Efficacy and Safety of Belimumab in Patients with Rheumatoid Arthritis: A Phase II, Randomized, Double-blind, Placebo-controlled, Dose-ranging Study

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ABSTRACT. ***Objective.*** To evaluate the efficacy/safety of belimumab in patients with rheumatoid arthritis (RA).

Methods. Patients fulfilling American College of Rheumatology (ACR) criteria for RA for ≥ 1 year who had at least moderate disease activity while receiving stable disease-modifying antirheumatic drug (DMARD) therapy and failed ≥ 1 DMARD were randomly assigned to placebo or belimumab 1, 4, or 10 mg/kg, administered intravenously on Days 1, 14, and 28, and then every 4 weeks for 24 weeks (n = 283). This was followed by an optional 24-week extension (n = 237) in which all patients received belimumab. Primary efficacy endpoint was the Week 24 ACR20 response.

Results. Week 24 ACR20 responses with placebo and belimumab 1, 4, and 10 mg/kg were 15.9%, 34.7% (p = 0.010), 25.4% (p = 0.168), and 28.2% (p = 0.080), respectively. Patients taking any belimumab dose who continued with belimumab in the open-label extension had an ACR20 response of 41% at 48 weeks. A similar ACR20 response (42%) at 48 weeks was seen in patients taking placebo who switched in the extension to belimumab 10 mg/kg. Greater response rates were observed in patients who at baseline were rheumatoid factor-positive, anticitrullinated protein antibody-positive, or tumor necrosis factor inhibitor-naive, or had elevated C-reactive protein levels, Disease Activity Score 28 > 5.1, or low B lymphocyte stimulator levels (< 0.858 ng/ml). Adverse event rates were similar across treatment groups.

Conclusion. In this phase II trial, belimumab demonstrated efficacy and was generally well tolerated in patients with RA who had failed previous therapies. [ClinicalTrials.gov identifier NCT00071812] (J Rheumatol First Release April 1 2013; doi:10.3899/jrheum.120886)

Key Indexing Terms:
BELIMUMAB
AUTOIMMUNE DISEASES
RHEUMATOID ARTHRITIS
B LYMPHOCYTE STIMULATOR

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Supported by Human Genome Sciences (HGS), Rockville, Maryland, USA, and in part by US National Institutes of Health grant M01 RR-00043 to the General Clinical Research Center at the University of Southern California Keck School of Medicine. Dr. Merrill has received consultancy fees, speaking fees, and/or honoraria from HGS. Dr. McKay owns stock in HGS. Drs. Zhong and Freimuth are employed by and own stock in HGS.

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Accepted for publication January 30, 2013.

Rheumatoid arthritis (RA) is a systemic autoimmune disorder characterized by persistent joint inflammation, progressive joint damage, and functional decline. Numerous therapeutic agents, alone and in combination, are routinely used in the treatment of RA, including disease-modifying antirheumatic drugs (DMARD) such as methotrexate, other DMARD (e.g., gold, sulfasalazine, leflunomide), glucocorticoids, and biologics (infliximab, etanercept, adalimumab, anakinra, abatacept, golimumab, certolizumab, and tocilizumab)[1,2,3]. A substantial percentage of patients, however, remain unresponsive to individual therapies[4].

The role for B cells in the pathogenesis of RA, and as a corollary, the rationale for B cell modulation in RA, are well established[5]. B cells can initiate and promote joint inflammation by serving as antigen-presenting cells for T cell activation, by releasing proinflammatory cytokines and chemokines, and by producing autoantibodies such as rheumatoid factor (RF) and anticitrullinated protein antibodies (ACPA). High-titer rheumatoid factor (RF) correlates with severe articular disease, formation of pathogenic immune complexes, and development of extraarticular

manifestations. Elevations of RF and ACPA can often predict development of RA (as well as radiographic joint damage) several years before disease onset[6,7,8,9]. Moreover, B cell depletion therapy with rituximab has efficacy in reducing disease activity and preventing further joint damage over 2 years[10,11].

The efficacy in RA of current B cell–directed therapy notwithstanding, other approaches are needed. One strategy centers on B lymphocyte stimulator (BLyS), a 285-amino acid type II transmembrane protein member of the tumor necrosis factor (TNF) ligand superfamily[12,13]. Cleavage of surface BLyS by a furin protease results in release of a soluble, biologically active 17-kDa molecule that binds to 3 receptors: B cell maturation antigen, transmembrane activator and calcium-modulator and cyclophilin ligand interactor, and BLyS-receptor 3, all expressed by B cells[14,15,16,17].

BLyS is elevated in the serum and synovial fluid of patients with RA, and is associated with increased RF levels[18,19,20]. The decline over time in serum autoantibody levels and disease activity following initiation of treatment in early RA is paralleled by a decline in serum BLyS levels[21]. Circulating BLyS levels in patients with RA treated with TNF antagonists decline in patients responding well clinically, but not in those responding poorly[22]. In the murine model of RA (i.e., collagen-induced arthritis), transmembrane activator and calcium-modulator and cyclophilin ligand interactor-immunoglobulin (Ig), which is a BLyS (and a proliferation-inducing ligand) inhibitor, has both preventive and therapeutic effects. These include reduction of collagen-specific antibodies and inhibition of the ongoing inflammation and destruction of bone and cartilage[23,24]. The mechanism of action of BLyS is important in the survival of B cells and its inhibition can lead to apoptosis of autoimmune B cell clones[25].

Belimumab, a recombinant human IgG1λ monoclonal antibody, binds to soluble human BLyS with high affinity and inhibits its biological activity[26]. Phase I, II, and III studies of belimumab in patients with systemic lupus erythematosus (SLE) showed belimumab to be well tolerated[27,28,29,30]. Biological activity was demonstrated by reduction in autoantibody titers, normalization of complement levels, and reduction of select B cell populations[31]. Those results suggest that belimumab may have a therapeutic role in other autoimmune diseases in which B cells play a prominent pathogenic role. Our report describes a phase II dose-ranging study of the efficacy and safety of belimumab in patients with active RA who were receiving standard RA therapy.

