ARTHRITIS & RHEUMATOLOGY
Vol. 66, No. 7, July 2014, pp 1693–1704
DOI 10.1002/art.38617

A Phase II Randomized Study of Subcutaneous Ixekizumab, an Anti–Interleukin-17 Monoclonal Antibody, in Rheumatoid Arthritis Patients Who Were Naive to Biologic Agents or Had an Inadequate Response to Tumor Necrosis Factor Inhibitors

Mark C. Genovese,[1] Maria Greenwald,[2] Chul-Soo Cho,[3] Alberto Berman,[4] Ling Jin,[5] Gregory S. Cameron,[5] Olivier Benichou,[5] Li Xie,[5] Daniel Braun,[5] Pierre-Yves Berclaz,[5] and Subhashis Banerjee[5]

Objective. **To evaluate ixekizumab, an anti–interleukin-17A (anti–IL-17A) monoclonal antibody, in 2 populations of rheumatoid arthritis (RA) patients: biologics-naive patients and patients with an inadequate response to tumor necrosis factor (TNF) inhibitors.**

Methods. **In this phase II, randomized, double-blind study, placebo or ixekizumab was administered subcutaneously to 260 biologics-naive patients and 188 patients with an inadequate response to TNF inhibitors at weeks 0, 1, 2, 4, 6, 8, and 10 with concomitant disease-modifying antirheumatic drugs. The primary objective was to determine the dose-response relationship of ixekizumab as measured by the proportion of biologics-naive patients meeting the American College of Rheumatology 20% improvement criteria (ACR20) at week 12.**

Results. **Using a logistic regression model defined a priori, a statistically significant dose-response relationship as measured by ACR20 response rates at week 12 was detected in biologics-naive patients ($P = 0.031$). For patients with an inadequate response to TNF inhibitors, ACR20 responses at week 12 were significantly better with ixekizumab than placebo ($P < 0.05$). Decreases in the Disease Activity Score in 28 joints using the C-reactive protein level (DAS28-CRP), Clinical Disease Activity Index (CDAI), and CRP level from baseline were observed at week 12 in the ixekizumab groups in both populations ($P < 0.05$ versus placebo). Onset of action was rapid in some dose groups in both populations, with improvements in the ACR20, DAS28-CRP, CRP levels, and CDAI observed by day 3 ($P < 0.05$). Adverse events occurred with similar frequencies overall in the ixekizumab and placebo groups. Infections were more frequent with ixekizumab than placebo (biologics-naive 25% versus 19%; inadequate responders to TNF inhibitors 27% versus 25%). No mycobacterial or invasive fungal infections were reported.**

Conclusion. **Ixekizumab improved RA signs and symptoms in RA patients who were either naive to biologics treatment or had an inadequate response to TNF inhibitors. The safety profile was similar to that of other biologic agents, with no unexpected safety concerns.**

Proinflammatory cytokines play a dominant role in the pathogenesis of synovial inflammation and

ClinicalTrials.gov identifier: NCT00966875.
Supported by Eli Lilly and Company.
[1]Mark C. Genovese, MD: Stanford University, Palo Alto, California; [2]Maria Greenwald, MD, FACR: Desert Medical Advances, Palm Desert, California; [3]Chul-Soo Cho, MD: Catholic University of Korea and St. Mary's Hospital, Seoul, Republic of Korea; [4]Alberto Berman, MD: Centro Médico Privado de Reumatología, Tucuman, Argentina; [5]Ling Jin, MD, Gregory S. Cameron, PhD, Olivier Benichou, MD, PhD, MBA, Li Xie, MS, Daniel Braun, MD, PhD, Pierre-Yves Berclaz, MD, PhD, Subhashis Banerjee, MD (current address: Bristol-Myers Squibb, Princeton, NJ): Eli Lilly and Company, Indianapolis, Indiana.

Dr. Genovese has received consulting fees and/or honoraria (less than $10,000) and research grants from Eli Lilly and Company. Drs. Greenwald and Berman have received research grants from Eli Lilly and Company. Drs. Jin, Cameron, Benichou, Braun, Berclaz, and Banerjee and Ms Xie own stock or stock options in Eli Lilly and Company.

Address correspondence to Mark C. Genovese, MD, Division of Immunology and Rheumatology, Stanford University Medical Center, 1000 Welch Road, Suite 203, Palo Alto, CA 94304. E-mail: genovese@stanford.edu.

Submitted for publication March 28, 2013; accepted in revised form February 27, 2014.

arthritis-associated bone loss in rheumatoid arthritis (RA). One of these cytokines, interleukin-17A (IL-17A), activates synovial fibroblasts, chondrocytes, and osteoclasts, which can lead to inflammation, bone erosion, and joint damage (1). In animal models of inflammatory arthritis, IL-17 neutralization reduces arthritis severity by diminishing joint inflammation and inhibiting structural damage (2,3).

In a recent phase I study of RA patients who were naive to treatment with biologic agents, intravenous ixekizumab (LY2439821), a humanized monoclonal antibody that neutralizes IL-17A, significantly improved signs and symptoms with no significant safety signal noted (4). The present study was conducted to confirm the efficacy of ixekizumab in a larger population of biologics-naive patients with RA; the primary objective was to determine the dose-response relationship of subcutaneous ixekizumab as measured by the proportion of patients meeting the American College of Rheumatology 20% improvement criteria (ACR20) (5) at week 12. In addition, it was not known whether IL-17A neutralization would be effective in patients who have an inadequate response to tumor necrosis factor (TNF) inhibitors. Since patients with an inadequate response to TNF inhibitors respond less well than biologics-naive patients to other biologic treatments (6,7), the present study included a population of patients with an inadequate response to TNF inhibitors, with a key secondary objective being evaluation of the efficacy of subcutaneous ixekizumab in these patients.

PATIENTS AND METHODS

Patients. Eligible patients were adults (18–75 years of age) with active RA according to the ACR 1987 revised criteria (8), ACR functional class I, II, or III (9), ≥6 swollen joints of 28 assessed and ≥6 tender joints of 28 assessed, and a serum C-reactive protein (CRP) level greater than the upper limit of normal (ULN; 10 mg/liter) or an erythrocyte sedimentation rate (ESR) of ≥28 mm/hour. Two population cohorts of RA patients were evaluated in the study: biologics-naive patients and patients with an inadequate response to TNF inhibitors.

Biologics-naive patients. In order to be enrolled in the biologics-naive population, patients could not have been previously treated with any biologic agent (e.g., TNF-, IL-1–, IL-6–, T cell–, or B cell–targeted therapies). Patients were required to have been taking methotrexate (MTX) for ≥12 weeks prior to baseline, to have been taking MTX at a stable dose (7.5–25 mg/week) for ≥8 weeks prior to baseline, and to continue taking MTX at a stable dose throughout the study. In addition to MTX, patients were allowed to receive hydroxychloroquine and/or sulfasalazine if they had been on a stable dose for ≥8 weeks prior to baseline. Use of leflunomide within 12 weeks or other traditional disease-modifying antirheumatic drugs (DMARDs) within 8 weeks of baseline was not permitted, with the exception of MTX, hydroxychloroquine, or sulfasalazine. Patients were excluded from this population if they experienced an inadequate response to a minimum of 3 months of treatment with ≥5 conventional DMARDs (e.g., leflunomide, azathioprine, cyclosporine, hydroxychloroquine, gold salts, and sulfasalazine), used alone or in combination, at therapeutic doses. Oral prednisone not exceeding 10 mg/day was allowed provided the dosage was stable for ≥4 weeks.

