Efficacy and Safety of Retreatment in Patients with Rheumatoid Arthritis with Previous Inadequate Response to Tumor Necrosis Factor Inhibitors: Results from the SUNRISE Trial

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ABSTRACT. ***Objective.*** To assess the efficacy and safety of 1 versus 2 courses of rituximab over 48 weeks in patients with rheumatoid arthritis (RA).

Methods. Adult patients taking methotrexate with a previous inadequate response to ≥ 1 tumor necrosis factor inhibitor received 1 course of open-label rituximab (2 × 1000 mg IV) at baseline. From Week 24, patients were randomized to receive an additional course of retreatment with rituximab or placebo. Efficacy responses at Week 48 relative to baseline were assessed.

Results. Of 559 patients who received the open-label first course of rituximab, 475 patients were randomized to a second course (rituximab retreatment: n = 318, placebo retreatment: n = 157). Relative to baseline, patients who took rituximab during retreatment had significantly improved efficacy at Week 48 compared to patients who took a placebo during retreatment [American College of Rheumatology (ACR20) criteria, 54% vs 45%, p = 0.02; change in Disease Activity Score-28 mean –1.9 vs –1.5, p = 0.006]. Differences in efficacy between groups were first observed following Weeks 28-32. Worsening of most components of the ACR core set occurred in the placebo-retreated patients with relative maintenance of these measures in rituximab-retreated patients. Randomized patients who had achieved week 24 ACR responses following the first course had greater odds of losing response if retreated with placebo (odds ratios for ACR20, ACR50, ACR70: 2.09, 2.03, and 4.09, respectively). Following retreatment, the proportion of patients experiencing any adverse events (AE), serious AE, infections, and serious infections were comparable between the rituximab and placebo retreatment groups.

Conclusion. Two courses of rituximab about 6 months apart resulted in improved and sustained efficacy at 1 year, compared with 1 course, with a similar safety profile. (First Release March 1 2010; J Rheumatol 2010;37:917–27; doi:10.3899/jrheum.090442)

Key Indexing Terms:
RITUXIMAB RHEUMATOID ARTHRITIS METHOTREXATE RETREATMENT

Rituximab, a genetically engineered monoclonal antibody targeting CD20+ B cells, has been shown to be effective in the treatment of rheumatoid arthritis (RA)[1-3]. Among biologic therapies, rituximab is unique in that improvement is long-lasting, with significant efficacy shown at 6 months following a single course of 2 infusions in randomized clinical trials. Sustained efficacy upon retreatment has been observed in open-label extension studies. Retreatment intervals in open-label extension studies have been variable, as patients were required to flare and have active disease prior to receiving retreatment. Retreatments typically occurred 30 to 40 weeks apart, depending on the trial[1-4]. This resulted in worsening disease activity on average between retreatment courses. Although efficacy is long-lasting, the majority of patients require retreatment to maintain disease control. A previous study has shown that disease flare, defined by loss of European League Against Rheumatism (EULAR) response, occurred on average at about 32 weeks[5]. Other analyses showed that the less that disease activity was allowed to worsen before retreatment with rituximab, the better the outcome after a second course[6,7].

The goal of RA treatment is remission or at least a state of low disease activity, to improve symptoms and function

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and reduce longterm disability and comorbidities. It has been shown that aggressive and "tight control" increases the likelihood of achieving these outcomes[8,9]. The goal of retreatment is thus to maintain tighter and more effective disease management and control.

To date, placebo-controlled retreatment of rituximab in a randomized, double-blind setting has not been studied. The objective of the Study for UNderstanding RItuximab Safety and Efficacy (SUNRISE) was to evaluate the efficacy and safety of 1 versus 2 courses of rituximab over 48 weeks in patients with RA who are receiving methotrexate (MTX) and who have had an inadequate response to tumor necrosis factor (TNF) inhibitors.

MATERIALS AND METHODS

Patients aged 18–80 years old with active RA for ≥ 6 months per the American College of Rheumatology (ACR) 1987 revised criteria[10] were eligible. Patients were required to have ≥ 8 swollen joints (of 66 joints assessed) and ≥ 8 tender joints (of 68 joints assessed), and either a C-reactive protein (CRP) level ≥ 0.6 mg/dl or an erythrocyte sedimentation rate (ESR) ≥ 28 mm/hour at screening. Enrolled patients were required to have a previous inadequate response to TNF inhibitors (i.e., treatment with etanercept for ≥ 3 months at doses of 25 mg twice weekly or 50 mg weekly, at least 4 infusions of ≥ 3 mg/kg infliximab, or 40 mg of adalimumab every other week for ≥ 3 months). Disease-modifying antirheumatic drug (DMARD) treatment must have been discontinued for ≥ 4 weeks prior to Day 1, and ≥ 8 weeks for the following: leflunomide (or ≥ 14 days after standard cholestyramine washout), infliximab, and adalimumab. Use of MTX for ≥ 12 weeks, at a stable dose of 10–25 mg/week for ≥ 4 weeks prior to infusion, was required. Corticosteroid use was permitted, if the dose was stable at ≤ 10 mg/day (prednisone or equivalent) for ≥ 4 weeks prior to infusion, and was continued at this dose throughout the study. Also, stable use of 1 nonsteroidal antiinflammatory drug was permitted.

Key exclusion criteria were a history of a rheumatic autoimmune disease other than RA, significant extraarticular involvement secondary to RA, ACR functional class IV disease, uncontrolled concomitant disease, and recurrent or active infection. Patients with concurrent use of any DMARD/biologic agent other than MTX were also excluded. All patients provided signed informed consent.

Study design. SUNRISE was conducted in 143 rheumatology centers in the United States. Patients were discontinued from all DMARD except MTX and continued to receive 10–25 mg/week MTX at a stable dose for the duration of the study. All patients received open-label intravenous (IV) rituximab (1000 mg given 2 weeks apart) in combination with MTX as their first course, with premedication with methylprednisolone 100 mg IV before each infusion.

From Week 24, patients who had a Disease Activity Score (DAS) in 28 joints based on ESR ≥ 2.6, i.e., who had not achieved DAS remission, were randomized double-blind at a ratio of 2:1 to receive either infusions of rituximab or placebo while continuing MTX. In addition to the described criteria, exclusion criteria for randomization/retreatment included active infection and uncontrolled concomitant illness. For patients who did not initially meet retreatment criteria at Week 24, randomization could occur through Week 40.