MATERIALS AND METHODS

Study design. In this multicenter, randomized, double-blind, placebo-controlled, 24-week study (ClinicalTrials.gov identifier NCT00071812), patients with RA who were receiving DMARD therapy were randomly assigned in a 1:1:1:1 ratio to additionally receive placebo or belimumab 1, 4, or 10 mg/kg by intravenous infusion on Days 0, 14, and 28, and then every 28 days for the remainder of 24 weeks. Patients completing the 24-week period could enter a 24-week open-label extension. Patients who had been on the active drug in the double-blind period either continued on the same dose or were switched to 10 mg/kg at the investigator's discretion, and those who had received placebo in the blinded portion of the study switched to belimumab 10 mg/kg during the extension. The primary objective of our study was to evaluate the efficacy and safety of belimumab in patients with RA.

Entry criteria. Adult patients (age 18–65 yrs) were eligible for enrollment if they fulfilled American College of Rheumatology (ACR) criteria for RA for ≥ 1 year, had at least moderate disease activity by Disease Activity Score (DAS) criteria [defined as presence of ≥ 6 swollen joints and ≥ 8 tender or painful joints at screening, plus either morning stiffness for ≥ 45 min, C-reactive protein (CRP) > 2.0 mg/dl, or erythrocyte sedimentation rate (ESR) > 28 mm/h], and failed ≥ 1 DMARD (including TNF antagonists) because of toxicity or lack of efficacy. Inclusion criteria mandated a stable DMARD regimen for ≥ 60 days and stable nonsteroidal anti-inflammatory drugs (NSAID) and/or low-dose (≤ 10 mg/day) prednisone for ≥ 30 days prior to Day 0 (first dose). The subset of patients who had failed ≥ 2 DMARD could be in the study if they were taking a stable dosage of NSAID and/or low-dose prednisone for ≥ 30 days and not taking DMARD for ≥ 60 days before Day 0. Key exclusion criteria included previous treatment with an investigational agent within 60 days; treatment with a corticosteroid injection, a TNF-α antagonist, or an interleukin 1 receptor antagonist within 60 days; infection requiring hospitalization or parenteral medication within 60 days; treatment with anti-CD20 or cyclophosphamide within 6 months; chronic infection (e.g., tuberculosis, cytomegalovirus, pneumocystis, and atypical mycobacteria) that was active (i.e., requiring ongoing antimicrobial/suppressive therapy) within 6 months; herpes zoster within 90 days; clinical evidence of significant unstable or uncontrolled acute or chronic diseases not due to RA, which could confound results; pregnancy; and breastfeeding.

Efficacy measures and biologic markers. The primary efficacy endpoint was response at Week 24, defined as 20% improvement in ACR response criteria (ACR20) using ESR as the acute-phase reactant[32]. Prespecified subgroup analyses of the primary endpoint included baseline disease activity, RA disease duration, TNF antagonist treatment, and presence of RF. Predetermined secondary endpoints included the proportions of patients achieving 50% and 70% improvements in ACR response (ACR50 and ACR70, respectively) at Week 24, change from baseline and improvement over 24 weeks in DAS 28-joint count score using ESR (DAS28)[33,34], modified total Sharp score of hand radiographs[35], and time to first ACR20 response and DAS28 improvement. Exploratory analyses of biological markers included B cell subsets, serum autoantibody (RF and ACPA) titers, ESR, CRP, serum IgG, IgA, IgM, and IgE levels, and BLyS. Efficacy and biomarker assessments were performed at baseline and every 4 weeks until Week 24 or up to Week 48 for those patients who entered the extension period. ACPA was measured using the first-generation test (IgG) by enzyme-linked immunosorbent immune assay. The reference ranges were as follows: negative, < 20 U; weak positive, 20–39 U; moderate positive, 40–59 U; and strong positive, ≥ 60 U. RF was measured by nephelometry using the Siemens BNII Nephelometer, with a cutoff of 12 IU/ml (reference range < 12). All testing was completed at Quest Diagnostic. Peripheral blood lymphocytes were forwarded to a central fluorescence-activated cell-sorting facility at Quest Diagnostic. Cells were stained with combinations of antibodies to identify B cells (CD19+ and CD20+), multiple B cell subsets [naive (CD20+/CD27) and memory (CD20+/CD27+), activated (CD20+/CD69+), plasmacytoid (CD20+/CD138+)], and plasma (CD20–/CD138+ and CD20/CD27^{HIGH}) cells.

Safety assessments. Treatment-emergent adverse events (AE) were recorded during the treatment period and through 8 weeks after the last dose of belimumab or placebo. Safety and tolerability evaluations, including physical examinations, laboratory evaluations, and vital signs,

were conducted every 2–4 weeks. Serum samples were drawn prior to dosing throughout the treatment period to test for antibelimumab antibodies. AE were coded using the *Medical Dictionary for Regulatory Activities*, version 7.1, and graded for severity using the Adverse Event Severity Grading Tables, modified from the National Institute of Allergy and Infectious Diseases, Division of Microbiology and Infectious Disease, Adult Toxicity Tables[36].

Statistical methods. Descriptive statistics were used to summarize demographic, baseline, and RA disease characteristics. The likelihood ratio chi-square test was used to analyze all categorical efficacy endpoints. The only exception was that DAS28 good response was analyzed using Fisher's exact test. Absolute changes from baseline in DAS28 score and modified Sharp score were analyzed using the 2-sample t test. Percentage changes from baseline in all biological markers were analyzed using the Wilcoxon test. All statistical tests were 2-sided and were performed to compare each belimumab treatment group and the placebo group at a significance level of 0.05 unless otherwise specified. Analysis was done in a modified intention-to-treat population, defined as all randomized patients who received ≥ 1 dose of study agent. Patients who did not adhere to the protocol-specified medication rules (e.g., changed NSAID, used prednisone > 10 mg/day, received corticosteroid injection during the last month of study, added a new or additional DMARD, or received prohibited RA medication), or who dropped out on or before the Week 24/48 visit, were considered nonresponders. Secondary analyses of the primary efficacy endpoint were performed on prespecified subgroups to test the consistency of treatment effects. For some endpoints when no dose response was observed, data of all belimumab doses were pooled in a posthoc analysis to increase the power of analysis. AE of special interest, i.e., infusion-related reactions (including hypersensitivity reactions), infections, and malignant neoplasms, were evaluated by creating composite definitions of these events using *Medical Dictionary for Regulatory Activities*–preferred terms. Data from the optional 24-week extension period were analyzed using descriptive statistics.