Patients with an inadequate response to TNF inhibitors. Patients enrolled in the population with an inadequate response to TNF inhibitors had to have been treated with ≥1 biologic TNF inhibitor and, in the opinion of the investigator, either had stopped treatment due to insufficient efficacy after ≥3 months of therapy at approved doses, or had been intolerant of such treatment, regardless of treatment duration. Patients in the group with an inadequate response to TNF inhibitors could not have used etanercept or anakinra for <28 days, infliximab or adalimumab for <56 days, abatacept for <3 months, rituximab for <12 months, or any other biologic DMARD for a duration equivalent to <5 half-lives prior to baseline. In addition, the patients with an inadequate response to TNF inhibitors had to have been regularly treated with ≥1 conventional DMARD in a stable treatment regimen that could include any combination of 1 or more of MTX, hydroxychloroquine, and sulfasalazine; all other conventional DMARDs (e.g., leflunomide) were allowed as single-agent use only. If patients were taking MTX, regular use for ≥12 weeks and a stable dosage (7.5–25 mg/week) for ≥8 weeks prior to baseline was required.

Study design. This 12-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study with an open-label extension period was conducted at 75 sites in 11 countries (Argentina, Chile, Germany, India, the Republic of Korea, Peru, Poland, Romania, Russian Federation, Taiwan, and the US). Two separate RA population cohorts, biologics-naive patients and patients with an inadequate response to TNF inhibitors, were randomized to treatment (3:2:2:2:3:2 and 1:1:1, respectively) by computer-generated random sequence using an interactive voice response system. Both populations received subcutaneous injections of ixekizumab or placebo at weeks 0, 1, 2, 4, 6, 8, and 10; biologics-naive patients received placebo or 3 mg, 10 mg, 30 mg, 80 mg, or 180 mg of ixekizumab, and patients with an inadequate response to TNF inhibitors received placebo or 80 mg or 180 mg of ixekizumab.

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 (Eli Lilly) 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.

End points. The primary end point was the dose-response relationship of ixekizumab as measured by the proportion of biologics-naive patients achieving an ACR20 response at week 12. Key secondary end points at week 12 included the proportion of biologics-naive patients and patients with an inadequate response to TNF inhibitors in whom

an ACR20 response was achieved. Other secondary end points included ACR50 and ACR70 responses, individual ACR core set components, Disease Activity Score in 28 joints using the CRP level (DAS28-CRP) (10), low disease activity (DAS28-CRP $\leq$3.2), remission (DAS28-CRP $<$2.6), and European League Against Rheumatism response based on a 28-joint count (EULAR28) (11) evaluated at all time points, where the measures were obtained (12–14).

The Clinical Disease Activity Index (CDAI), which is a composite score of the sum of tender joint counts (of 28 joints assessed), swollen joint counts (of 28 joints assessed), patient's global assessment, and physician's global assessment, but which excludes any acute-phase reactant analysis, was also used as a post hoc efficacy measure (15). The patient's assessment of physical function was measured by a standardized Health Assessment Questionnaire (HAQ) disability index (DI) (16,17). Efficacy measures were collected at baseline; on day(s) 1, 2, or 3 (based on patient's preference); and at weeks 1, 2, 4, 8, and 12. Safety was monitored throughout the study. Adverse events (AEs), routine laboratory values, and vital signs were monitored throughout and are reported here through week 12. Treatment-emergent AEs were defined as those that first occurred or worsened after the first dose of study drug. Infections, systemic allergic reactions/hypersensitivities, and injection-site reactions were AEs of special interest. Abnormal laboratory findings of special interest included cytopenias (leukopenia, neutropenia, and thrombocytopenia) and results of liver biochemical tests (elevated levels of alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin, and alkaline phosphatase).

Statistical analysis. All analyses were conducted on a modified intent-to-treat basis and included data from all randomized patients who received $\geq$1 dose of study drug. For ACR response rates, patients who discontinued early, regardless of response status at the time of discontinuation, or who had a missing response at any time point, were imputed as nonresponders at that time point. For other categorical variables and all continuous variables, the last observation carried forward approach was used for missing data. Separate analyses were done within each population (biologics-naive patients and patients with an inadequate response to TNF inhibitors).

For the biologics-naive population, a sample size of

Table 1. Demographic and baseline clinical characteristics of the biologics-naive RA patients and RA patients with an inadequate response to TNF inhibitors*

	Biologics-naive RA patients						RA patients with an inadequate response to TNF inhibitors		
		Ixekizumab						Ixekizumab	
	Placebo (n = 54)	3 mg (n = 40)	10 mg (n = 35)	30 mg (n = 37)	80 mg (n = 57)	180 mg (n = 37)	Placebo (n = 64)	80 mg (n = 65)	180 mg (n = 59)
Age, years	53 ± 10	52 ± 10	54 ± 11	53 ± 12	53 ± 11	52 ± 11	53 ± 10	55 ± 11	52 ± 10
Female, no. (%)	47 (87)	33 (83)	27 (77)	31 (84)	52 (91)	30 (81)	55 (86)	57 (88)	51 (86)
Weight, kg	70 ± 18	70 ± 16	75 ± 23	73 ± 22	71 ± 17	71 ± 16	77 ± 22	75 ± 18	79 ± 23
BMI, kg/m^2	27 ± 7	27 ± 5	29 ± 8	28 ± 8	28 ± 6	27 ± 6	29 ± 8	29 ± 7	29 ± 8
No. of tender joints (28 assessed), mean	15.9	15.1	18.1	15.7	16.8	16.9	15.5	15.3	14.9
No. of swollen joints (28 assessed), mean	11.9	10.7	13.6	11.7	13.8	13.8	12.5	12.6	11.9
Pain (100-mm VAS), mean	62	59	65	66	66	64	67	59	58
Patient's global assessment (100-mm VAS), mean	67	60	64	66	64	69	68	62	63
Physician's global assessment (100-mm VAS), mean	60	56	59	59	58	65	58	62	57
HAQ DI, mean	1.5	1.3	1.5	1.7	1.6	1.6	1.7	1.7	1.5
CRP, mean mg/liter	19.2	13.0	20.5	14.4	19.5	22.7	20.7	20.1	20.9
DAS28-CRP, mean	5.9	5.6	6.1	5.8	6.0	6.1	5.9	5.8	5.8
CDAI	40 ± 15	37 ± 14	44 ± 16	40 ± 16	43 ± 14	44 ± 13	41 ± 14	40 ± 13	39 ± 15
RF positive, no. (%)	40 (76)	26 (67)	25 (71)	25 (68)	43 (75)	28 (76)	48 (75)	46 (71)	43 (73)
Anti-CCP positive, no. (%)	41 (76)	29 (73)	28 (80)	30 (81)	39 (68)	24 (67)	47 (73)	44 (68)	43 (73)
Disease duration, years	6 ± 6	8 ± 8	7 ± 8	7 ± 7	7 ± 8	6 ± 5	10 ± 6	13 ± 9	11 ± 7
MTX, mg/week	14 ± 5	14 ± 4	15 ± 5	15 ± 6	14 ± 4	14 ± 6	16 ± 6	18 ± 5	15 ± 6
Prednisone, mg/day	6 ± 2	7 ± 2	6 ± 2	7 ± 3	6 ± 3	7 ± 3	7 ± 3	7 ± 3	7 ± 3
Prednisone use, no. (%)	27 (50)	19 (48)	15 (43)	22 (60)	29 (51)	19 (51)	29 (45)	36 (55)	34 (58)

* Except where indicated otherwise, values are the mean ± SD. No statistically significant differences were noted in any of the parameters across treatment groups in each population. RA = rheumatoid arthritis; TNF = tumor necrosis factor; BMI = body mass index; VAS = visual analog scale; HAQ DI = Health Assessment Questionnaire disability index; DAS28-CRP = Disease Activity Score in 28 joints using the C-reactive protein (CRP) level; CDAI = Clinical Disease Activity Index; RF = rheumatoid factor; anti-CCP = anti–cyclic citrullinated peptide; MTX = methotrexate.