Clinical endpoints. The primary endpoint was ACR20 at Week 48 relative to baseline in the rituximab retreatment group versus the placebo retreatment group[11]. Key secondary efficacy endpoints included the ACR50 and ACR70 scores, ACRn[12], the change from baseline to Week 48 using DAS28-ESR, and the proportion of patients with EULAR responses. In addition, assessments were done of changes in components of the ACR core set [swollen joint count (SJC), tender joint count (TJC), physician's global assessment of disease activity, patient's global assessment of disease activity, patient's assessment of pain, patient's assessment of physical function, the Health Assessment Questionnaire Disability Index (HAQ-DI), CRP level, and ESR][10,11,13].

Subset analyses were performed to evaluate ACR responses at Week 48 by patients' Week 24 responses to the first course. The mean change in DAS28 at Week 48 between Week 24 EULAR responders and EULAR nonresponders was assessed.

Safety. Adverse events (AE) were collected according to system organ class and graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (Version 3.0). Serious AE (SAE) were defined as events that were fatal, immediately life-threatening, required inpatient hospitalization or prolongation of an existing hospitalization, medically significant, or required intervention to prevent one of the above outcomes. Safety summaries were produced by retreatment group up to Week 48. Safety analyses were based on patients who received any amount of study drug. Patients were analyzed according to the actual treatment received. Verbatim descriptions of treatment-emergent AE were mapped to *Medical Dictionary for Drug Regulatory Affairs* thesaurus terms. Infusion reactions were defined as any AE reported during or within 24 hours of an infusion. Laboratory assessments included routine laboratory tests and specific tests for human antichimeric antibodies (HACA).

Statistical analysis. The intent-to-treat (ITT) population included all patients who were randomized into the double-blind, placebo-controlled, retreatment segment and received any amount of retreatment with rituximab. The difference in ACR20 response rates between the placebo retreatment group and the rituximab retreatment group was tested using the Cochran–Mantel–Haenszel test statistic, stratified according to baseline rheumatoid factor (RF) status and ≥ 20% improvement in both SJC and TJC at Week 24 from baseline (Day 1).

The secondary endpoints of the ACR50 and ACR70 responses were analyzed using the same statistical methodology as described for the ACR20 response. All statistical tests were 2-sided and were performed at the $\alpha = 0.05$ level of significance. Descriptive summaries included the mean, standard deviation (SD), median, and range for continuous variables, and counts and percentages for categorical variables.

Results were summarized descriptively by treatment group and proportions calculated with p values and corresponding adjusted 95% CI of the difference between response rates. An analysis of covariance (ANCOVA) model was used; explanatory terms in the model were retreatment group, baseline Das28-ESR score, baseline RF status, and ≥ 20% improvement in both SJC and TJC at Week 24 from baseline.

Sample size determination. It was determined that 375 patients should be randomized 2:1 for 80% power to detect a 16% difference in ACR20 response rates from baseline to Week 48 between the rituximab retreatment group and the placebo group using Fisher's exact test. Assuming a dropout rate of up to 25% during the open-label treatment segment, and 10% achieving DAS remission at Week 24, it was determined that about 555 patients should be enrolled in the trial. Assumptions were based on preliminary data from the DANCER Extension trial[3,4]. This was an active comparator study (1 vs 2 rituximab courses), and was not powered to show differences in secondary efficacy endpoints.

RESULTS

Baseline patient and disease characteristics. Of 559 patients who were enrolled and received open-label rituximab (Figure 1A), 475 patients were randomized double-blind to receive retreatment with either placebo or rituximab. The ITT primary analysis population consisted of all randomized patients (n = 475). In the ITT population, patients in both the placebo and rituximab retreatment groups were well balanced with respect to baseline demographic and disease characteristics at the time of open-label