Informed consent. Our study was conducted in accord with the ethical principles of the Declaration of Helsinki. All participating sites received approval from an institutional review board or ethics committee before patient enrollment. All patients provided written informed consent before any study-related procedures were performed. An independent data-monitoring committee reviewed safety data quarterly.

RESULTS

Study population. Of 415 patients with RA screened at 54 sites (49 in the United States and 5 in Poland), 307 patients were randomized. Of those 307 patients, 24 never received any study treatment and were excluded. The modified intention-to-treat population comprised 283 patients randomly assigned to placebo (n = 69) or belimumab 1 mg/kg (n = 72), 4 mg/kg (n = 71), or 10 mg/kg (n = 71; Figure 1). Of these patients, 248 (88%) completed the blinded 24-week period and 237 elected to continue in the 24-week extension. In the extension, 162 switched to belimumab 10 mg/kg [56 from placebo, 53/64 (83%) from 1 mg/kg, and 53/61 (87%) from 4 mg/kg] and 75 remained on the initially randomized belimumab dose of 1 mg/kg (n = 11), 4 mg/kg (n = 8), or 10 mg/kg (n = 56). The completion rate in the extension period was similar to that in the blinded period (n = 196; 83%) and the groups did not differ in reasons for discontinuation during the initial 24-week period or in the 24-week extension.

The treatment groups were balanced in baseline demographic and disease characteristics (Table 1). At baseline, patients had a mean disease duration of 8.8–11.8 years, mean DAS28 of 6.3, mean tender joint counts of 26.8–29.5, and mean swollen joint counts of 19.1–20.9. The predetermined analyses of ACR20 and DAS28 were based on ESR, which was used preferentially to CRP because 100% of patients had measurable ESR, whereas only ~60% had CRP above the level of detection; elevated CRP was not an entry criterion.

Efficacy. At 24 weeks, ACR20 responses in patients who received placebo and belimumab 1, 4, and 10 mg/kg were 15.9%, 34.7% (p = 0.010), 25.4% (p = 0.168), and 28.2% (p = 0.080), respectively (Table 2). Figure 2A depicts ACR20 responses over time. The median time to ACR20 response (based on ESR) in patients who had a response was ~16 weeks in patients treated with either placebo or belimumab.

When all patients treated with belimumab were considered together in a posthoc analysis, more of them than those treated with placebo achieved an ACR20 response (29.4% vs 15.9%; p = 0.021) and an ACR50 response (10.7% vs 4.3%; p = 0.085). No difference in ACR70 response was observed (Figure 2B). In the open-label extension period with all patients receiving belimumab, an additional 12% had an ACR20 response (29% at 24 weeks to 41% at 48 weeks). A similar ACR20 response at 48 weeks was seen in patients who switched from placebo to belimumab 10 mg/kg (16% at 24 weeks to 42% at 48 weeks).

Mean changes from baseline in DAS28 response at Week 24 in patients who received placebo and belimumab 1, 4, and 10 mg/kg were –0.9, –1.3 (p = 0.096), –0.9 (p = 0.786), and –1.5 (p = 0.005), respectively (Table 2). Improvement (good/moderate response) in DAS28 (defined as > 1.2-unit decrease from baseline or > 0.6-unit decrease from baseline coupled with a DAS28 absolute score ≤ 5.1[37]) in patients who received placebo and belimumab 1, 4, and 10 mg/kg occurred in 40.6%, 50.0% (p = 0.261), 42.3% (p = 0.841), and 60.6% (p = 0.018), respectively. In the extension period, the proportion with good/moderate response increased to 67% of patients treated with belimumab during the blinded portion of the trial, and a similar response (66%) was achieved by those who switched from placebo to 10 mg/kg. For patients achieving a good/moderate DAS28 response, median time to DAS28 improvement occurred sooner with belimumab versus placebo (63 vs 111 days; p = 0.039). When DAS28 improvement was defined as a good response, i.e., DAS28 absolute score ≤ 3.2 and > 1.2-unit decrease from baseline[37], similar results were seen, but the proportion of patients achieving this level of response was lower.

No significant differences in the changes in modified total Sharp score of hand radiographs were observed at Week 24 between patients treated with belimumab and placebo (Table 2).