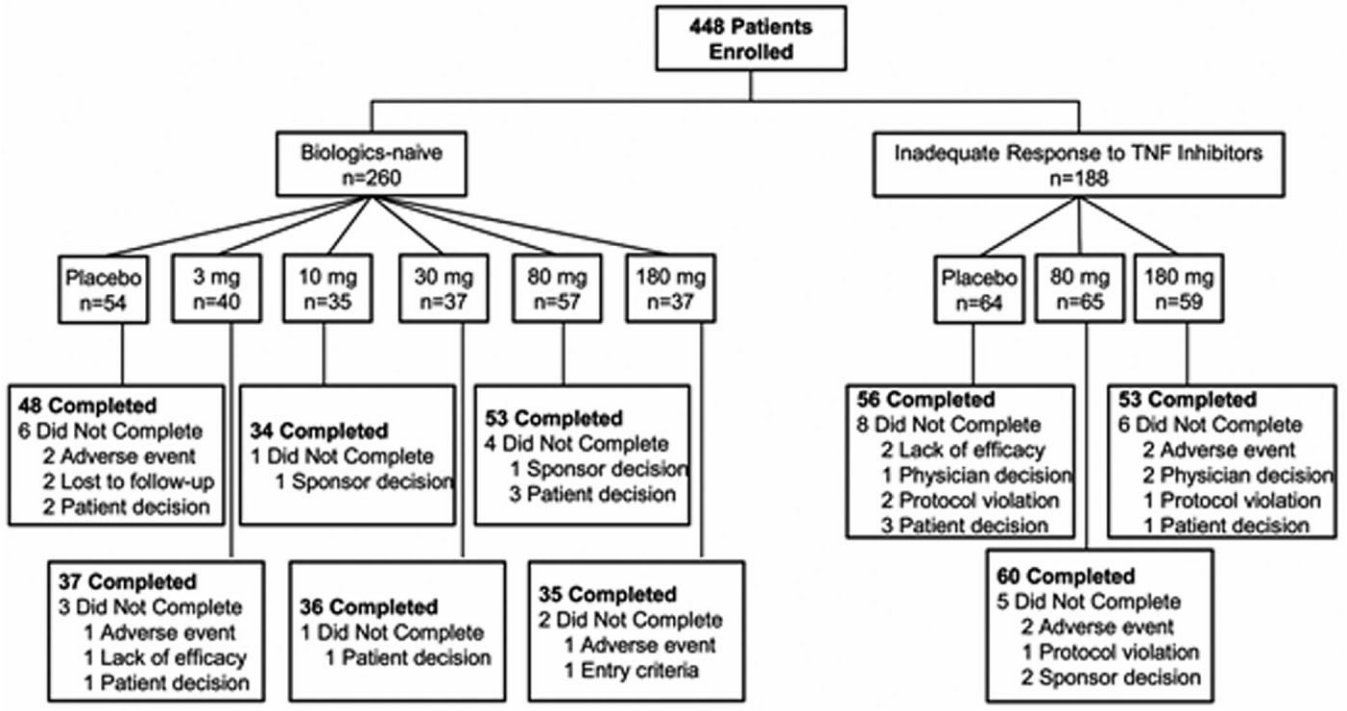

Figure 1. Patient disposition up to week 12. TNF = tumor necrosis factor.

224 evaluable patients at week 12 was predicted to provide ≥94% unadjusted power to detect a statistically significant dose-response relationship by logistic regression across the ixekizumab and placebo groups, based on an ACR20 response using a 2-sided maximum likelihood ratio test ($\alpha = 0.10$; alpha level selected to balance Type I and Type II errors). For the population of patients who had an inadequate response to TNF inhibitors, a sample size of 159 evaluable patients at week 12 provided ≥80% power to detect a 25% difference in the ACR20 response between each of the ixekizumab groups versus the placebo group (assuming a 25% response rate for placebo), using a 1-sided Pearson's chi-square test ($\alpha = 0.05$).

The primary objective for the biologics-naive population was analyzed using a logistic regression model with dose and the square of dose as continuous predictor variables (dose = 0 for placebo). A 2-sided maximum likelihood ratio test was used to test the dose-response relationship ($\alpha = 0.10$). The goodness of fit for the logistic regression model was determined by the Hosmer-Lemeshow test, which showed lack of fit; therefore, the log-transformed dose was evaluated. Within both populations, biologics-naive patients and patients with an inadequate response to TNF inhibitors, the differences between each treatment group and the placebo group in ACR20, ACR50, ACR70, DAS28-CRP categorical parameters, and EULAR28 were analyzed using a 1-sided Pearson's chi-square test. Fisher's exact test was used if the chi-square assumption was violated. All other secondary continuous efficacy measures were analyzed using analysis of covariance with treatment and baseline value in the model, including the ACR core set components and CDAI (both 2-sided) and DAS28-CRP (1-sided). Analyses were performed for all time points when data were collected without any adjustments for multiplicity.

RESULTS

Patient baseline demographic and clinical characteristics and disposition. A total of 448 RA patients were randomized: 260 biologics-naive RA patients in one part of the study and 188 patients with an inadequate response to TNF inhibitors in the other. Overall, the mean age of enrolled patients was 53 years, 86% were women, and the average duration of RA was >8 years. Within each population, the baseline demographics for the dosing groups were similar (Table 1). A total of 17 (7%) of the patients in the biologics-naive population and 19 (10%) in the group with an inadequate response to TNF inhibitors discontinued before the week 12 visit. The most common reasons for early discontinuation were AEs and patient decision (Figure 1).

Efficacy. *Biologics-naive patients.* Using a logistic regression model defined a priori, a statistically significant dose-response relationship as measured by ACR20 response rates at week 12 was detected in biologics-naive