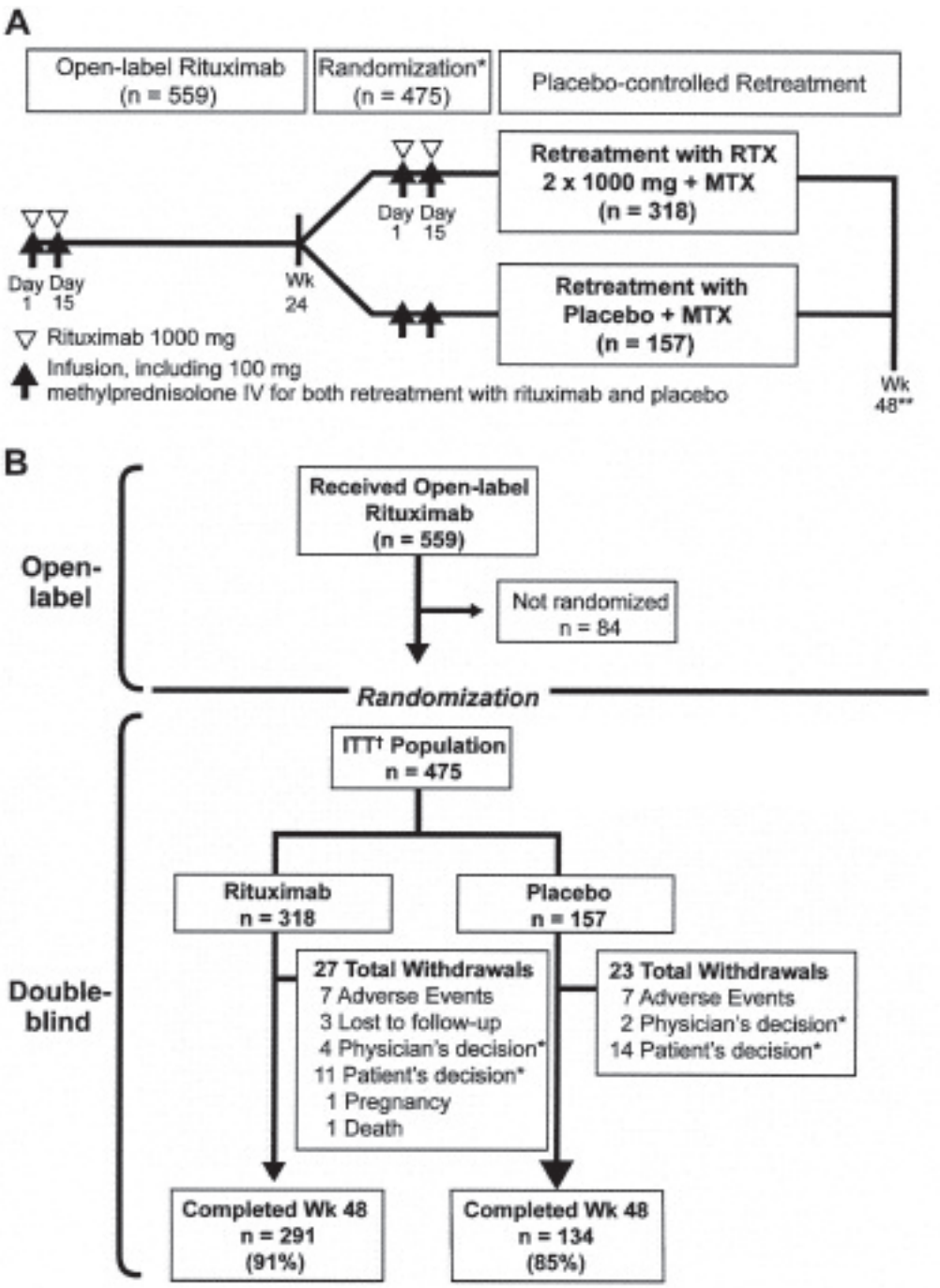

Figure 1. A. Study design. *Randomization/retreatment from Week 24 for patients with DAS ≥ 2.6. **Primary endpoint: ACR20 from baseline at Week 48. B. Baseline patient and disease disposition. *Physician/patient decisions were for reasons other than adverse events. †90% (n = 426) retreated between Weeks 24 and 28. RTX: rituximab; MTX: methotrexate; DAS: Disease Activity Score; ACR: American College of Rheumatology; ITT: intent-to-treat.

receipt of rituximab (Table 1). The average age of patients was 54 years in both groups. The majority were white (80%), and more than 79% were women. More than 75% of patients were RF-positive. The mean MTX dose was about 16 mg/week at baseline in both groups. The duration of RA ranged between 11 and 12 years. For patients receiving concomitant steroids (about 50% and 52% in the placebo and rituximab retreatment groups, respectively), the baseline prednisone dose was 7.4 mg/day in the placebo retreatment group and 7.1 mg/day in the rituximab retreatment group. The proportion of Week 24 ACR20/50/70 responders was slightly higher in the placebo retreatment group compared with the rituximab retreatment group (ACR20: 48% vs 45%; ACR50: 27% vs 21%; ACR70: 11% vs 8%).

Table 1. Baseline demographic and disease characteristics, prior to open-label rituximab.

Characteristics	Placebo Retreatment, n = 157	Rituximab Retreatment, n = 318
Mean age (SD), yrs	54 (11)	54 (11)
Range	28–80	25–80
Female, n (%)	124 (79)	257 (81)
Race, n (%)		
White	126 (80)	248 (78)
Black	12 (8)	26 (8)
Hispanic	15 (10)	30 (9)
Other	4 (2)	9 (3)
Disease characteristics		
Rheumatoid factor-positive, n (%)[a]	118 (75)	244 (77)
Anti-CCP-positive, n (%)[b]	119 (78)	223 (74)
Mean (IU/ml) for RF-positive patients	523	628
Mean (SD) RA duration, yrs	11 (8.5)	12 (9.2)
Mean (SD) tender joint count (68–joint count)	33 (18.0)	32 (15.6)
Mean (SD) swollen joint count (66–joint count)	22 (13.2)	22 (11.5)
Mean (SD) DAS28	6.7 (1.0)	6.7 (1.0)*
Mean (SD) C-reactive protein, mg/dl	2.2 (3.0)	1.9 (2.4)
Mean erythrocyte sedimentation rate (SD), mm/h	44.6 (26.30)	42.4 (26.10)**
Mean (SD) HAQ-DI	1.5 (0.6)	1.5 (0.6)**
Mean (SD) MTX dose, mg/week	16.4 (4.6)	16.4 (4.6)
Mean (SD) prednisone dose, mg/day	7.4 (2.62)	7.1 (3.00)
Number (%) patients on steroids	79 (50.3)	164 (51.6)
Prior use of TNF inhibitor(s), n (%)		
1 previous TNF inhibitor	84 (53)	181 (57)
2 previous TNF inhibitors	55 (35)	101 (32)
3 previous TNF inhibitors	18 (12)	35 (11)
Mean no. of previous DMARD (%) (excluding MTX, including TNF inhibitors)	4.1 (1.9)	4.1 (2.0)

Anti-CCP: anti-cyclic citrullinated peptide; DAS28-ESR: Disease Activity Score 28 and erythrocyte sedimentation rate; DMARD: disease-modifying antirheumatic drug; MTX: methotrexate. [a] Rheumatoid factor positivity is defined as ≥ 15 IU/ml. [b] Anti-CCP positivity is defined as ≥ 20 units. * Five patients were not measured. ** Three patients were not measured.

Disposition. Treatment disposition for patients who completed 48 weeks (at least 24 weeks open-label, followed by double-blind period) is shown in Figure 1B. A total of 91% and 85% of patients retreated with rituximab or placebo, respectively, completed 48 weeks. Approximately 90% (n = 426) of randomized/retreated patients were randomized between Weeks 24 to 28. Thus, retreatment occurred at about 6 months in 90% of the ITT population (Figure 1B).

A higher proportion of withdrawals were seen in the retreatment with placebo group compared with the retreatment with rituximab group. Seven patients in each retreatment group discontinued because of AE. Other reasons for withdrawal are shown in Figure 1B. Of the patients who received only a single course of open-label rituximab, 7 patients remained in the treatment period through Week 48.

