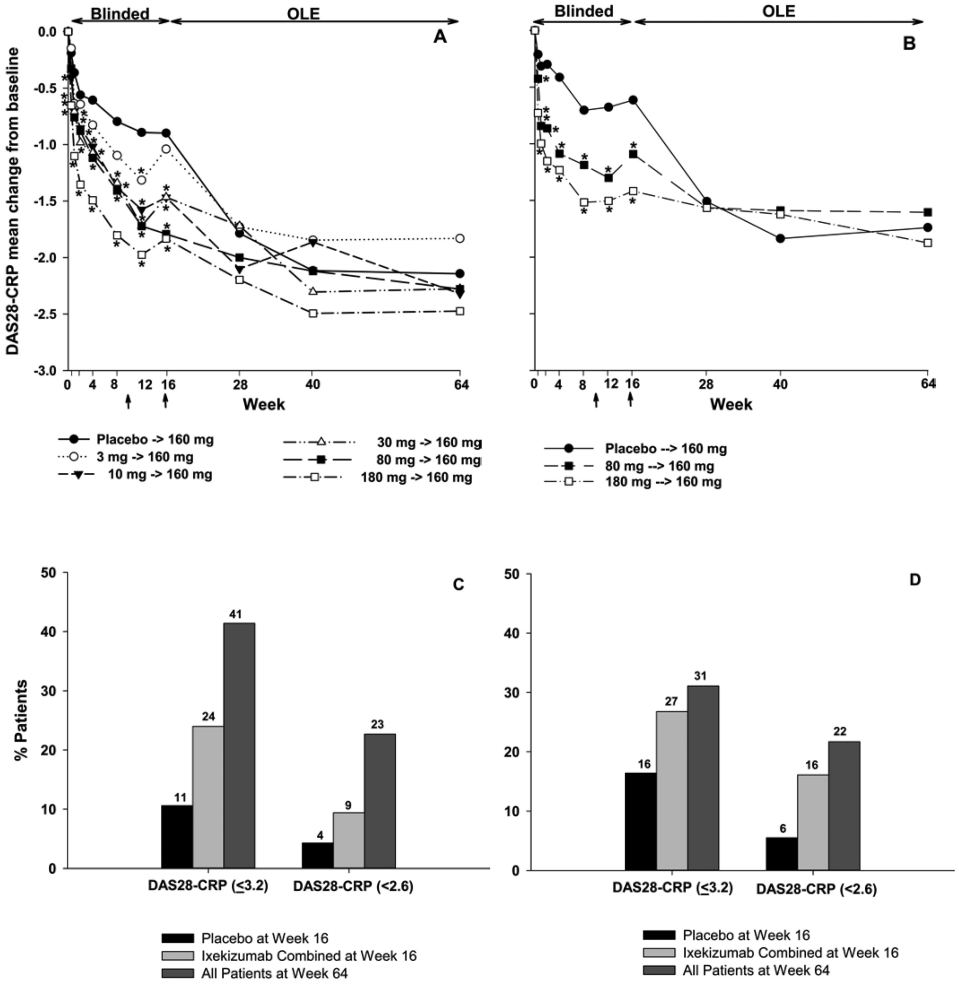

Figure 3. A and B: Mean change from baseline in DAS28-CRP in biologic-naive (A) and TNF-IR (B) populations in the double-blind period (weeks 0–16) and the OLE (weeks 16–64). All data are reported as observed data. Arrows indicate last dose in the double-blind period at Week 10 and first dose in the OLE at Week 16. * $p \leq 0.05$. C and D: Percent of biologic-naive (C) or TNF-IR (D) patients who achieve DAS28-CRP ≤ 3.2 or DAS28-CRP < 2.6 at Week 16 or Week 64. DAS28: Disease Activity Score at 28 joints; CRP: C-reactive protein; TNF-IR: tumor necrosis factor– inadequate responder; OLE: open-label extension.