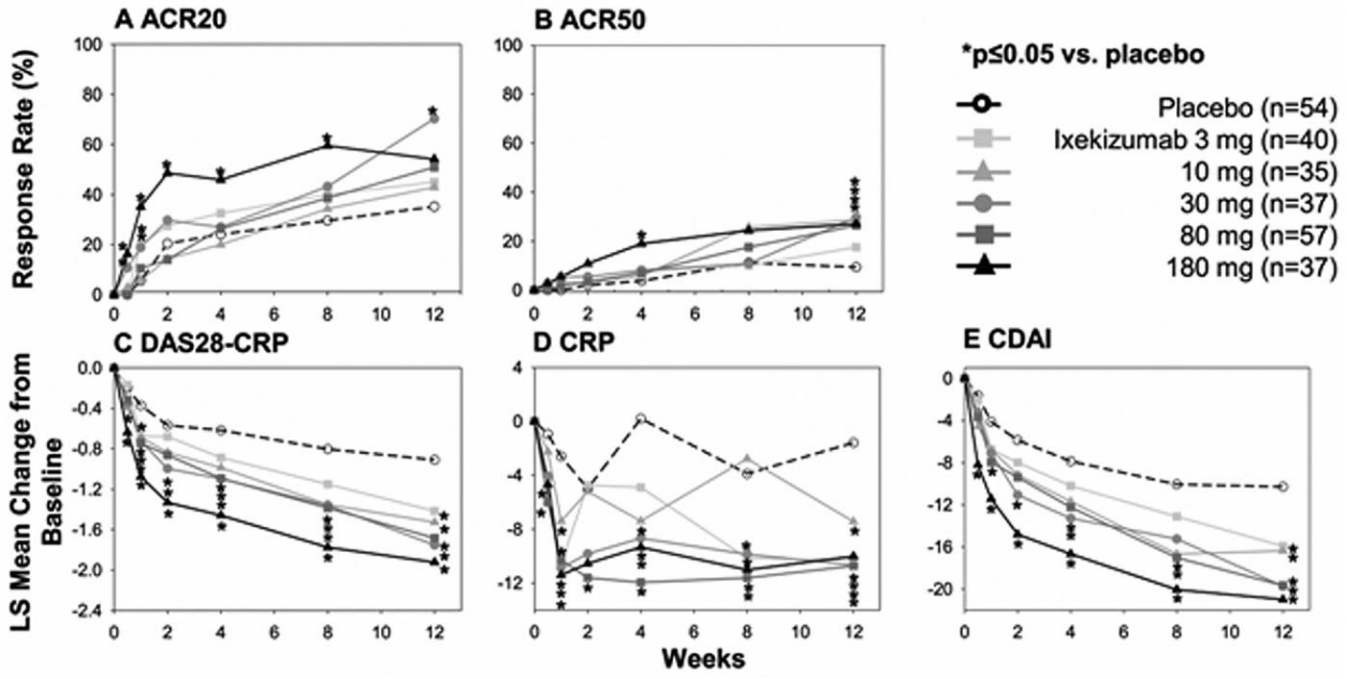

Figure 2. Outcome measures in biologics-naive patients with rheumatoid arthritis who were treated with ixekizumab. **A** and **B**, American College of Rheumatology 20% improvement criteria (ACR20) (**A**) and ACR50 (**B**). ACR20 and ACR50 response rates were analyzed using a 1-sided test and nonresponder imputation. **C–E**, Disease Activity Score in 28 joints using the C-reactive protein level (DAS28-CRP) (**C**), CRP level (**D**), and Clinical Disease Activity Index (CDAI) (**E**). CRP and CDAI were analyzed using a 2-sided test and the last observation carried forward method. Categorical responses were analyzed by Fisher's exact test, and continuous variables were analyzed by analysis of covariance with treatment and baseline in the model. Tests were not adjusted for multiple testing. LS = least squares.

patients ($P = 0.031$). Although the analysis was not powered for pairwise comparisons, an ACR20 response was observed in statistically significantly greater percentages of patients treated with ixekizumab, at multiple time points and doses, compared with placebo. A statistically significantly greater response was observed in the 30-mg group at week 12 ($P = 0.001$) (Figure 2). At week 12, the proportions of patients in whom ACR50 and ACR70 responses were achieved were statistically significantly greater in the majority of ixekizumab groups than in the placebo group (Table 2). The clinical efficacy response was characterized by a rapid onset of action, with an ACR20 response achieved in statistically significantly greater percentages of patients by day 3 in the 30-mg and 180-mg ixekizumab groups versus placebo, and by week 1 in the 3-mg, 30-mg, and 180-mg ixekizumab groups versus placebo (Figure 2). Changes in most ACR component scores were better with the 30-mg, 80-mg, and 180-mg doses of ixekizumab than with placebo at week 12 (Table 2).

A reduction in disease activity was also observed using DAS28-CRP scores, with improvements seen by day 3 with 10-mg and 180-mg ixekizumab versus placebo, and by week 1 with all ixekizumab doses versus placebo (Figure 2). These improvements persisted to the 12-week end point ($P < 0.05$ for all ixekizumab groups at all time points except for 10 mg at week 2 and for 3 mg at weeks 2, 4, and 8). Using EULAR response criteria at week 12, 73% and 76% of patients in the 80-mg and 180-mg groups, respectively, were responders versus 44% of placebo-treated patients ($P < 0.05$) (Table 2). A DAS28-CRP of ≤3.2 was achieved in a higher number of patients receiving 180 mg ixekizumab (30%) than in those receiving placebo (13%) at week 12 ($P < 0.05$) (Table 2). Decreases from baseline were also observed in mean CDAI scores in the 30-mg, 80-mg, and 180-mg ixekizumab groups at most time points, with improvements seen as early as by day 3 in the 180-mg group and by week 1 in the 80-mg and 180-mg groups (Figure 2). The mean CRP values decreased rapidly in all ixekizumab groups, with near-nadir values achieved at week 1 (Figure 2). Patient CRP values were relatively stable in the 30-mg, 80-mg, and 180-mg groups after week 1, and CRP levels in all ixekizumab groups were lower than

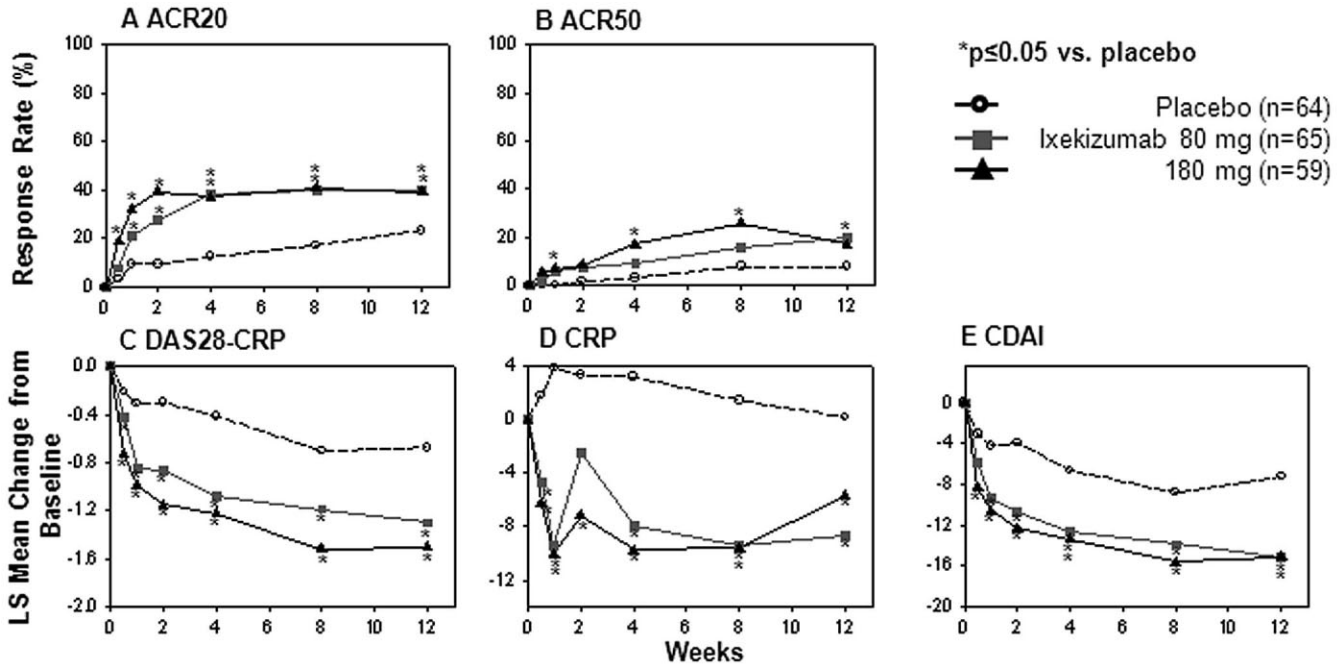

Figure 3. Outcome measures in patients with rheumatoid arthritis with an inadequate response to tumor necrosis factor inhibitors who were treated with ixekizumab. **A** and **B,** American College of Rheumatology 20% improvement criteria ACR20 (**A**) and ACR50 (**B**). ACR20 and ACR50 response rates were analyzed using a 1-sided test and nonresponder imputation. **C–E,** Disease Activity Score in 28 joints using the C-reactive protein level (DAS28-CRP) (**C**), CRP level (**D**), and Clinical Disease Activity Index (CDAI) (**E**). CRP and CDAI were analyzed using a 2-sided test and the last observation carried forward method. Categorical responses were analyzed by Fisher's exact test, and continuous variables were analyzed by analysis of covariance with treatment and baseline in the model. LS = least squares.

those in the placebo group at week 12, with no clear dose-related differences observed (Figure 2).

