

Efficacy and Safety of Belimumab and Azathioprine for Maintenance of Remission in Antineutrophil Cytoplasmic Antibody–Associated Vasculitis: A Randomized Controlled Study

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Objective. To evaluate the safety and efficacy of belimumab as adjunctive therapy to maintain remission in antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV).

Methods. In this multicenter, double-blind, placebo-controlled study, patients with AAV (ages ≥ 18 years) were randomized 1:1 to receive azathioprine (2 mg/kg/day), low-dose oral glucocorticoids (≤ 10 mg/day), and either intravenous belimumab (10 mg/kg) or placebo, following remission induction with rituximab or cyclophosphamide along with glucocorticoids. The primary end point was time to first protocol-specified event (PSE), with first PSE defined as a Birmingham Vasculitis Activity Score (BVAS) of ≥ 6 , presence of ≥ 1 major BVAS item, or receipt of prohibited medications for any reason, resulting in treatment failure (adjusted for ANCA type [proteinase 3 (PR3) or myeloperoxidase (MPO)], disease stage at induction, and induction regimen). Vasculitis relapse was defined as the PSE of either a BVAS activity score of ≥ 6 or receipt of prohibited medications for vasculitis. Changes in treatment practice led to truncation of the study population from ~ 300 patients to ~ 100 patients.

Results. The intent-to-treat population totaled 105 patients with AAV, of whom 52 (40 with PR3-ANCAs, 12 with MPO-ANCAs) received placebo and 53 (41 with PR3-ANCAs, 12 with MPO-ANCAs) received belimumab; 27 of the patients were in rituximab-induced disease remission, while 78 were in cyclophosphamide-induced disease remission at baseline. Compared with placebo, treatment with belimumab did not reduce the risk of a PSE (adjusted hazard ratio [HR] 1.07, 95% confidence interval [95% CI] 0.44–2.59; $P = 0.884$) or vasculitis relapse (adjusted HR 0.88, 95% CI 0.29–2.65; $P = 0.821$). The overall rate of PSEs was low (11 [21.2%] of 52 patients receiving placebo, 10 [18.9%] of 53 patients receiving belimumab). Vasculitis relapse in the placebo group ($n = 8$) occurred independent of the induction regimen, disease stage, or ANCA type. All vasculitis relapses in the belimumab group ($n = 6$) occurred in patients who had PR3-ANCA–associated vasculitis with cyclophosphamide-induced disease remission. Adverse events occurred in 49 (92.5%) of 53 patients receiving belimumab and 43 (82.7%) of 52 patients receiving placebo, with no new safety concerns.

Conclusion. Belimumab plus azathioprine and glucocorticoids for the maintenance of remission in AAV did not reduce the risk of relapse.

INTRODUCTION

Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) (related types of antineutrophil cytoplasmic

antibody [ANCA]–associated vasculitis [AAV]) are organ- and life-threatening systemic vasculitides characterized by the presence of autoantibodies. B cells have been implicated in the pathogenesis of AAV (1,2).

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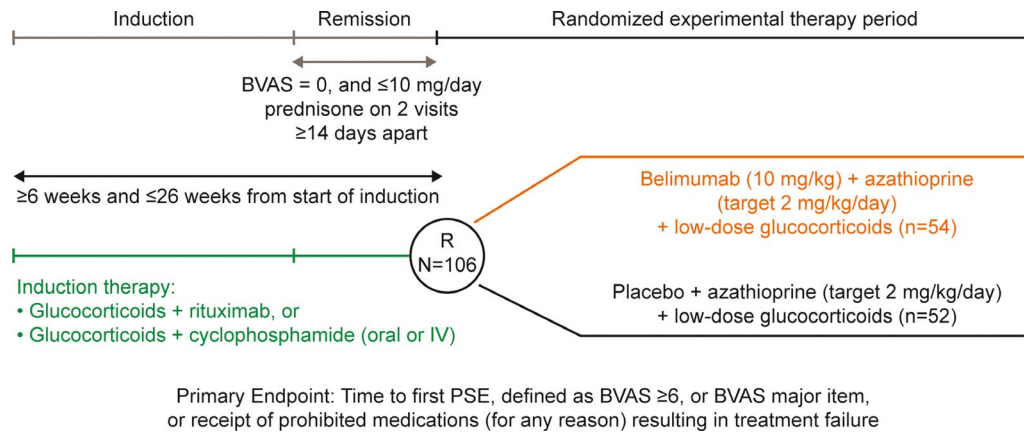


Figure 1. Study design. BVAS = Birmingham Vasculitis Activity Score; IV = intravenous; R = randomization; PSE = protocol-specified event.