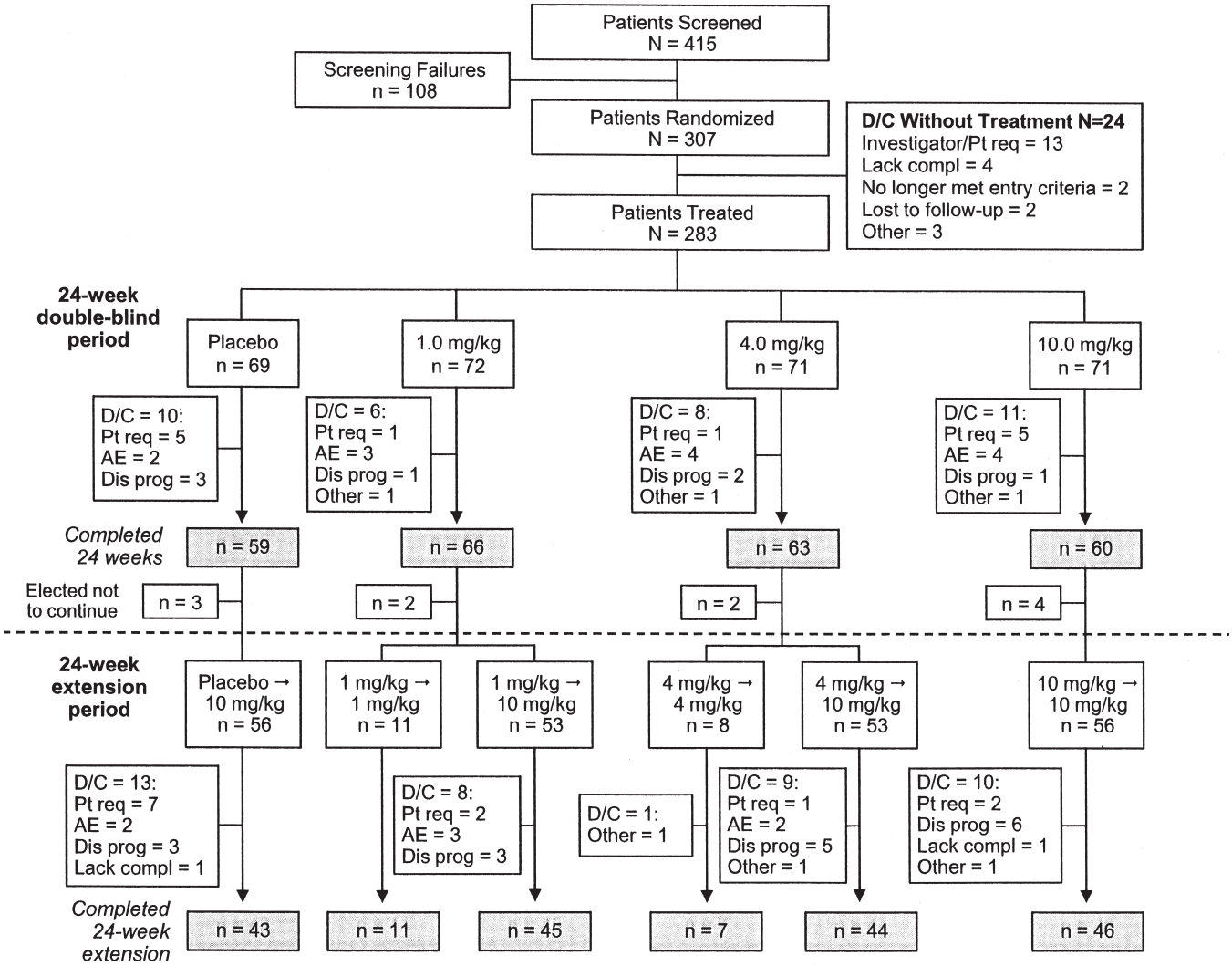

Figure 1. Patient disposition. AE: adverse event; compl: compliance; crit: criteria; D/C: discontinued; Dis prog: disease progression/lack of efficacy; Pt req: patient request.

Subgroup analyses of ACR20 response at Week 24. Exploratory analyses showed that ACR20 responses were greater in patients treated with belimumab than in those treated with placebo who, at baseline, were TNF antagonist-naive (36% vs 13%; p = 0.003), RF-positive (29% vs 12%; p = 0.005), or ACPA-positive (30% vs 14%; p = 0.014), or had elevated CRP [29% vs 9%; p = 0.014 (CRP ≥ 1.5 mg/dl)] or a DAS28 score > 5.1 (31% vs 15%; p = 0.016; Figure 2C). Thirty percent of patients had detectable BLyS levels > 0.858 ng/ml. In those patients, ACR20 response was not different between patients treated with belimumab and placebo, but unexpectedly was greater in patients with low BLyS levels (< 0.858 ng/ml) at baseline (32% vs 10%; p = 0.001).

Biological markers: B cell subsets. At Week 24, overall belimumab treatment was associated with median percentage reductions of 16% for CD19+ cells, 20% for CD20+ cells, and 48% for both naive and activated B cells compared with increases of 8%, 5.9%, 4.3%, and 10%, respectively, with placebo (p < 0.001 for each comparison; Figure 3A–3C). Median reductions in plasmacytoid cells (CD20+/CD138+) were not significantly different in patients treated with belimumab versus placebo (33% vs 20%; p = 0.569), and there were no changes in plasma cells (CD20–/CD138+ and CD20/CD27^{HIGH}) in either treatment group (data not shown). Memory B cells were stable in patients treated with placebo, but increased by Week 4 in those treated with belimumab (100% median increase vs 3% with placebo; p < 0.001; Figure 3D). Although memory cells then gradually declined in patients treated with belimumab, they remained elevated at Week 24 (median increase 73% vs 5.4% with placebo; p < 0.001). With continued belimumab treatment through 48 weeks, CD19+, CD20+, naive, activated and plasmacytoid B cells continued to decrease, memory B cells continued to normalize, and plasma cells remained stable.

Biological markers: RF and ACPA. In patients who were

Table 1. Baseline patient characteristics.

	Placebo, n = 69	Belimumab 1 mg/kg, n = 72	Belimumab 4 mg/kg, n = 71	Belimumab 10 mg/kg, n = 71	All, n = 214
Female, n (%)	56 (81.2)	56 (77.8)	60 (84.5)	54 (76.1)	170 (79.4)
White, n (%)	62 (89.9)	61 (84.7)	64 (90.1)	68 (95.8)	193 (90.2)
Age, yrs, mean ± SD	50.7 ± 8.8	50.6 ± 8.3	50.7 ± 10.2	49.5 ± 9.3	50.3 ± 9.3
Disease duration, yrs, mean ± SD	10.5 ± 7.1	11.8 ± 9.9	8.8 ± 7.9	11.1 ± 9.4	10.6 ± 9.2
Mean no. tender joints ± SD	29.5 ± 14.5	26.8 ± 13.3	29.2 ± 15.4	28.8 ± 14.3	28.3 ± 14.3
Mean no. swollen joints ± SD	20.9 ± 9.1	19.1 ± 9.9	19.7 ± 11.7	20.8 ± 10.2	19.9 ± 10.6
CRP+, n (%)					
≥ 0.9 mg/dl	40 (58.0)	46 (63.9)	41 (57.7)	40 (56.3)	127 (59.3)
≥ 1.5 mg/dl	33 (47.8)	35 (48.6)	34 (47.9)	29 (40.8)	98 (45.8)
Mean CRP ± SD, mg/dl	3.9 ± 2.5	3.7 ± 2.8	4.2 ± 4.0	3.6 ± 2.5	3.8 ± 3.1
RF+ (≥ 12 IU/ml, n (%)	58 (84.1)	62 (86.1)	56 (78.9)	62 (87.3)	180 (84.1)
Mean RF ± SD, IU/ml	562.0 ± 1355.1	614.6 ± 1071.2	481.6 ± 1005.4	428.8 ± 616.1	509.2 ± 915.0
ACPA+ (≥ 20 units), n (%)	56 (81.2)	58 (80.6)	51 (71.8)	52 (73.2)	161 (75.2)
Mean ACPA ± SD	129.9 ± 56.4	118.3 ± 50.1	112.1 ± 59.9	122.3 ± 54.9	117.6 ± 54.7
Mean ESR ± SD, mm/h	37.9 ± 27.4	35.1 ± 22.9	38.2 ± 29.3	36.0 ± 27.2	36.4 ± 26.5
Mean DAS28 ± SD	6.3 ± 1.2	6.3 ± 1.0	6.3 ± 1.2	6.3 ± 1.1	6.3 ± 1.1
Mean modified total Sharp score ± SD	29.2 ± 28.6	29.9 ± 28.4	24.2 ± 25.0	25.7 ± 23.1	26.6 ± 25.6
Mean no. failed DMARD ± SD	2.3 ± 1.2	2.3 ± 1.3	2.2 ± 1.2	2.2 ± 1.3	2.2 ± 1.3
Current DMARD used, n (%)					
0	4 (5.8)	7 (9.7)	4 (5.6)	4 (5.6)	15 (7.0)
1	48 (69.6)	54 (75.0)	50 (70.4)	52 (73.2)	156 (72.9)
2	17 (24.6)	10 (13.9)	17 (23.9)	14 (19.7)	41 (19.2)
≥ 3	—	1 (1.4)	—	1 (1.4)	2 (0.9)
Type of current DMARD, n (%)					
Methotrexate	55 (79.7)	45 (62.5)	56 (78.9)	50 (70.4)	151 (70.6)
Antimalarial	10 (14.5)	11 (15.3)	10 (14.1)	12 (16.9)	33 (15.4)
Leflunomide	4 (5.8)	11 (15.3)	4 (5.6)	8 (11.3)	23 (10.8)
Sulfasalazine	5 (7.3)	7 (9.7)	11 (15.5)	5 (7.0)	23 (10.8)