Patients with an inadequate response to TNF inhibitors. In RA patients with an inadequate response to TNF inhibitors, statistically significant differences in ACR20 responses were observed between each of the ixekizumab groups and the placebo group by week 1 ($P < 0.05$ for each comparison) and persisted through week 12 (Figure 3), with responses seen as early as day 3 in the 180-mg ixekizumab group ($P < 0.05$). At week 12, ACR50 responses in the ixekizumab-treated patients were numerically higher than those in the placebo group, with statistically significant differences observed in the 80-mg group for the ACR50 response (Table 2). ACR70 response rates were similar in the ixekizumab and placebo groups.

Decreases in the DAS28-CRP from baseline were observed in both ixekizumab groups by day 3 and persisted through the 12-week end point ($P < 0.05$ versus placebo, both doses at each time point) (Figure 3). At week 12, 60% and 66% of patients in the 80-mg and 180-mg groups, respectively, were EULAR responders versus 37% of placebo-treated patients ($P < 0.05$ for each comparison) (Table 2). Although both ixekizumab groups had higher percentages of patients with a DAS28-CRP of ≤3.2 and a DAS28-CRP of <2.6 versus placebo, only the 180-mg group reached statistical significance for both thresholds at week 12 (Table 2). For CDAI scores, statistically significant decreases from baseline versus placebo were observed as early as day 3 in the 180-mg group and by week 1 in the 80-mg group, and persisted through week 12 (Figure 3). The CRP values decreased in both treatment groups beginning by day 3 ($P < 0.05$ versus placebo for each comparison) and reaching near-nadir values by week 1 (Figure 3), with no clear differences observed between dose groups at week 12.

Safety. The frequency of treatment-emergent AEs was similar overall across all treatment arms in either population, although biologics-naive patients receiving higher ixekizumab doses had somewhat higher rates than those receiving placebo. The majority of treatment-emergent AEs were mild to moderate. Table 3 displays the treatment-emergent AEs that occurred in

Table 2. Efficacy end points at week 12*

	Biologics-naive RA patients						RA patients with an inadequate response to TNF inhibitors		
		Ixekizumab						Ixekizumab	
	Placebo (n = 54)	3 mg (n = 40)	10 mg (n = 35)	30 mg (n = 37)	80 mg (n = 57)	180 mg (n = 37)	Placebo (n = 64)	80 mg (n = 65)	180 mg (n = 59)
ACR20, %	35	45	43	70†	51	54	23	40†	39†
ACR50, %	9	18	29†	30†	26†	27†	8	20†	17
ACR70, %	2	5	14†	14†	7	14†	3	3	10
DAS28-CRP ≤3.2, %	13	23	29	24	18	30†	11	22	32†
DAS28-CRP <2.6, %	6	5	17	14	5	16	5	14	22†
EULAR28 response, %	44	68†	60	76†	73†	76†	37	60†	66†
Change from baseline									
No. of tender joints (28 assessed), LSM	−3.1	−6.5†	−6.1†	−7.3†	−7.5†	−8.8†	−2.9	−6.0†	−6.1†
No. of swollen joints (28 assessed), LSM	−3.1	−5.2	−6.1†	−6.6†	−6.8†	−5.9†	−1.6	−5.5†	−5.3†
Pain (100-mm VAS), LSM	−15.9	−21.2	−20.7	−28.7†	−24.4†	−24.9	−7.4	−11.2	−19.9†
Patient's global assessment (100-mm VAS), LSM	−18.4	−19.7	−19.2	−28.6†	−22.4	−28.0†	−8.6	−13.2	−21.9†
Physician's global assessment (100-mm VAS), LSM	−15.7	−22.6	−22.1	−26.7†	−24.9†	−26.5†	−9.0	−24.8†	−22.5†
HAQ DI, LSM	−0.2	−0.4	−0.4	−0.5†	−0.5†	−0.5†	−0.2	−0.2	−0.3
CRP, mg/liter, LSM	−0.9	−10.2†	−7.8†	−11.0†	−10.9†	−10.2†	1.3	−9.7†	−8.1†
DAS28-CRP, LSM	−0.8	−1.4†	−1.5†	−1.7†	−1.7†	−1.9†	−0.6	−1.3†	−1.6†
CDAI, LSM	−9.5	−15.6†	−16.5†	−19.4†	−19.2†	−20.4†	−6.4	−15.3†	−15.6†

* Nonresponder imputation was used for the American College of Rheumatology 20% improvement criteria (ACR20), ACR50, and ACR70, and the last observation carried forward method was used for other measures. The ACR component scores and Clinical Disease Activity Index (CDAI) were analyzed using 2-sided tests; the other measures shown were analyzed using 1-sided tests. Tests were not adjusted for multiple comparisons. RA = rheumatoid arthritis; TNF = tumor necrosis factor; DAS28-CRP = Disease Activity Score in 28 joints using the C-reactive protein level; EULAR28 = European League Against Rheumatism response based on the 28-joint count; LSM = least squares mean; VAS = visual analog scale; HAQ DI = Health Assessment Questionnaire disability index.
† $P \leq 0.05$ versus placebo.

>5% of ixekizumab-treated patients (all doses combined) in either population. In the biologics-naive population, the most frequently reported treatment-emergent AEs across all ixekizumab-treated patients versus placebo, respectively, were headache (4% versus 11%) and urinary tract infection (UTI) (5% versus 7%). The most frequently reported treatment-emergent AEs in the patients with an inadequate response to TNF inhibitors treated with ixekizumab versus placebo, respectively, were injection-site pain (11% versus 5%), injection-site erythema (7% versus 3%), headache (7% versus 8%), and UTI (7% versus 3%). Five patients in the biologics-naive population discontinued the study due to an AE (peripheral edema [placebo], ischemic stroke [placebo], leukopenia [3 mg], furuncle [30 mg], and serum sickness–like reaction [180 mg]). Six patients with an inadequate response to TNF inhibitors discontinued due to an AE (2 patients due to RA exacerbation [180 mg], and 1 patient each due to atrial fibrillation [80 mg], femoral neck fracture [80 mg], urticaria [80 mg], and ischemic stroke [180 mg]).

No patients in either population died during the 12-week study period. In the biologics-naive population, serious AEs (SAEs) occurred in 1 patient (2%) in the placebo group who had an ischemic stroke, and in 7 patients (3%) treated with ixekizumab as follows: aortic aneurysm (10 mg); anxiety (30 mg); chest pain and dyspnea, without evidence of myocardial injury or ischemia (80 mg); acute vestibular syndrome (80 mg); ischemic stroke (80 mg); systemic inflammatory response syndrome and hypoesthesia (80 mg); and serum sickness–like reaction (180 mg).