ACR and EULAR responses. The proportion of ACR20 responders at Week 48 was significantly higher for patients retreated with rituximab than for patients retreated with placebo (54% vs 45%, respectively; p = 0.0195; Figure 2A). A sensitivity analysis showed that efficacy in the subset of patients retreated between Weeks 24 and 28 (n = 426) was consistent with the primary analysis (p = 0.0265), indicating that the small proportion of patients who were retreated at later points did not affect the results. ACRn scores were significantly different between treatment groups (adjusted mean 16.1 vs 2.6; p = 0.0046). Mean changes in DAS28 (adjusted mean –1.9 vs –1.5; p = 0.0058) were also significantly different between the rituximab and placebo retreatment groups (Figure 2C). For the ITT population, there were no significant differences in ACR50, ACR70, or EULAR responses (Figures 2A and 2B) between the rituximab and placebo retreatment groups.

Randomized patients who achieved clinical responses to the first rituximab course were more likely to achieve response with retreatment. Patients who achieved ACR responses at Week 24 had 2- to 4-fold increased odds of losing response if not retreated with rituximab [odds ratio (OR) for losing response were 2.09, 2.03, and 4.09 for ACR 20/50/70, respectively; Figures 3 and 4]. In those patients retreated with placebo, loss of response was evident by

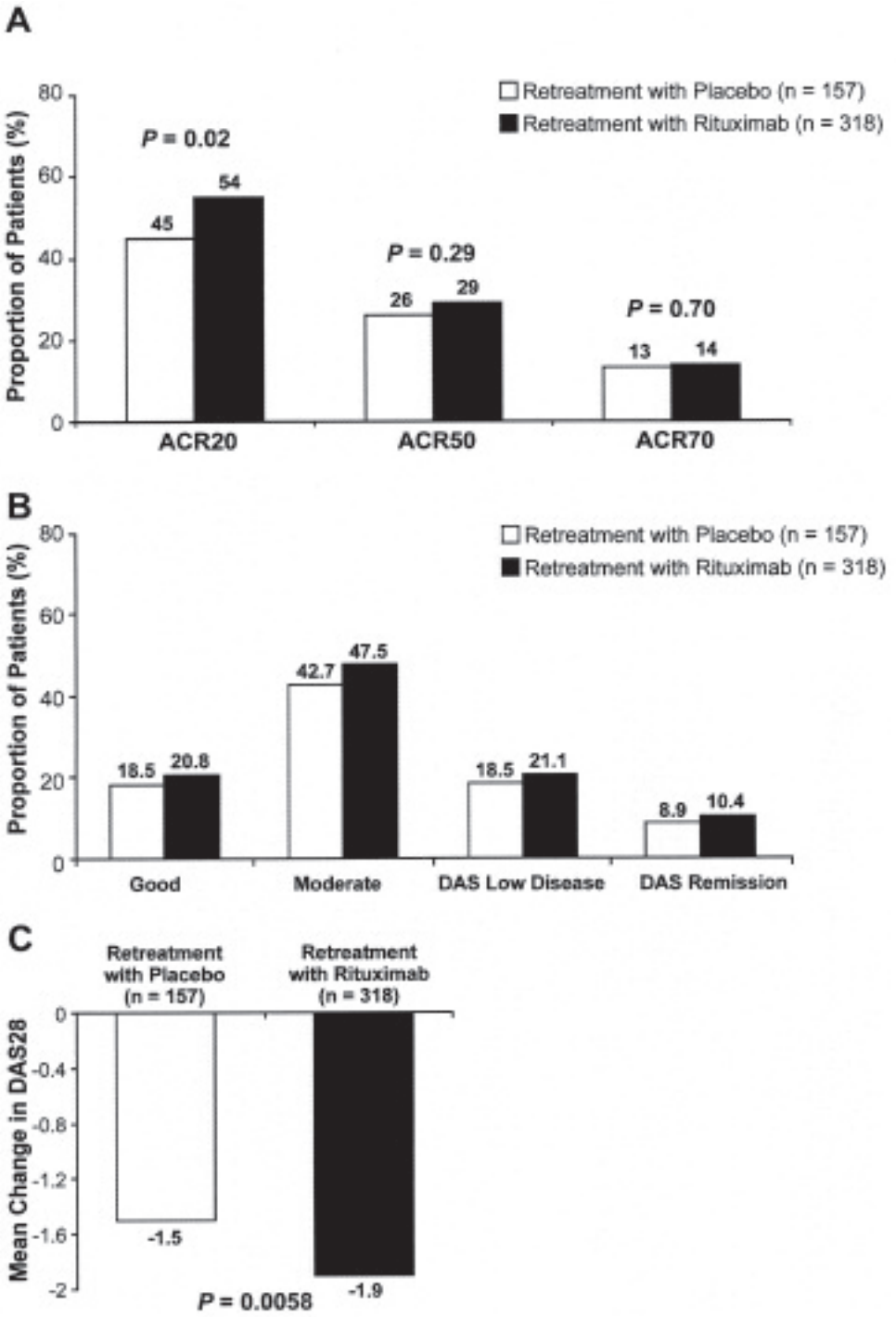

Figure 2. A. Week 48 ACR 20/50/70 responses. B. EULAR scores (left) and DAS results (right). C. Mean change in DAS28 scores.

Week 32 (Figure 4). Similarly, patients who achieved EULAR responses to the first course at Week 24 showed greater improvements in DAS28 when retreated with rituximab compared to placebo. Patients who did not achieve responses to the first course were no more likely to achieve response to a second course than to placebo. Patients who were RF-positive at baseline had a trend toward improved retreatment effect at Week 48 compared with RF-negative patients (ACR20 RF-positive: rituximab retreatment, 57%, placebo retreatment, 43%; vs ACR20 RF-negative: rituximab retreatment, 43%, placebo retreatment, 49%).