The current recommendation for the maintenance of remission in AAV consists of treatment with low-dose glucocorticoids in combination with one of the following therapies: azathioprine, methotrexate, mycophenolate mofetil, or rituximab (3). Rituximab, a B cell-depleting agent shown to reduce the risk of relapse in GPA and MPA, is becoming the standard therapy for the induction of remission in AAV (4–8). Cyclophosphamide has similar efficacy as that of rituximab as an induction therapy (3,7). Despite use of the above therapies, relapse is a major clinical problem in AAV, and there remains uncertainty as to the best approach for preventing relapses after remission is obtained.

Several lines of evidence support a role for the B lymphocyte stimulator (BLyS) in the pathogenesis of AAV. BLyS is expressed by neutrophils, key cells in AAV pathogenesis, and elevated levels of circulating BLyS have been reported in patients with AAV (1,9–16). In addition, patients with systemic lupus erythematosus demonstrate increased levels of BLyS following treatment with rituximab; such BLyS elevation may be linked to the production of autoantibodies by autoreactive B cells (17–21). Belimumab, a human IgG1 λ monoclonal antibody against BLyS, is licensed for the treatment of adults with active, autoantibody-associated systemic lupus erythematosus who are receiving standard therapy (22,23).

The current study, Belimumab in Remission of Vasculitis (BREVAS), examined the safety and efficacy of belimumab plus azathioprine and low-dose oral glucocorticoids for the maintenance of remission in AAV, following induction of remission with either rituximab or cyclophosphamide with glucocorticoids. The treatments were tested within a randomized controlled trial setting.

PATIENTS AND METHODS

Study design. In this multinational, multicenter, double-blind, placebo-controlled study (GlaxoSmithKline [GSK] study no. BEL115466; see Appendix A for a list of the collaborators) (23), patients with GPA or MPA were randomized 1:1 to receive treatment with either intravenous (IV) belimumab (10 mg/kg) or placebo alongside azathioprine (2 mg/kg/day) and low-dose oral glucocorticoids (≤ 10 mg/day) (Figure 1). The 37 participating centers were in 15 countries (in Australia, Central America, Eastern Europe, North America, South America, and Western Europe). Randomization was performed on day 0; both the sites and study sponsor remained blinded with regard to treatment allocation at all times. The randomization schedule was produced by Human Genome Sciences (HGS).

Subjects were stratified by ANCA type (anti-PR3 ANCA versus anti-MPO ANCA), disease stage at induction (initial versus relapsing disease), and induction regimen (IV or oral cyclophosphamide versus rituximab). Subjects were assigned to their treatment group via an Interactive Web Response System based on the parameters entered by the sites. When HGS was acquired by GSK, the randomization schedule was migrated to the GSK system Randall. The first patient was enrolled on March 20, 2013 and the last patient visit took place on February 6, 2017. The study agent was administered on days 0, 14, 28, and every 28 days thereafter until either study completion or relapse.

The BREVAS study was originally a phase III study investigating the maintenance or remission of AAV following a standard induction regimen. The study was truncated after initiation, primarily due to a change in AAV standard of care that affected recruitment. Furthermore, the study design changed from “event-driven” to “fixed completion” 12 months after the last patient was

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randomized, leading to variable durations of treatment. The sample size was reduced from ~300 patients to ~100 patients.

Institutional review board approval and ethics considerations. This study was reviewed and approved by the appropriate ethics committee or institutional review board in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Guidelines for Good Clinical Practice, as well as the ethics procedures outlined in the Declaration of Helsinki (24) and applicable country-specific requirements. Written informed consent was obtained from each patient prior to any study-specific procedures.

Patients. Inclusion criteria. Eligible patients were ages ≥ 18 years, had a clinical diagnosis of GPA or MPA according to the 2012 Chapel Hill Consensus Conference definitions (25), and tested positive (current or historical) for either PR3-ANCA or MPO-ANCA. Patients must have experienced either new-onset or relapsing GPA or MPA in the 26 weeks prior to day 0, that required treatment under one of the following remission induction regimens: a single course of rituximab (375 mg/m²/week for 4 weeks) plus high-dose glucocorticoids; 2 doses of IV rituximab (1 gm), separated by a 2-week interval, plus high-dose glucocorticoids; oral cyclophosphamide (2 mg/kg/day); or pulses of IV cyclophosphamide (15 mg/kg), administered 2 weeks apart for 3 doses followed by further pulses every 3 weeks, plus high-dose glucocorticoids. Additionally, patients had to be in remission on day 0 (with remission defined as a Birmingham Vasculitis Activity Score [BVAS; version 3] of 0) (26) and receiving glucocorticoids (presented as prednisone-equivalent doses) at ≤ 10 mg/day (on 2 consecutive measurements ≥ 14 days apart, and 6–26 weeks after the first dose of induction therapy). Physicians were free to adjust the oral glucocorticoid dose in the range below 10 mg/day. A minimum period of 6 weeks was required between the first dose of induction therapy and randomization.