ACPA: anticitrullinated protein antibodies; CRP: C-reactive protein; DAS28: Disease Activity Score 28-joint count; DMARD: disease-modifying antirheumatic drug; ESR: erythrocyte sedimentation rate; RF: rheumatoid factor.

Table 2. Primary and major secondary efficacy endpoints at Week 24.*

Measure	Placebo, n = 69	Belimumab 1 mg/kg, n = 72	Belimumab 4 mg/kg, n = 71	Belimumab 10 mg/kg, n = 71	All, n = 214
ACR20, % responders	15.9	34.7, p = 0.010	25.4, p = 0.167	28.2, p = 0.080	29.4, p = 0.021
ACR50, % responders	4.3	9.7, p = 0.207	8.5, p = 0.318	14.1, p = 0.042	10.7, p = 0.085
ACR70, % responders	2.9	5.6, p = 0.430	1.4, p = 0.539	2.8, p = 0.977	3.3, p = 0.877
Mean change in DAS28 score†	–0.9	–1.3, p = 0.096	–0.9, p = 0.786	–1.5, p = 0.005	–1.2, p = 0.059
DAS28 good/moderate improvement, %	40.6	50.0, p = 0.261	42.3, p = 0.841	60.6, p = 0.018	50.9, p = 0.133
DAS28 good improvement, %	4.3	11.1, p = 0.209	7.0, p = 0.719	11.3, p = 0.208	9.8, p = 0.215
Mean change in total Sharp score‡	0.7	0.3, p = 0.194	0.3, p = 0.256	0.6, p = 0.871	0.4, p = 0.288

* P values for comparisons between each belimumab group and the placebo group for ACR20/50/70 and DAS28 good/moderate responses were obtained with likelihood ratio chi-square test, for DAS28 good responses with Fisher's exact test, and for change from baseline in DAS28 and modified Sharp scores with 2-sample t test. † n = 70 and 213 in the belimumab 10-mg/kg and all-belimumab groups, respectively. ‡ n = 67, 70, 66, 68, and 204 in the placebo, belimumab 1-mg/kg, 4-mg/kg, and 10-mg/kg and all-belimumab groups, respectively. ACR: American College of Rheumatology; DAS28: Disease Activity Score 28-joint count.