Changes in ACR core set. Mean changes from baseline in components of the ACR core criteria set at Week 48 are presented in Figure 5A. Worsening of most components of the

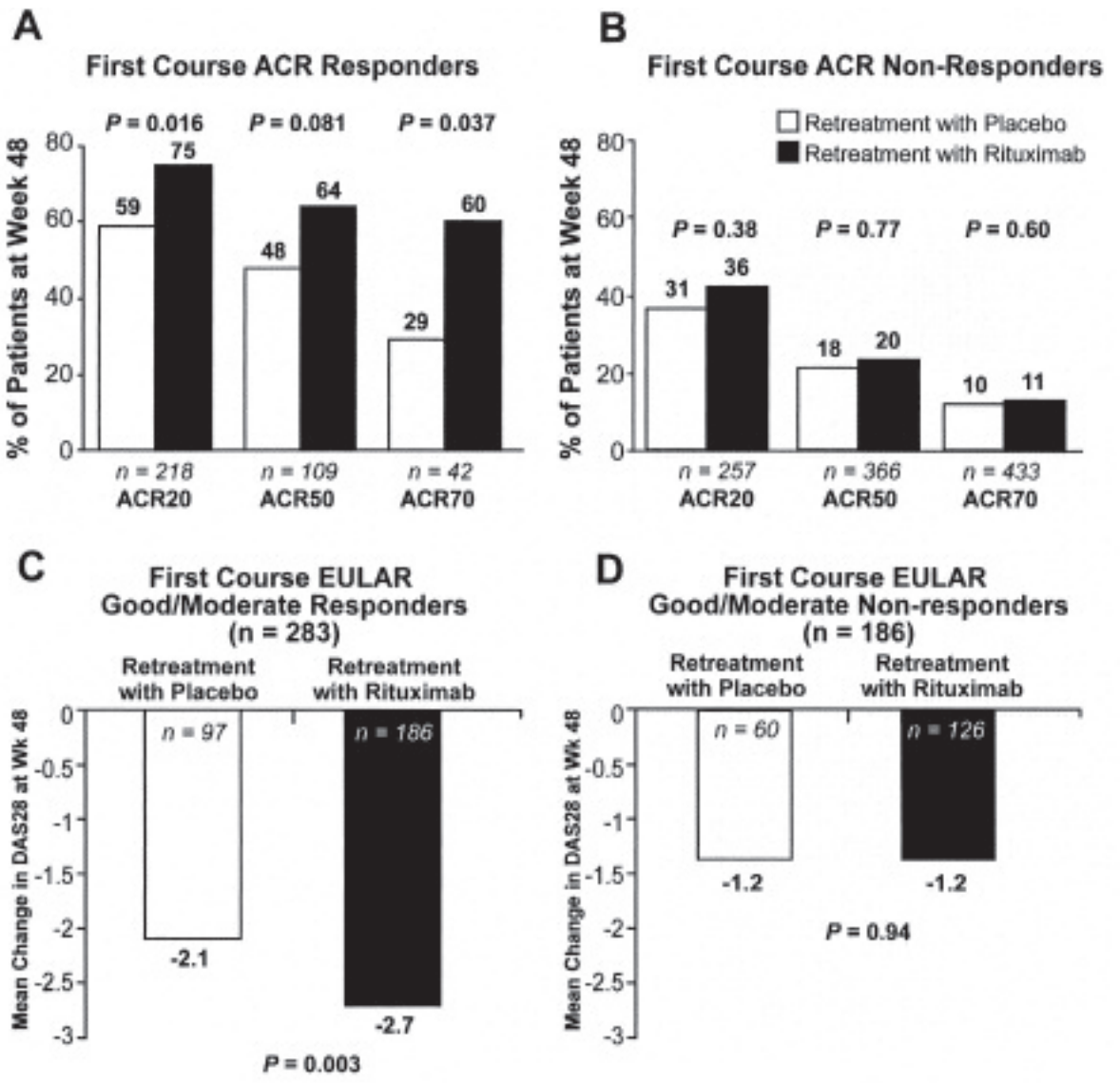

Figure 3. Week 48 results. A. ACR20/50/70 responders. B. ACR nonresponders. C. EULAR responders. D. EULAR nonresponders. DAS: Disease Activity Score.

ACR core set was observed in the placebo retreatment group after Weeks 28 to 32, and this was in contrast to maintenance of improvement of these measures in the rituximab retreatment group (Figure 5B). Increases in these measures were seen in the placebo retreatment group, compared with the rituximab retreatment group: SJC, TJC, patient's assessment of pain, patient's global assessment of disease activity, physician's global assessment, ESR, and CRP. There were no differences in HAQ-DI scores over time between the placebo retreatment and rituximab retreatment groups.

Pharmacodynamics and immunogenicity. Peripheral CD19+ B cells depleted to a median of 0 following the open-label course of rituximab in all patients and continued to be undetectable in the rituximab retreatment group. In the placebo retreatment group, peripheral CD19+ B cell repletion began following the Week 24 visit, when median levels began to increase (Figure 6).

Median RF levels decreased in both retreatment groups, but decreases were greater in the rituximab retreatment group (placebo retreatment, median change –21.1%; rituximab retreatment, median change –53.3%). There were no appreciable changes over time in levels of anti-citrullinated peptide antibodies.

Immunoglobulin (Ig) levels between placebo retreatment and rituximab retreatment groups were evaluated. There were no notable differences in the proportion of patients with IgG or IgA below the lower limit of normal (LLN) from prerandomization to Week 48 in either group. The proportion of patients with IgM below the LLN increased in both groups, but more so in the rituximab retreatment group (Table 2).