in the types of TEAE were observed during the OLE, despite longer exposure to ixekizumab. Incidence rates of SAE during the OLE were slightly elevated, but comparable to levels seen in the placebo groups of the double-blinded phase. By inhibiting pathways important in host defense, cytokine-targeted biologic agents such as ixekizumab may be associated with an increased risk of infections. The current study demonstrated that infections were mostly mild or moderate through 64 weeks of treatment, and infection rates observed during the 48-week OLE exposure to ixekizumab trended slightly toward increased levels compared with the first 16 weeks. Similar to the double-blind period of the study, no mycobacterial or invasive fungal infections were observed in the OLE. The frequency of allergic/hypersensitivity events in the OLE was similar to those in the double-blind period of the study, and these events were mild or moderate in severity with none leading to discontinuation. The 5 malignancies reported during the OLE — metastatic lung adenocarcinoma, basal cell carcinomas (twice in same patient), and endometrial and ovarian cancer — all occurred in 3 TNF-IR patients. There were 3 deaths during the OLE. The 2 deaths (1 patient with meningitis and the second patient of an unknown cause) in the biologic-naive subpopulation occurred 5 months or more after discontinuation of ixekizumab. One TNF-IR patient died of metastatic lung adenocarcinoma about 7 months after the first dose and 5 weeks after the last dose of ixekizumab. At Week 64, patients in the biologic-naive and TNF-IR subpopulations showed a 9% and a 5% decrease, respectively, in mean absolute neutrophil counts from values at study entry. The 1 biologic-naive patient who experienced a Grade 3 neutropenia at Week 48 was also receiving methotrexate and sulfasalazine at the time. This patient had

a spontaneous recovery to Grade 2 neutropenia while receiving treatment until Week 64.

In the double-blind period of our study, patients in both subpopulations with moderate to severe RA treated with ixekizumab for 16 weeks saw a rapid and significant improvement in the signs and symptoms of their disease[5]. Clinical improvements in ACR20, ACR50, and ACR70, as well as DAS28-CRP, observed with ixekizumab treatment in the double-blind period were maintained or improved in both subpopulations enrolled in the OLE through 64 weeks by a responder index. Additional analysis of ACR20 rates using a nonresponder imputation (NRI) demonstrated results similar to those of the responder index (Appendix 1). For patients initially assigned to placebo in the double-blind period, clinical improvements in these disease measures during the OLE were comparable with the improvements seen in those patients originally treated with ixekizumab in the double-blind period of the study.

There were several limitations to the OLE of our study. Because all patients electing to participate in the OLE received ixekizumab, there was no placebo group for comparison of the efficacy and safety through 48 weeks of exposure to the study drug. Additionally, because participation in the OLE was optional, those patients in whom ixekizumab was effective and who did not experience AE in the double-blind period would most likely have continued in our study. The analyses of efficacy reported were based on the number of observations made at each visit and did not account for the number of discontinuations over the course of the study. An NRI analysis of the data, however, did confirm the improvement or maintenance of response rates over time. Further, our study was limited to 64 weeks of treatment, and it not known whether longer exposure to ixekizumab would alter the safety profile or improve the efficacy of this treatment. Finally, there was a hiatus from ixekizumab treatment between weeks 10 to 16 with decreases in clinical responses observed prior to retreatment in the OLE; hence, overall responses may not represent those expected with continuous treatment over 64 weeks.

Ixekizumab was well tolerated in biologic-naive and TNF-IR patients with moderate to severe RA. Overall, the safety profile from our study, including AE, SAE, and laboratory variables, does not highlight any specific safety risk or pattern of event clustering with ixekizumab treatment. Despite longer exposure, the safety findings in the OLE through 64 weeks were consistent overall with those in the double-blind period through 16 weeks. Clinical improvements observed with ixekizumab treatment in the double-blind phase were maintained or improved in the patients who participated in the OLE through Week 64; however, larger phase III studies need to be performed to fully understand the safety and efficacy of longterm ixekizumab treatment.

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APPENDIX 1. ACR20 response rates in biologic-naive (A) and TNF-IR (B) populations in the double-blind period (weeks 0–16) and the OLE (weeks 16–64) by NRI. ACR: American College of Rheumatology; TNF-IR: tumor necrosis factor–inadequate responder; OLE: open-label extension; NRI: nonresponder imputation.