Exclusion criteria. Key exclusion criteria included the following: the coexistence of another autoimmune disease; any known intolerance or contraindications to azathioprine and methotrexate; receipt of any B cell-targeted therapy (excluding rituximab) at any time, or any other investigational agent within 60 days of day 0 or 5 half-lives of the agent (whichever was longest); any acute or chronic infections requiring hospitalization (within 60 days of day 0) and/or receipt of parenteral antibacterial drugs, antiviral drugs, antifungal drugs, or antiparasitic drugs (within 60 days of day 0); and serologic evidence of infection with human immunodeficiency virus, hepatitis B virus, or hepatitis C virus.

Efficacy end points and assessments. The primary objective of this study was to evaluate the efficacy and safety of belimumab in combination with azathioprine for the maintenance of

remission in patients with GPA or MPA, following a standard remission induction regimen. Efficacy assessments and measurements of disease severity were performed according to the BVAS (version 3) and Vasculitis Damage Index (VDI) scales (26,27). The primary end point was time to first protocol-specified event (PSE), with first PSE defined as a BVAS score of ≥ 6 , presence of ≥ 1 predefined major item on the BVAS, or receipt of prohibited medications for any reason, resulting in treatment failure, as adjudicated by the sponsor. As treatment failure could occur for reasons other than vasculitis, a sensitivity analysis of vasculitis relapse was performed. Vasculitis relapses were defined as a BVAS score of ≥ 6 , presence of a predefined BVAS major item, or the receipt of prohibited medications for the treatment of vasculitis, and were adjudicated by the sponsor.

The major secondary efficacy end point was time from day 0 to the first major vasculitis relapse, defined as the presence of ≥ 1 major BVAS item. Efficacy assessments for clinical disease activity (BVAS scores) were performed at screening and on day 0, followed by assessments at week 2, week 4, and every 4 weeks thereafter until study exit. Other efficacy end points included absolute change in the VDI, and proportion of patients in remission (defined as a BVAS score of 0 and glucocorticoid dose ≤ 10 mg/day) at double-blind week 48 of year 1 and double-blind week 24 of year 2, as well as by visit.

Prohibited medications and therapies resulting in treatment failure. Patients who received prohibited medications or therapies at any time during the double-blind phase of this study were considered to have experienced a PSE from the day on which a treatment failure was declared. Treatment with the study agent was subsequently discontinued. Prohibited medications and therapies included the following: other immunomodulatory investigational agents, rituximab, cyclophosphamide, other immunosuppressive agents (except for methotrexate for azathioprine intolerance), glucocorticoids for vasculitis (>10 mg/day), glucocorticoids for other reasons (>20 mg/day for >14 days or IV glucocorticoid pulses of >125 mg), and plasmapheresis. Glucocorticoid doses were expressed as prednisone-equivalent doses.

Safety assessments. The assessment of safety included the monitoring of adverse events (AEs), Columbia-Suicide Severity Rating Scale scores (28), and immunogenicity.

Biomarker analysis. Levels of biomarkers, including ANCA (perinuclear, cytoplasmic, MPO, and PR3), serum complement (C3 and C4), and serum immunoglobulins (IgA, IgM, and IgG), and B cell levels were measured at baseline (day 0) and at multiple time points thereafter. BLYS protein concentrations were measured on day 0 only.

Statistical analysis. Initially, this study aimed to evaluate the superiority of belimumab compared with placebo in

reducing the risk of relapse in patients with AAV who were in remission. However, after the reduction in sample size, the study became exploratory in nature. Therefore, statistical analysis was performed for the primary outcome measure only. Consequently, *P* values were not generated for other comparisons. Summaries presented by induction regimen relating to relapses, AEs, and biomarkers were not prespecified in the analysis plan. The final sample size was based on feasibility, rather than statistical considerations.