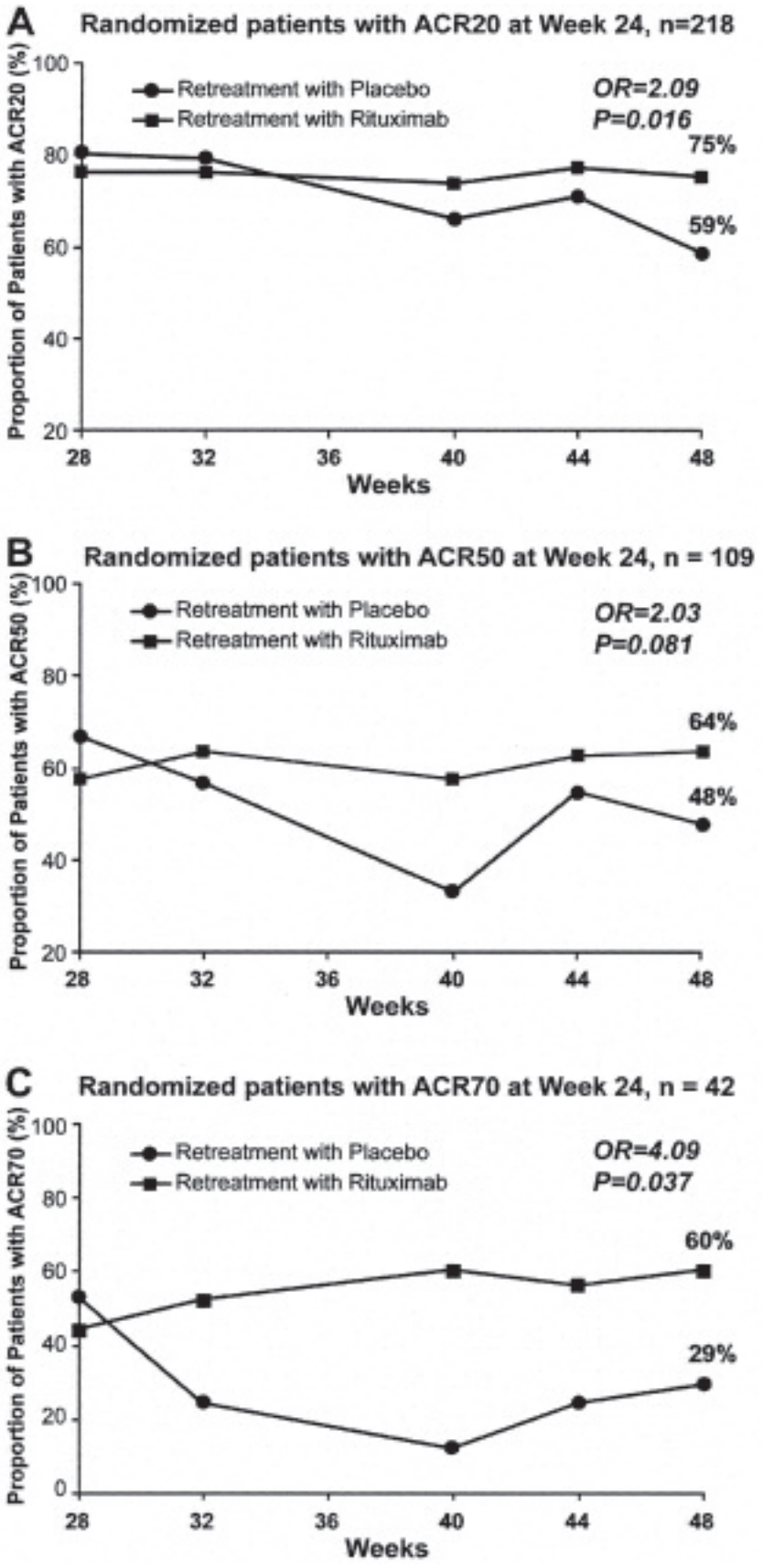

Figure 4. Maintenance of ACR20 (A), ACR50 (B), and ACR70 (C) responses over time. Odds ratios represent odds of losing response if not retreated with active rituximab.