In the population of patients with an inadequate response to TNF inhibitors, SAEs occurred in 1 patient (2%) in the placebo group (vertebra dislocation) and in 11 patients (9%) treated with ixekizumab. In the 80-mg group, SAEs occurred in 5 patients as follows (n = 1 for each event): pneumonia; appendicitis; empyema (subcutaneous abscess that was coded as empyema) and a femoral neck fracture (experienced by the same patient at different times); atrial fibrillation; and device dislocation (hip prosthesis). In the 180-mg group, the SAEs

Table 3. Summary of adverse events and adverse events of special interest*

	Biologics-naive RA patients							RA patients with an inadequate response to TNF inhibitors			
		Ixekizumab							Ixekizumab		
	Placebo (n = 54)	3 mg (n = 40)	10 mg (n = 35)	30 mg (n = 37)	80 mg (n = 57)	180 mg (n = 37)	All doses (n = 206)	Placebo (n = 64)	80 mg (n = 65)	180 mg (n = 59)	All doses (n = 124)
SAEs†	1 (2)	0 (0)	1 (3)	1 (3)	4 (7)	1 (3)	7 (3)	1 (2)	5 (8)‡	6 (10)	11 (9)
Treatment-emergent AEs	27 (50)	20 (50)	19 (54)	22 (60)	34 (60)	21 (57)	116 (56)	40 (63)	41 (63)	38 (64)	79 (64)
Treatment-emergent AEs in ≥5% of patients (all doses)											
Injection-site pain	1 (2)	1 (3)	1 (3)	1 (3)	2 (4)	2 (5)	7 (3)	3 (5)	6 (9)	7 (12)	13 (11)
Headache	6 (11)	0 (0)	4 (11)	2 (5)	2 (4)	1 (3)	9 (4)	5 (8)	6 (9)	2 (3)	8 (7)
UTI	4 (7)	1 (3)	2 (6)	3 (8)	2 (4)	2 (5)	10 (5)	2 (3)	4 (6)	4 (7)	8 (7)
Injection-site erythema	0 (0)	2 (5)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1)	2 (3)	3 (5)	5 (9)	8 (7)
URI	0 (0)	1 (3)	0 (0)	3 (8)	2 (4)	2 (5)	8 (4)	4 (6)	3 (5)	4 (7)	7 (6)
Exacerbation of RA	1 (2)	1 (3)	2 (6)	2 (5)	2 (4)	0 (0)	7 (3)	2 (3)	3 (5)	4 (7)	7 (6)
Selected AEs of special interest and abnormal laboratory results											
Infections	10 (19)	8 (20)	7 (20)	11 (30)	15 (26)	10 (27)	51 (25)	16 (25)	20 (31)	14 (24)	34 (27)
Injection-site reaction	1 (2)	4 (10)	1 (3)	1 (3)	3 (5)	3 (8)	12 (6)	5 (8)	11 (17)	15 (25)	27 (22)
Allergic/hypersensitivity reaction§	0 (0)	1 (3)	0 (0)	3 (8)	6 (11)	2 (5)	12 (6)	2 (3)	4 (6)	2 (3)	6 (5)
Neutropenia¶ #	0 (0)	1 (3)	0 (0)	1 (3)	2 (4)	0 (0)	4 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Elevated ALT#	2 (4)	1 (3)	0 (0)	0 (0)	2 (4)	0 (0)	3 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Elevated AST#	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)

* Values are the number (%). RA = rheumatoid arthritis; TNF = tumor necrosis factor; UTI = urinary tract infection; URI = upper respiratory infection; ALT = alanine aminotransferase; AST = aspartate aminotransferase.
† See Results for most frequently reported serious adverse events (SAEs).
‡ One patient from South Asia with preexisting diabetes mellitus developed a foot abscess and then systemic inflammatory response syndrome at the end of the dosing period. Subsequent to discontinuation from dosing, this patient also had an episode each of cellulitis, sepsis, and strongyloides infection, which were successfully treated.
§ Allergic reactions were distinct from injection-site reactions and were selected reported terms consistent with hypersensitivity, with reference to the Medical Dictionary for Regulatory Activities Standard Medical Queries for anaphylactic reaction, angioedema, and severe cutaneous adverse reaction.
¶ Includes only patients with at least 1 postbaseline measurement. One patient had grade 2 neutropenia at baseline.
# Includes only patients with laboratory values that were Common Terminology Criteria for Adverse Events grade 2 or higher postbaseline.

occurred in 6 patients as follows (n = 1 for each event): anemia and Whipple's disease (both in 1 patient who had arthropathy associated with Whipple's disease and was misclassified as having RA at study entry); appendicitis; ischemic stroke; breast cancer; uterine leiomyoma; and atrial fibrillation, mitral valve incompetence, and congestive heart failure (reported as 3 events in the same patient). No mycobacterial or invasive fungal infections were observed in either population.

AEs categorized as systemic allergic/hypersensitivity events occurred in 0 patients in the placebo group and 12 ixekizumab-treated patients (6%) in the biologics-naive population, and in 2 patients (3%) in the placebo group and 6 ixekizumab-treated patients (5%) in the population with an inadequate response to TNF inhibitors. One of these events was an SAE reported as a serum sickness–like reaction experienced by a patient in the biologics-naive population (180 mg) that led to discontinuation. All other allergic reactions were mild or moderate in severity, with none leading to discontinuation.

In the biologics-naive population, injection-site reactions were observed in 1 patient (2%) in the placebo group and 12 ixekizumab-treated patients (6%). Of these reactions, most were localized pain (Table 3). In the population with an inadequate response to TNF inhibitors, injection-site reactions occurred in 5 patients (8%) in the placebo group and 27 ixekizumab-treated patients (22%). The most common reactions were localized pain and erythema.

Common Terminology Criteria for Adverse Events (CTCAE) grade 2 neutropenia (<1,500–1,000 cells/mm^3) was observed in 0 patients given placebo and 4 ixekizumab-treated patients in the biologics-naive pop-

ulation: 1 patient in the 3-mg group, 1 in the 30-mg group, and 2 in the 80-mg group (15). There were no grade 3 or 4 neutropenias observed at any dose in the biologics-naive population, and the lowest neutrophil count observed was 1,180 cells/mm^3 in a patient who received the 3-mg ixekizumab dose (baseline 2,270 cells/mm^3). No grade 2 or higher neutropenia was observed in the population with an inadequate response to TNF inhibitors. In the biologics-naive population, mean absolute neutrophil counts decreased from baseline to week 12 by 11% to 17% in the ixekizumab groups. These differences were statistically significant compared with placebo ($P < 0.05$). However, in the population with an inadequate response to TNF inhibitors, the decreases from baseline in mean absolute neutrophil counts at week 12 were 4–5% in the 2 ixekizumab groups, which were not statistically different from that seen in the placebo group (3% increase). No statistically significant changes in total lymphocyte counts were observed in either population.

Only 1 patient in the biologics-naive population (in the placebo group) showed transient CTCAE grade 3 ALT and AST elevations (>5.0–20.0 × ULN) (18). There was no concomitant elevation of serum alkaline phosphatase or serum total bilirubin levels in this patient. No grade 3 ALT or AST elevations were observed in the population with an inadequate response to TNF inhibitors.

During this 12-week study period, in the biologics-naive population, a neoplasm was reported in 1 patient receiving placebo (uterine leiomyoma) and 1 patient in the 3-mg ixekizumab group (breast cancer). In the first patient, time to onset of the neoplasm after randomization was <30 days, and in the second patient it was ~8 months following treatment initiation and 5.5 months after the last dose (3-mg group). In the population of patients with an inadequate response to TNF inhibitors, neoplasms were reported in 5 patients, including transitional cell carcinoma of the bladder (80 mg), soft tissue neoplasm (80 mg), breast cancer (180 mg), melanocytic nevus (180 mg), and uterine leiomyoma (180 mg). The patient with breast cancer in the population with an inadequate response to TNF inhibitors had a mammogram at screening revealing "asymmetrical nodular mass-like densities" considered stable when compared to earlier mammograms, and "benign calcifications" in both breasts. Time to onset of these neoplasms was <80 days in 1 patient (breast cancer), <60 days in 1 patient (bladder transitional cell carcinoma), and <30 days in 3 patients (soft tissue neoplasm, melanocytic nevus, and uterine leiomyoma).