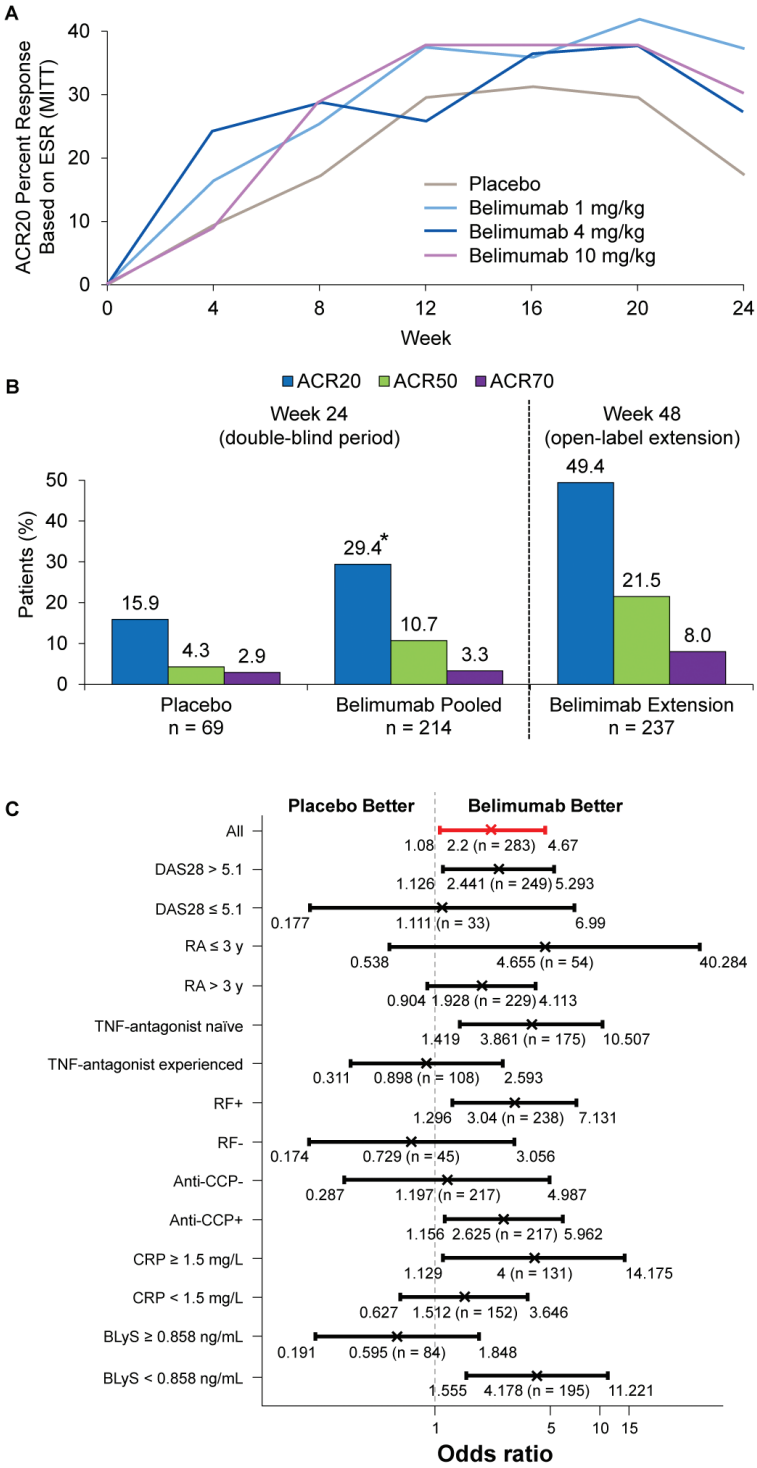

Figure 2. American College of Rheumatology (ACR) response [based on erythrocyte sedimentation rate (ESR), where elevated ESR was considered > 28 mm/h]. A. ACR20 responses over the first 24 weeks by treatment group. B. ACR20/50/70 responses at Week 24 in patients who received placebo and belimumab pooled (1, 4, and 10 mg/kg) in a posthoc analysis and at Week 48 in patients in the belimumab extension, which included patients irrespective of original assignment (placebo or belimumab 1, 4, or 10 mg/kg); after Week 24, all patients taking placebo, and 83% and 87% taking belimumab 1 and 4 mg/kg, respectively, switched to belimumab 10 mg/kg. C. ACR20 responses at Week 24 with OR (generated using unadjusted logistic-regression model) for subgroups (all belimumab vs placebo); vertical broken line indicates no effect. All comparisons of ACR20 responses between each belimumab group and the placebo group were performed using likelihood ratio chi-square test. Anti-CCP: anticitrullinated protein antibodies; BLyS: B lymphocyte stimulator; CRP: C-reactive protein; DAS28: Disease Activity Score 28-joint count; MITT: modified intention to treat; RA: rheumatoid arthritis; RF: rheumatoid factor; TNF: tumor necrosis factor. *$p < 0.05$.

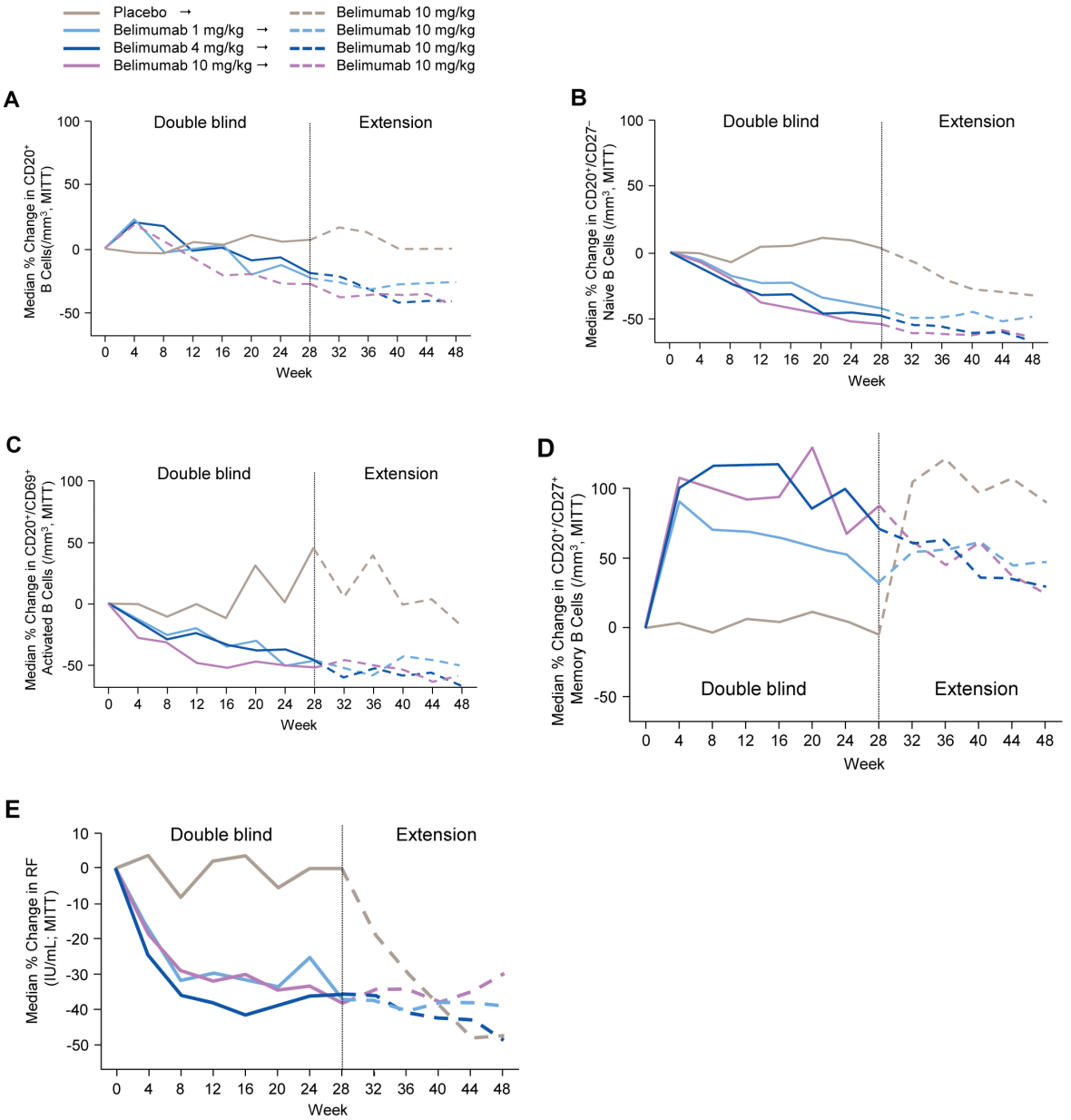

Figure 3. Median percentage changes from baseline in (A) CD20+ B cells, (B) CD20+/CD27– (naive) B cells, (C) CD20+/CD69+ (activated) B cells, and (D) CD20+/CD27+ (memory) B cells for the 24-week treatment and 24-week extension periods [modified intention to treat (MITT)], including all patients with a result at a given timepoint who had a baseline value > 0. E. Rheumatoid factor (RF) in patients with positive RF (≥ 12 IU/ml) at baseline for the 24-week treatment and 24-week extension periods. Treatment groups are based on treatment assignments in the double-blind 24-week treatment period. Vertical dashed line indicates day of first dose in the extension period of the study, after which all patients taking placebo and 83% and 87% taking belimumab 1 and 4 mg/kg, respectively, switched to belimumab 10 mg/kg.