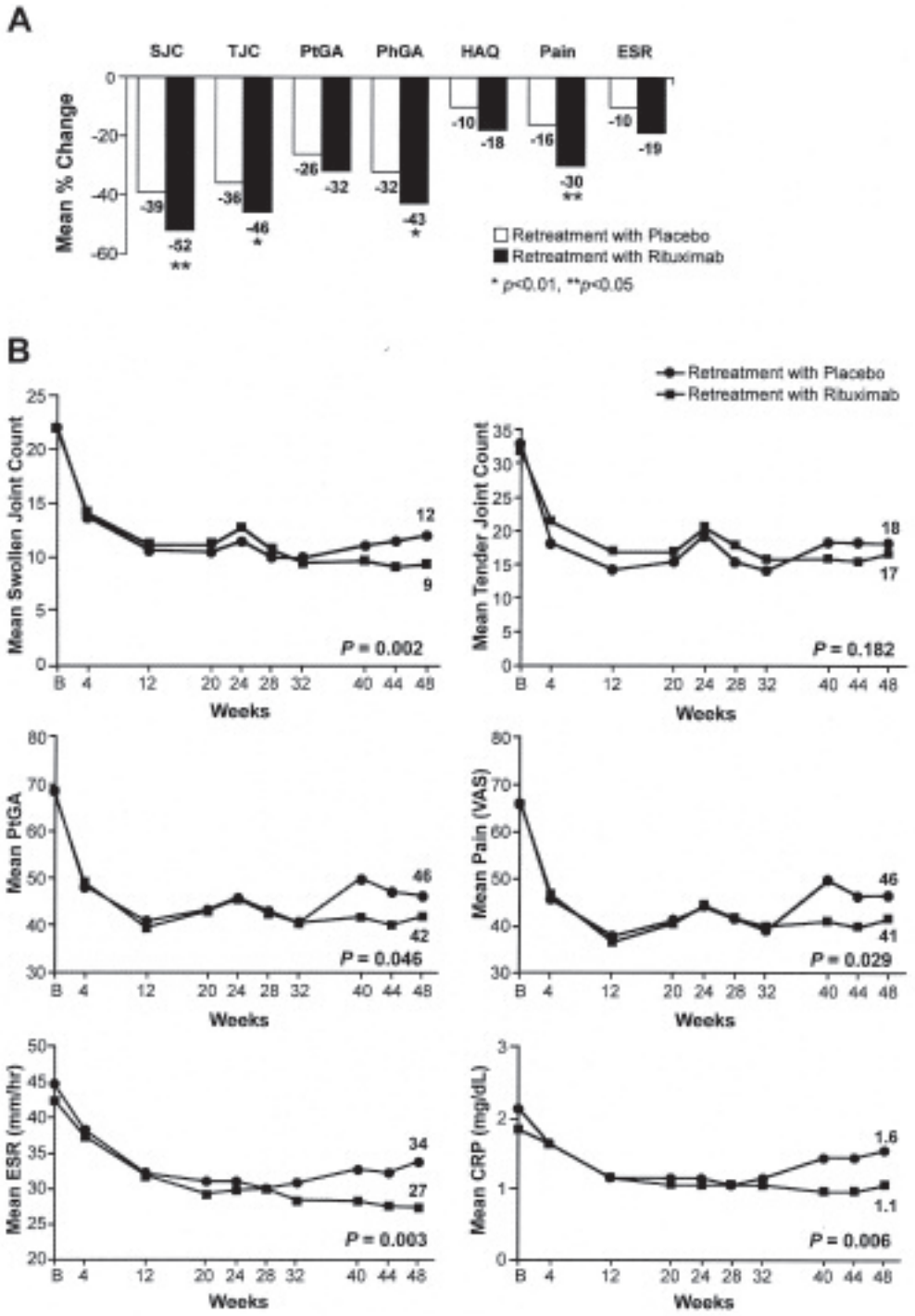

Figure 5. A. Mean changes in ACR core criteria in the ITT population from baseline to Week 48. Negative change indicates improvement. Last observation was carried forward to impute missing components. B. Changes over time in ACR core criteria. Pain is measured by visual analog scale. SJC: swollen joint count; TJC: tender joint count; PtGA/PhGA: patient/physician global assessment of disease activity; HAQ: Health Assessment Questionnaire; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; VAS: visual analog scale.

By Week 24, 7% of patients had tested HACA-positive. By Week 48, patients who received rituximab retreatment had a lower rate of positive HACA results than those who received placebo retreatment (placebo retreatment, 12%; rituximab retreatment, 1%). An association between HACA positivity prior to retreatment and retreatment infusion reac-

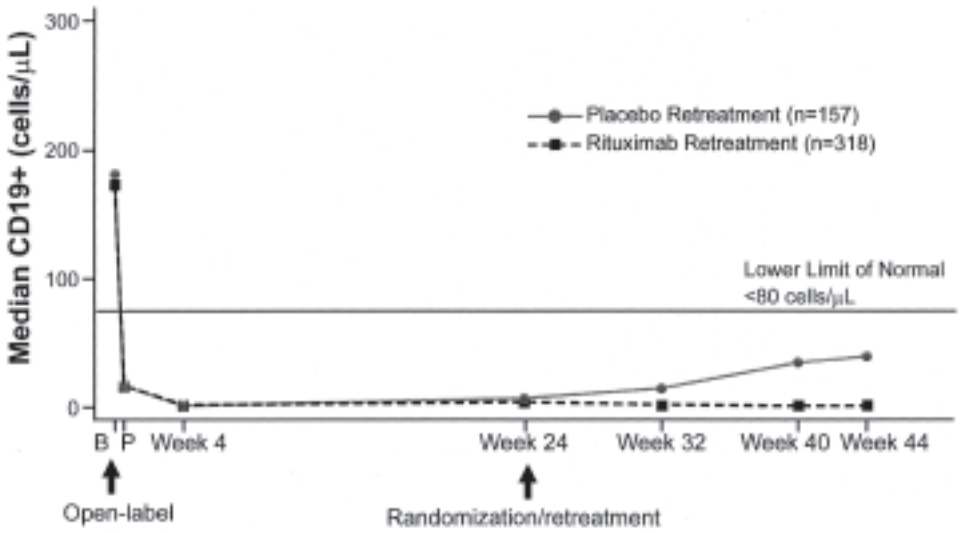

Figure 6. Median CD19+ absolute counts (cells/μl) at baseline and through Week 44 by retreatment group. Peripheral CD19 counts were not measured at Week 48. B*: baseline; P*: post-baseline; MTX: methotrexate.

Table 2. Proportion of patients (%) with immunoglobulin (Ig) levels below laboratory lower limit of normal (LLN) by retreatment group. Normal ranges for IgG, IgM, and IgA are 6.72–14.4, 0.57–2.85, and 0.59–3.96 mg/ml, respectively.

	Percentage of Patients with Immunoglobulin < LLN	
	Week 24 (prerandomization)	Week 48 (primary endpoint)
IgG		
Placebo retreatment	5	4
Rituximab retreatment	7	7
IgM		
Placebo retreatment	9	14
Rituximab retreatment	14	26
IgA		
Placebo retreatment	0	0
Rituximab retreatment	0.3	0.4

tions was not observed, and there was no association between HACA positivity and retreatment efficacy, as measured by ACR scores. However, the sample size of HACA-positive patients was small, with 14 and 21 patients in the placebo and rituximab retreatment groups, respectively, being HACA-positive by Week 24. Of these, 2 and 5 patients experienced infusion reactions and none were SAE.

AE and SAE. During the retreatment period, the proportion of patients experiencing any AE (77% vs 71%) and serious AE (7% in both groups) was comparable between the placebo retreatment group and the rituximab retreatment group, respectively (Table 3). The most common SAE was pneumonia, which was observed in 1 placebo-retreated patient (0.6%) and 2 rituximab-retreated patients (0.6%). AE and SAE were characteristic for those typically observed in patients with RA. There was 1 pregnancy, which ended in elective abortion. A total of 7 patients in each retreatment group withdrew because of AE (4% in the placebo-retreated group and 2% in the rituximab-retreated group).

Infusion reactions were reported less frequently during retreatment infusions than during the first-course infusions (first course, first infusion: 26%; first course, second infusion: 11%; Figure 7). During retreatment, infusion reactions were reported more frequently in the rituximab retreatment group than in the placebo retreatment group during the first retreatment infusion (second course, first infusion: 10% of patients in the placebo retreatment group and 16% in the rituximab retreatment group). During the second retreatment infusion (second course, second infusion), infusion reaction rates were similar between the 2 retreatment groups (placebo retreatment: 10%, rituximab retreatment: 8%). Infusion reactions were typically mild to moderate, with 1 patient experiencing a serious infusion reaction (SAE of transient hypotension during the first course, first infusion). The most

Table 3. Summary of safety events during randomized retreatment period. Data are number of patients (%).

Safety Events	Retreatment with Placebo (n = 155)	Retreatment with Rituximab (n = 320)
Adverse events	119 (77)	226 (71)
Serious adverse events	11 (7)	22 (7)
Infections	59 (38)	120 (38)
Serious infections	3 (2)	7 (2)
Adverse events leading to withdrawal	7 (4)	7 (2)
Deaths*	1 (0.6)	1 (0.3)

* One additional death in rituximab retreatment group after the Week 48 cutoff date.