DISCUSSION

This phase II study met its primary objective, because a statistically significant dose-response relationship (measured by ACR20 response rates at week 12), was detected in biologics-naive RA patients, using a logistic regression model defined a priori, although a linear dose-response was not visually apparent. A continuous measure of disease activity, the DAS28, was also evaluated. As shown in Figures 2 and 3, DAS28-CRP reductions were observed across most dose groups in both populations, with greater decreases in the DAS28-CRP seen with increases in dose. Since the DAS28 is a composite score that includes the CRP level (which also decreased with ixekizumab treatment in both populations), the possibility that DAS28 findings were predominantly driven by decreases in the CRP level was considered. Similar to the observed DAS28-CRP responses, results obtained using the CDAI (a simplified, continuous measure that does not include acute-phase reactants, the CRP, or the ESR) validated the efficacy of ixekizumab. For both biologics-naive patients and patients with an inadequate response to TNF inhibitors, ixekizumab reduced disease activity in a dose-dependent manner as measured by the CDAI, suggesting that CRP decreases alone did not explain the improvements in the DAS28 seen with ixekizumab treatment.

Other antibodies that target IL-17 signaling, such as secukinumab and brodalumab, have been studied as potential RA treatments. Like ixekizumab, secukinumab is an anti–IL-17A monoclonal antibody, although it utilizes an IgG1 Fc region. In a proof-of-concept trial, secukinumab treatment resulted in significant differences from placebo at week 6, which were maintained through week 16 (19). The results of a phase IIb study of secukinumab in predominantly biologics-naive RA patients have recently been published (20). In contrast to the efficacy seen in the current phase IIb study with ixekizumab in both the biologics-naive RA patients and RA patients with an inadequate response to TNF inhibitors, in a study of patients receiving secukinumab the primary end point (ACR20 response rate) was not met, although improvements were observed at the higher doses in many parameters, including the CRP (20). Brodalumab, a monoclonal antibody directed against the IL-17 receptor, showed no evidence of clinical efficacy in RA patients (21). However, unlike secukinumab and ixekizumab, brodalumab treatment had no meaningful effect on CRP levels. Although it is not known why the efficacy findings with brodalumab differ from those with the anti–IL-17A antibodies, it is possible that the broda-

lumab doses tested did not result in a complete blockade of IL-17 signaling in involved tissue in the RA patients, since there was no statistically significant effect on CRP levels.

Ixekizumab safety was studied throughout 12 weeks of treatment. The most frequently reported treatment-emergent AEs were UTI, headache, and upper respiratory tract infection in biologics-naive patients, and injection-site pain, headache, and UTI in those with an inadequate response to TNF inhibitors. No dose-related trends in the incidence rate or event severity were observed in patients with these AEs. Of the SAEs, the most notable were systemic inflammatory response syndrome and serum sickness–like reaction. Both patients recovered with appropriate medical management. The reasons underlying the observed difference in incidence of SAEs in the patients with an inadequate response to TNF inhibitors treated with ixekizumab versus those treated with placebo are unclear, although a wide variety of SAE types were reported and some appeared to be preexisting (e.g., anemia and Whipple's disease in 1 patient).

Similar to other subcutaneous biologic therapies (22–25), injection-site reactions were more frequent in patients receiving ixekizumab. None of these events was severe in intensity or associated with treatment discontinuation. Only 1 patient (in the placebo group) in the biologics-naive population showed transient CTCAE grade 3 ALT and AST elevations. No grade 3 ALT or AST elevations were observed in the population of patients with an inadequate response to TNF inhibitors. As observed with other biologics in RA (26,27), ixekizumab-treated patients in this study demonstrated decreases in neutrophil count that were not seen in the placebo group. No grade 3 or 4 neutropenia (absolute neutrophil count $<1{,}000/\mu l$) was observed in either population. Grade 2 neutropenia with ixekizumab treatment was observed in 4 patients in the biologics-naive population but was not observed in the population with an inadequate response to TNF inhibitors, with no obvious dose dependence. Notably, most patients enrolled in this study were taking concomitant MTX, which has also been associated with decreases in the neutrophil count (28). While concomitant therapies may have contributed to these findings, the role of IL-17A inhibition in the observed decreases in mean neutrophil counts in these patients is unclear, since no change in mean neutrophil counts was observed in a 12-week study of ixekizumab in psoriasis patients (29).

As detailed in the results, the 7 neoplasms reported in this study were of both benign and malignant types. Among the patients who experienced neoplasms, the latency from onset of ixekizumab exposure to diagnosis of each neoplasm was short in general, there was no clustering of neoplasms by type or by dose, and/or confounding factors were present in addition to study drug exposure. One confounding factor in the patients with an inadequate response to TNF inhibitors was previous exposure to TNF inhibitors.

As is true for many phase II studies, there were several limitations to this trial. While statistically significant treatment responses were observed for most efficacy end points at week 12, clear dose separations were not observed in ACR scores. The continuous measures, DAS28 and CDAI, showed more distinct dose separations. Additionally, a wider range of ixekizumab doses was not explored in the cohort of patients with an inadequate response to TNF inhibitors, and the study excluded patients with refractory disease that had an inadequate response to ≥ 5 conventional DMARDs. There were relatively small numbers of patients in each population in this study. The efficacy of ixekizumab in a larger population of biologics-naive RA patients and RA patients with an inadequate response to TNF inhibitors needs to be evaluated. It should be noted that tests were not adjusted for multiplicity testing. The response rates with ixekizumab, at least in the biologics-naive population, were not as high as those reported earlier with many biologics in larger studies. While many RA trials have presented data with treatment up to 24 weeks (5,6,30,31), this study was limited to a 12-week blinded treatment period. It is unclear whether longer exposure to ixekizumab would improve the degree of clinical efficacy in either population or change the safety profile. Additionally, differential responses to agents with distinct modes of action may reflect pathogenic heterogeneity in this disease.

In conclusion, in patients with RA who were either naive to biologic agents or had an inadequate response to TNF inhibitors, ixekizumab treatment resulted in a rapid and significant improvement in clinical signs and symptoms of RA during the 12-week treatment period without significant safety concerns. A statistically significant dose-response relationship as measured by ACR20 response rates at week 12 in biologics-naive RA patients was detected using a logistic regression model defined a priori, although a linear dose-response was not visually apparent. Overall, these data suggest that ixekizumab may offer an alternative mode of treatment for RA, especially among patients whose disease has failed to respond to other treatments, including anti-TNF agents. Recent reports suggest that inadequate response

to TNF inhibitors in RA patients may be associated with increased IL-17 levels (32,33). Further studies are needed to establish the long-term safety and efficacy of ixekizumab in the treatment of RA.

ACKNOWLEDGMENTS

The authors would like to thank Joseph Durrant, Laurie Hariu, and Cindi Wood (inVentiv Health Clinical, Princeton, NJ) for editorial assistance and Kelly Guerrettaz (inVentiv Health Clinical, Princeton, NJ) for assistance with manuscript preparation.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Genovese had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Genovese, Cho, Berman, Jin, Cameron, Benichou, Xie, Berclaz, Banerjee.

Acquisition of data. Genovese, Greenwald, Cho, Berman, Jin, Cameron, Berclaz.

Analysis and interpretation of data. Genovese, Greenwald, Cho, Berman, Jin, Cameron, Xie, Braun, Berclaz, Banerjee.

ROLE OF THE STUDY SPONSOR

The study was designed jointly by representatives of Eli Lilly and the investigators. Data were collected and analyzed by a contract research organization (Parexel, Inc.) with oversight by Eli Lilly. Publication of this article was not contingent upon approval by Eli Lilly.