RF-positive (≥ 12 IU/ml) at baseline, RF decreased by a median 1.9% versus 31% at Week 24 in patients treated with placebo versus all belimumab doses combined (Figure 3E). The decrease in RF observed in the first 24 weeks was maintained with continued belimumab treatment (median reductions of 32% at Week 28 and 37% at Week 48). In contrast, in patients who were ACPA-positive (≥ 20 units) at baseline, changes in ACPA were inconsistent, with patients treated with belimumab showing a decrease at several timepoints compared with those on placebo. At Week 24, there was no significant difference between placebo and belimumab in median ACPA reduction (–1.8% vs –9.2%).

Biological markers: Ig concentrations. Modest but statistically significant reductions in IgG, IgA, IgM, and IgE were observed by Week 8 in patients treated with all belimumab doses combined vs placebo ($p < 0.001$ for each comparison).

This persisted at Week 24 ($p < 0.005$ for each comparison) and the reductions remained stable throughout the extension period (Table 3).

Safety. During the first 24 weeks of treatment, the incidence rates of AE and serious AE were similar between patients treated with placebo and belimumab (Table 3). Discontinuations due to AE were uncommon, and arthralgia was the only AE leading to discontinuation that was reported in > 1 patient. The incidence rates of infections were similar in patients treated with placebo and belimumab, and severe infections were infrequent (~1.5% overall).

There were more infusion-related reactions in the first 24 weeks with belimumab compared with placebo (Table 3). Three infusion-related reactions during the placebo-controlled and extension periods were hypersensitivity reactions. One patient developed mild hypersensitivity deemed to be caused by environmental allergies during her fifth belimumab infusion (10 mg/kg). In the extension period, 1 patient previously taking placebo had flushing and urticaria of the chest and face during the first infusion of belimumab 10 mg/kg. Another patient previously receiving belimumab 1 mg/kg developed severe symptoms (angioedema, erythema of hands, pruritus of hands and feet, facial swelling, and urticaria of the feet and left torso) during the second infusion of belimumab 10 mg/kg. This latter AE resulted in discontinuation of treatment.

There were no significant differences in Grade 3/4 laboratory abnormalities between the placebo and belimumab groups (Table 3). A Grade 3 IgG abnormality (250–399 mg/dl) was observed at 2 timepoints in a patient (belimumab 1 mg/kg) with a Grade 2 abnormality at screening. By Week 48, the IgG level had returned to baseline.

One death (cardiac arrest with placebo) was reported during the double-blind period. Another death (pneumonia with belimumab 10 mg/kg) occurred ~6 months after a patient's sixth and last dose. This patient had a history of chronic obstructive pulmonary disease, pulmonary fibrosis, asthma, and emphysema. Solid-organ malignancies were reported in 3 patients treated with belimumab, including vulvar cancer (1 mg/kg), breast cancer (10 mg/kg), and in the extension period, lung squamous cell carcinoma (4

Table 3. Adverse events (AE) at weeks 24 and 48. Data are n (%) unless otherwise indicated.

		Double-blind Period (Week 24) Belimumab			Extension Period (Week 48)
	Placebo, n = 69	1 mg/kg, n = 72	4 mg/kg, n = 71	10 mg/kg, n = 71	All, n = 214	All Belimumab, n = 237
≥ 1 AE	62 (89.9)	61 (84.7)	64 (90.1)	66 (93.0)	191 (89.3)	217 (91.6)
≥ 1 severe AE*	6 (8.7)	7 (9.7)	10 (14.1)	9 (12.7)	26 (12.1)	30 (12.7)
≥ 1 serious AE	5 (7.2)	5 (6.9)	5 (7.0)	6 (8.5)	16 (7.5)	26 (11.0)
Discontinuation due to AE	2 (2.9)	3 (4.2)	4 (5.6)	4 (5.6)	11 (5.1)	7 (3.0)
Deaths	1 (1.4)	0	0	1 (1.4)†	1 (0.5)†	0
Malignancies (excluding NMSC)	0	1 (1.4)	1 (1.4)	0	2 (0.93)	1 (0.42)
By MedDRA system organ class > 40% in all belimumab groups‡						
Infections and infestations	30 (43.5)	31 (43.1)	37 (52.1)	30 (42.3)	98 (45.8)	124 (52.3)
≥ 1 severe infection AE	1 (1.5)	1 (1.4)	1 (1.4)	1 (1.4)	3 (1.4)	5 (2.1)
≥ 1 serious infection AE	1 (1.5)	1 (1.4)	2 (2.8)	1 (1.4)	4 (1.9)	4 (1.7)
Musculoskeletal and connective tissue disorders	24 (34.8)	31 (43.1)	27 (38.0)	31 (43.7)	89 (41.6)	116 (49.0)
Treatment-emergent AE > 10% in all-belimumab groups‡						
Arthralgia	16 (23.2)	21 (29.2)	15 (21.1)	24 (33.8)	60 (28.0)	75 (31.6)
Infusion-related reactions	4 (5.8)	8 (11.1)	8 (11.3)	11 (15.5)	27 (12.6)	13 (5.5)
Hypersensitivity reactions	0	0	0	1 (1.4)	1 (0.5)	2 (0.8)
Upper respiratory tract infections	9 (13.0)	6 (8.3)	9 (12.7)	10 (14.1)	25 (11.7)	38 (16.0)
Laboratory abnormalities > 2% in all-belimumab group‡						
Lymphocytes						
Grade 3	3 (4.3)	1 (1.4)	4 (5.6)	5 (7.0)	10 (4.7)	11 (4.6)
Grade 4	0	0	0	1 (1.4)	1 (0.5)	3 (1.3)
Hyperglycemia						
Grade 3	2 (2.9)	1 (1.4)	4 (5.6)	3 (4.2)	8 (3.7)	4 (1.7)
Ig levels, % median change from baseline						
IgG§	–3.6	–7.0	–11	–10	–9.7	–9.2
IgA	–0.6	–9.7	–12	–11	–11	–14
IgM	–4.1	–20	–20	–19	–20	–25
IgE	–5.8	–29	–26	–40	–31	–37