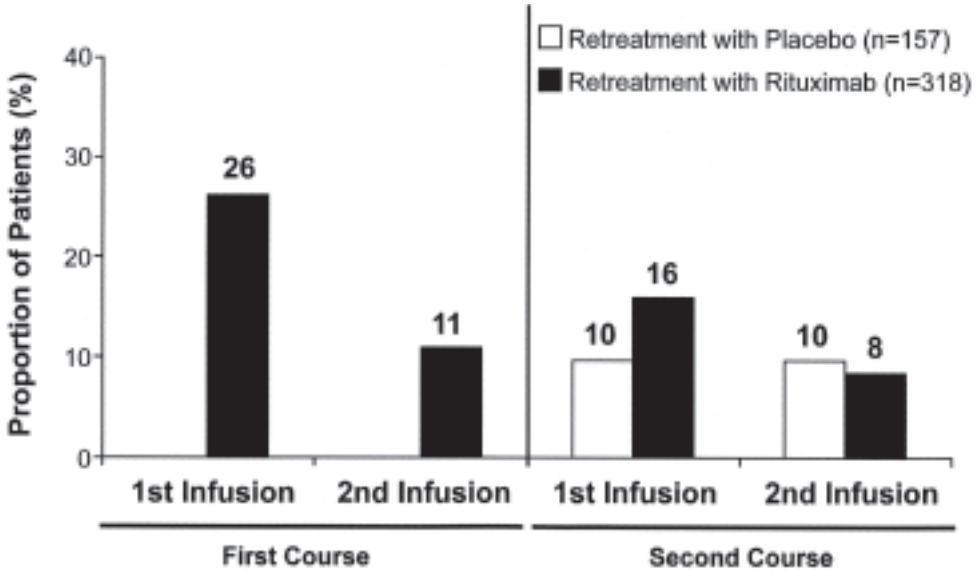

Figure 7. Proportions of patients with infusion reactions during open-label and double-blind phases. One serious adverse event (hypotension) occurred during the first infusion of the first course and no serious adverse events in subsequent 3 infusions. Patients received preinfusion methylprednisolone 100 mg IV.

common infusion AE were pruritus, headache, nausea, pyrexia, and throat irritation.

There were no differences in the proportion of patients with overall infections (38%) or serious infections (2%) between rituximab retreatment and placebo retreatment groups during the placebo-controlled period. Serious infections by treatment group are shown in Table 4. Of the randomized patients with an IgG level < LLN, there were no serious infections. There were no cases of tuberculosis, disseminated fungal infections, or atypical, opportunistic infections.

Deaths. Two deaths occurred during the 48-week trial period (acute respiratory distress syndrome in a 58-year-old woman in the rituximab retreatment group and sudden death of unknown etiology in a 76-year-old man in the placebo retreatment group). A third death occurred shortly after the 48-week trial period in a 60-year-old diabetic man in the rituximab retreatment group, attributed to cardiorespiratory arrest following *C. difficile* colitis infection.

Table 4. Serious infections† during randomized retreatment period. Data are number of patients (%).

Serious Infections	Retreatment with Placebo (n = 155)	Retreatment with Rituximab (n = 320)
Total serious infections	3 (2)	7 (2)
Pneumonia*	1	2
Abdominal wall abscess	1	0
Gastroenteritis	0	1
Perirectal abscess	0	1
Urosepsis	0	1
Pyelonephritis	1	0
Bursitis	0	1
Acute respiratory distress syndrome*	1	1

† Infectious serious adverse events or non-SAE infections treated with intravenous antibiotics. * Same patient, led to death.

DISCUSSION

Our study evaluated 1 versus 2 courses of rituximab over 48 weeks in patients with RA with a previous inadequate response to ≥ 1 TNF inhibitor. Patients had severe disease activity at baseline, and had previously failed multiple therapies. Our study provides data on the efficacy and safety of rituximab retreatment and provides guidance on retreatment interval. Patients who received rituximab retreatment had improved efficacy at Week 48 compared with placebo-retreated patients, as measured by ACR20 response and change in DAS28. In addition, rituximab-retreated patients demonstrated significantly greater mean changes in most of the components of the ACR response criteria than did the placebo-retreated patients.

In the sample size tested, differences in the proportions of patients with ACR50, ACR70, and EULAR responses at Week 48 were not statistically significant between groups. This may be due to the relative durability of a single course of therapy. Patients most likely to benefit from retreatment with rituximab were those who showed benefit from initial rituximab treatment. Among patients who achieved an ACR20, ACR50, and ACR70 response at Week 24, those retreated with rituximab were more likely to maintain or improve upon that level of response at Week 48 than patients retreated with placebo. Therefore, there is no clear indication to retreat patients who did not have clinical benefit from the first course of rituximab.

The majority of patients were retreated at Week 24. Patients who were retreated with placebo showed worsening of disease activity compared with those retreated with ritux-

imab by most measures of the ACR core set (TJC, SJC, ESR, CRP, patient's and physician's global assessment of disease, and patient's assessment of pain) following Week 28. In addition, Week 24 ACR responders retreated with placebo typically lost response by Week 32. Because the goals of retreatment include maintenance of efficacy and prevention of flare, retreatment should occur prior to worsening, and therefore Week 24 appeared to be an appropriate time to retreat in most patients. Consistent with our findings, Thurlings, *et al* have recently reported that disease activity–guided retreatment with rituximab according to the international consensus statement, at intervals of at least 6 months, was able to maintain the clinical response and prevent major disease relapses in a small cohort (n = 30)[14]. At the time that this trial was initiated, there were limited data on retreatment with additional courses of rituximab and it was not certain whether 2 courses about 6 months apart resulted in improved efficacy over a single course at 1 year. Subsequently, data have emerged showing tighter disease control with retreatment about every 6 months in patients who have not achieved DAS remission, as shown in our study, as well as other analyses from other clinical trials[15].

Retreatment with rituximab was well tolerated. SAE and serious infection rates were similar between patients who received rituximab and those who received placebo, and similar to those reported in previous clinical trials with rituximab[2,3].

Patients with RA who received 2 courses of rituximab have improved clinical efficacy at 48 weeks, compared with patients who received 1 course, with a comparable safety profile. First-course responders not retreated with rituximab were more likely to lose response, and should be retreated prior to disease worsening to maintain tight disease control.

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