REFERENCES

1. McInnes IB. Cytokines. In: Firestein GS, Budd RC, Harris ED Jr, McInnes IB, Ruddy S, Sergent JS, editors. Kelley's textbook of rheumatology. 9th ed. Philadelphia: Elsevier; 2009. p. 367–77.
2. Chao CC, Chen SJ, Adamopoulos IE, Davis N, Hong K, Vu A, et al. Anti-IL-17A therapy protects against bone erosion in experimental models of rheumatoid arthritis. Autoimmunity 2011; 44:243–52.
3. Lubberts E, Koenders MI, Oppers-Walgreen B, van den Bersselaar L, Coenen-de Roo CJ, Joosten LA, et al. Treatment with a neutralizing anti-murine interleukin-17 antibody after the onset of collagen-induced arthritis reduces joint inflammation, cartilage destruction, and bone erosion. Arthritis Rheum 2004;50:650–9.
4. Genovese MC, Van den Bosch F, Roberson SA, Bojin S, Biagini IM, Ryan P, et al. LY2439821, a humanized anti–interleukin-17 monoclonal antibody, in the treatment of patients with rheumatoid arthritis: a phase I randomized, double-blind, placebo-controlled, proof-of-concept study. Arthritis Rheum 2010;62:929–39.
5. Felson DT, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C, et al. American College of Rheumatology preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum 1995;38:727–35.
6. Cohen SB, Emery P, Greenwald MW, Dougados M, Furie RA, Genovese MC, et al, for the REFLEX Trial Group. Rituximab for rheumatoid arthritis refractory to anti–tumor necrosis factor therapy: results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheum 2006;54:2793–806.
7. Genovese MC, Becker JC, Schiff M, Luggen M, Sherrer Y, Kremer J, et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor α inhibition. N Engl J Med 2005;353: 1114–23.
8. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–24.
9. Hochberg MC, Chang RW, Dwosh I, Lindsey S, Pincus T, Wolfe F. The American College of Rheumatology 1991 revised criteria for the classification of global functional status in rheumatoid arthritis. Arthritis Rheum 1992;35:498–502.
10. Prevoo ML, van't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight–joint counts: development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995:38:44–8.
11. Van Gestel AM, Haagsma CJ, van Riel PL. Validation of rheumatoid arthritis criteria that include simplified joint counts. Arthritis Rheum 1998;41:1845–50.
12. Villaverde V, Balsa A, Cantalejo M, Fernandez-Prada M, Madero MR, Munoz-Fernandez S, et al. Activity indices in rheumatoid arthritis. J Rheumatol 2000;27:2576–81.
13. Lassere MN, van der Heijde D, Johnson KR, Boers M, Edmonds J. Reliability of measures of disease activity and disease damage in rheumatoid arthritis: implications for smallest detectable difference, minimal clinically important difference, and analysis of treatment effects in randomized controlled trials. J Rheumatol 2001;28:892–903.
14. Vander Cruyssen B, Van Looy S, Wyns B, Westhovens R, Durez P, Van den Bosch F, et al. DAS28 best reflects the physician's clinical judgment of response to infliximab therapy in rheumatoid arthritis patients: validation of the DAS28 score in patients under infliximab treatment. Arthritis Res Ther 2005;7:R1063–71.
15. Aletaha D, Nell VP, Stamm T, Uffmann M, Pflugbeil S, Machold K, et al. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. Arthritis Res Ther 2005;7:R796–806.
16. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum 1980;23:137–45.
17. Fries JF, Spitz PW, Young DY. The dimensions of health outcomes: the Health Assessment Questionnaire, disability and pain scales. J Rheumatol 1982;9:789–93.
18. Cancer Therapy Evaluation Program. Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0. August 9, 2006. URL: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf.
19. Hueber W, Patel DD, Dryja T, Wright AM, Koroleva I, Bruin G, et al. Effects of AIN457, a fully human antibody to interleukin-17A, on psoriasis, rheumatoid arthritis, and uveitis. Sci Transl Med 2010;2:52ra72.
20. Genovese MC, Durez P, Richards HB, Supronik J, Dokoupilova E, Mazurov V, et al. Efficacy and safety of secukinumab in patients with rheumatoid arthritis: a phase II, dose-finding, double-blind, randomised, placebo controlled study. Ann Rheum Dis 2012;72: 863–9.
21. Pavelka K, Chon Y, Newmark R, Erondu N, Lin SL. A randomized, double-blind, placebo-controlled, multiple-dose study to evaluate the safety, tolerability, and efficacy of brodalumab (AMG 827) in subjects with rheumatoid arthritis and an inadequate response to methotrexate [abstract]. Arthritis Rheum 2012;64 Suppl:S362.
22. Kay J, Matteson EL, Dasgupta B, Nash P, Durez P, Hall S, et al. Golimumab in patients with active rheumatoid arthritis despite treatment with methotrexate: a randomized, double-blind,

placebo-controlled, dose-ranging study [published erratum appears in Arthritis Rheum 2010;62:3518]. Arthritis Rheum 2008;58: 964–75.
23. Van de Putte LB, Atkins C, Malaise M, Sany J, Russell AS, van Riel PL, et al. Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. Ann Rheum Dis 2004;63:508–16.
24. Mertens M, Singh JA. Anakinra for rheumatoid arthritis: a systematic review. J Rheumatol 2009;36:1118–25.
25. Kerensky TA, Gottlieb AB, Yaniv S, Au SC. Etanercept: efficacy and safety for approved indications. Expert Opin Drug Saf 2012; 11:121–39.
26. Genovese MC, Cohen S, Moreland L, Lium D, Robbins S, Newmark R, et al, for the 20000223 Study Group. Combination therapy with etanercept and anakinra in the treatment of patients with rheumatoid arthritis who have been treated unsuccessfully with methotrexate. Arthritis Rheum 2004;50:1412–9.
27. Navarro-Millan I, Singh JA, Curtis JR. Systematic review of tocilizumab for rheumatoid arthritis: a new biologic agent targeting the interleukin-6 receptor. Clin Ther 2012;34:788–802.
28. Kinder AJ, Hassell AB, Brand J, Brownfield A, Grove M, Shadforth MF. The treatment of inflammatory arthritis with methotrexate in clinical practice: treatment duration and incidence of adverse drug reactions. Rheumatology (Oxford) 2005;44:61–6.
29. Leonardi C, Matheson R, Zachariae C, Cameron G, Li L, Edson-Heredia E, et al. Anti–interleukin-17 monoclonal antibody ixekizumab in chronic plaque psoriasis. N Engl J Med 2012;366:1190–9.
30. Genovese MC, Schiff M, Luggen M, Becker JC, Aranda R, Teng J, et al. Efficacy and safety of the selective co-stimulation modulator abatacept following 2 years of treatment in patients with rheumatoid arthritis and an inadequate response to anti-tumour necrosis factor therapy. Ann Rheum Dis 2008;67:547–54.
31. Karsdal MA, Schett G, Emery P, Harari O, Byrjalsen I, Kenwright A, et al. IL-6 receptor inhibition positively modulates bone balance in rheumatoid arthritis patients with an inadequate response to anti-tumor necrosis factor therapy: biochemical marker analysis of bone metabolism in the tocilizumab RADIATE study (NCT00106522). Semin Arthritis Rheum 2012;42:131–9.
32. Chen DY, Chen YM, Chen HH, Hsieh CW, Lin CC, Lan JL. Increasing levels of circulating Th17 cells and interleukin-17 in rheumatoid arthritis patients with an inadequate response to anti-TNF-α therapy. Arthritis Res Ther 2011;13:R126.
33. Alzabin S, Abraham SM, Taher TE, Palfreeman A, Hull D, McNamee K, et al. Incomplete response of inflammatory arthritis to TNFα blockade is associated with the Th17 pathway. Ann Rheum Dis 2012;71:1741–8.