* Includes life-threatening AE. † Death was reported in the patient ~6 months after the final dose of belimumab in the 24-week treatment period. ‡ Determined by all-belimumab group during the double-blind period. § No Grade 4 IgG (< 250 mg/dl) was observed. Ig: immunoglobulin; MedDRA: Medical Dictionary for Regulatory Activities; NMSC: nonmelanoma skin cancer.

mg/kg). The mortality rates per 100 patient-years during the double-blind period were, therefore, 2.91 with placebo and 0.92 with belimumab; the rate over the 48 weeks of the double-blind and extension periods was 0.48 with belimumab. Nonmelanoma skin cancers occurred in 3 patients treated with belimumab, including squamous cell carcinoma of the skin (1 patient on 10 mg/kg, and 1 patient who switched from 4 to 10 mg/kg) and basal cell carcinoma of the skin (switched from 1 to 10 mg/kg).

DISCUSSION

This phase II, randomized, controlled trial of belimumab added to standard RA therapy in patients with RA met its primary endpoint at Week 24 by demonstrating significantly higher ACR20 responses in patients treated with belimumab 1 mg/kg, but not with 4 or 10 mg/kg, and in a posthoc analysis with all belimumab doses combined compared with standard therapy alone. This finding was consistent with the greater improvements in time to DAS28 moderate/good response observed in patients treated with belimumab, particularly with 10 mg/kg. Overall, however, there was no dose response evident in clinical outcomes or biomarkers over 24 weeks in the range of belimumab doses tested (1, 4, and 10 mg/kg). In the 24-week extension, patients who continued to receive belimumab and those who switched from placebo to 10 mg/kg achieved higher proportions of ACR20 response than were seen in the first 24 weeks.

More consistent dose responses of some clinical and biomarker endpoints were observed in studies of belimumab in SLE in the same range of dosing[28,29,31]. Any explanation of this difference remains speculative, but greater occupancy of BLyS receptor 3 by BLyS on SLE B cells than on RA B cells could result in greater BLyS-triggered survival signals being delivered to SLE B cells and lead to a greater dose of belimumab being necessary to fully neutralize BLyS in patients with RA[38].

Exploratory analysis of the present phase II trial identified subgroups of patients with RA who responded better when belimumab rather than placebo was added to standard therapy. Patients who at baseline were RF-positive or ACPA-positive and had high disease activity (DAS28 > 5.1) or elevated CRP levels (≥ 1.5 mg/dl) had better responses to belimumab than to placebo at Weeks 24 and 48 compared with patients without these baseline characteristics. In SLE, the best responders to belimumab were those who at baseline were autoantibody-positive and had low complement levels and high disease activity (Safety of Estrogens in Lupus Erythematosus National Assessment–Systemic Lupus Erythematosus Disease Activity Index score > 10)[39]. Thus in both RA and SLE, the patients who respond best to belimumab are those who are autoantibody-positive and have greater disease activity.

An unexpected outcome of the exploratory analysis was that patients with RA with low baseline BLyS levels responded better to belimumab than to placebo, whereas patients with higher baseline BLyS levels did not. On the one hand, this counterintuitive outcome could simply be a spurious one, because the high-BLyS subgroup had a 30% response rate with placebo, almost twice that of the placebo group as a whole (16%). On the other hand, the unexpected outcome may make sense if even the belimumab 10-mg/kg dose were insufficient in those patients with the highest levels of BLyS. Synovial fluid levels of BLyS are greater than serum levels in patients with RA, and these 2 measures are strongly correlated with each other[19]. Although synovial fluid BLyS levels were not measured in our study, it is plausible that synovial fluid BLyS levels were greater in the high compared with the low BLyS group. In murine collagen-induced arthritis, local silencing of BLyS in the joints markedly attenuates disease, while local augmentation of BLyS aggravates disease[40]. The ability of belimumab to enter inflamed joints and neutralize synovial fluid BLyS is unknown, so it may be that even at the highest dose tested (10 mg/kg every 4 weeks), only limited amounts of belimumab were delivered to the sites of ongoing inflammation (joints). Further studies will be needed to address this possibility.

One of the limitations of our study was that the population enrolled differed from that of many other RA studies, most of which have background treatments limited to 1 drug such as methotrexate. In addition, many RA studies have excluded a substantial subset of patients with clinically active RA by requiring an abnormal CRP level (at least twice the upper limit of normal) at baseline. Similar to the Anti-TNF-Research Study Program of the Monoclonal Antibody D2E7 in RA trial of adalimumab in patients with RA[41], abnormal CRP or ESR was not required for entry into our study (40.9% of patients had a normal CRP at baseline and all patients had ESR > 0). Because patients with high CRP levels responded better to belimumab than did those with normal levels, our results may have been more robust if we had limited our study to patients with high CRP levels. Because a range of prior therapies including ≥ 1 TNF antagonist, as well as ≥ 1 concurrent DMARD (21% of patients were receiving ≥ 2 DMARD) was allowed, the study group represents a more heterogeneous standard-therapy population than most recent RA trials.

Belimumab added to DMARD RA therapy for 24 weeks had a safety profile similar to that of placebo plus DMARD RA therapy. The incidence rates of AE, serious AE, and laboratory abnormalities, and reasons for discontinuation were similar between the belimumab and placebo groups. There was no dose relation for infection or serious infection rates, nor was any specific type of infection increased with any belimumab dose. The preservation of memory B cells and plasma cells coupled to the very modest reduction in IgG may have contributed to the low infection rates across treatment groups. There were more infusion reactions with

belimumab than with placebo, but most were mild–moderate and occurred during the first 3 doses. Hypersensitivity reactions were rare, and no anaphylaxis was reported.

In patients with RA who failed ≥ 1 previous DMARD, belimumab added to DMARD therapy was well tolerated and provided a greater ACR20 response than standard therapy alone.

ACKNOWLEDGMENT

The authors thank Gina Eriksson of Human Genome Sciences Inc. for editorial assistance in the development of the first draft of the manuscript, and Geoff Marx of BioScience Communications, New York, New York, for editorial assistance throughout the submission process.

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