Unless otherwise stated, all analyses were performed using the intent-to-treat (ITT) population, defined as all randomized patients who received at least 1 dose of study agent (belimumab or placebo). Patients who discontinued placebo or belimumab for reasons other than a PSE were expected to continue their participation in the study until they experienced a PSE or completed the study (whichever came first); these patients were included in evaluation of the primary end point.

The primary efficacy end point, time to first PSE, was analyzed via a Cox proportional hazards model adjusted for ANCA type (PR3 or MPO), disease stage at induction, and induction regimen. Continuous variables were summarized using the sample number, mean ± SD values, and median (minimum to maximum) values. Categorical variables were summarized using frequency counts and percentages.

RESULTS

Study population and patient demographics.

Overall, 164 patients with AAV were screened, and 106 were randomized to receive either belimumab (*n* = 54) or placebo

(*n* = 52), of whom 105 received ≥1 dose of study agent and were included in the ITT population. Distribution of the patients is summarized in Figure 2. Patient demographics were generally similar across the treatment groups in the ITT population (Table 1). An imbalance was evident across the age categories: the proportion of elderly patients (age ≥65 years) was higher in the belimumab group (18 [34.0%] of 53 patients) than in the placebo group (8 [15.4%] of 52 patients).

Disease characteristics at baseline were generally balanced across the treatment groups, except for the proportion of patients with relapsing disease and the duration of disease at baseline (Table 1). All patients included in the ITT population were in remission (BVAS score of 0) at baseline, and most had a VDI score higher than 0 (83 [79.0%] of 105 patients in the total population; 40 [76.9%] of 52 receiving placebo and 43 [81.1%] of 53 receiving belimumab) (Table 1). The median total VDI score was 2.0 (range 0–8) for patients in the placebo group, and 3.0 (range 0–11) for patients in the belimumab group.

The median disease duration was longer in the placebo group compared with the belimumab group (median 833 days versus 482 days). More patients included in the ITT population had been diagnosed as having GPA (83 of 105 total, including 41 [78.8%] of 52 in the placebo group and 42 [79.2%] of 53 in the belimumab group) than had been diagnosed as having MPA (22 of 105 total, including 11 [21.2%] of 52 in the placebo group and 11 [20.8%] of 53 in the belimumab group). Prior to the study, the majority of patients (78 [74.3%] of 105) had followed a cyclophosphamide induction regimen, while 27 (25.7%) of 105 had received rituximab induction therapy (Table 1).

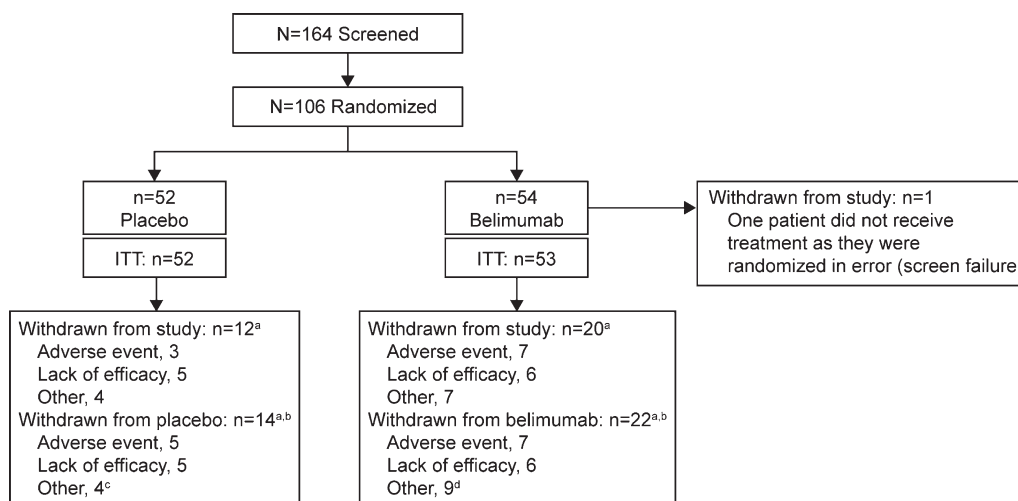


Figure 2. Distribution of patients in the intent-to-treat (ITT) population. a = not all patients who withdrew due to lack of efficacy met the protocol-specified event (PSE) criteria (*n* = 1 in the belimumab group and *n* = 2 in the placebo group did not meet the criteria), and in some cases in which patients experienced a PSE, the reason for discontinuation was reported as an adverse event rather than lack of efficacy. b = includes patients withdrawn from the study; patients who discontinued treatment with placebo or belimumab continued in the study until relapse, study withdrawal, or study completion. c = reasons for withdrawal included patient decision (*n* = 2), study termination (Italy) (*n* = 1), and protocol deviation (*n* = 1). d = reasons for withdrawal included patient decision (*n* = 3), study termination (Italy) (*n* = 1), protocol deviation (*n* = 3), and investigator decision (*n* = 2).

Table 1. Demographic and baseline disease characteristics of the patients in the intent-to-treat population*

	Placebo (n = 52)	Belimumab 10 mg/kg (n = 53)
Sex, no. (%) female	25 (48.1)	26 (49.1)
Race, no. (%)		
White	44 (84.6)	46 (86.8)
American Indian or Alaskan Native	5 (9.6)	6 (11.3)
African American/African Heritage	1 (1.9)	1 (1.9)
Asian	2 (3.8)	0
Age, mean \pm SD years	54 \pm 14	56 \pm 14
Age group, no. (%)		
<65 years	44 (84.6)	35 (66.0)
\geq 65 years	8 (15.4)	18 (34.0)
Disease classification, no. (%)		
GPA	41 (78.8)	42 (79.2)
MPA	11 (21.2)	11 (20.8)
BVAS total, median (min–max) [†]	0 (0–0)	0 (0–0)
ANCA type, no. (%) [‡]		
PR3-ANCAs	40 (76.9)	41 (77.4)
MPO-ANCAs	12 (23.1)	12 (22.6)
ANCA positivity by immunoassay, no./total (%)	22/50 (44.0)	24/49 (49.0)
Induction regimen, no. (%)		
IV cyclophosphamide	24 (46.2)	21 (39.6)
Oral cyclophosphamide	15 (28.8)	18 (34.0)
Rituximab	13 (25.0)	14 (26.4)
Current disease stage, no. (%)		
Initial diagnosis	24 (46.2)	19 (35.8)
Relapsing disease	28 (53.8)	34 (64.2)
Disease duration, median (min–max) days	833 (107–5,445)	482 (3–7,538)
Previous cyclophosphamide use, no./total (%)	34/45 (75.6)	35/47 (74.5)
Cumulative lifetime exposure to cyclophosphamide [§]		
No. with exposure (when known)	34	35
Median (min–max) dose, gm	11 (4–355)	10 (1–149)
Any damage on VDI items, no. (%)		
Overall	40 (76.9)	43 (81.1)
Musculoskeletal	4 (7.7)	9 (17.0)
Skin/mucous membranes	2 (3.8)	1 (1.9)
Ocular	7 (13.5)	11 (20.8)
Ear, nose, and throat	24 (46.2)	28 (52.8)
Pulmonary	14 (26.9)	17 (32.1)
Cardiovascular	13 (25.0)	15 (28.3)
Peripheral vascular disease	0	1 (1.9)
Gastrointestinal	1 (1.9)	0
Renal	9 (17.3)	15 (28.3)
Neuropsychiatric	14 (26.9)	12 (22.6)
Other	8 (15.4)	7 (13.2)

Table 1. (Cont'd)

	Placebo (n = 52)	Belimumab 10 mg/kg (n = 53)
Maintenance therapy, no./total (%)		
Azathioprine	46/51 (90.2)	47/52 (90.4)
Methotrexate	5/51 (9.8)	5/52 (9.6)
Average daily prednisone dose, mean \pm SD mg/day¶	7.47 \pm 2.198	7.18 \pm 2.818

* GPA = granulomatosis with polyangiitis; MPA = microscopic polyangiitis; min = minimum; max = maximum; PR3 = proteinase 3; MPO = myeloperoxidase; IV = intravenous; VDI = Vasculitis Damage Index.

† All organ system scores on the Birmingham Vasculitis Activity Score (BVAS) scale were 0 at baseline.

‡ Historical diagnosis, i.e., all patients must have been positive for antineutrophil cytoplasmic antibodies (ANCA) at some stage prior to screening.

§ Outliers are due to previous and prolonged receipt of oral cyclophosphamide.

¶ Glucocorticoid dose converted to prednisone-equivalent daily dose, averaged over 7 days up to, but not including, day 0.

Among patients receiving maintenance therapy at baseline (51 in the placebo group and 52 in the belimumab group), 46 patients (90.2%) and 47 patients (90.4%), respectively, were treated with azathioprine; the remaining 5 patients in each group received methotrexate as maintenance therapy, due to known tolerability issues (Table 1). In both treatment groups, the baseline levels of BLYS were highest in patients with rituximab-induced disease remission (mean \pm SD BLYS levels 4.5 \pm 4.00 ng/ml in those receiving placebo versus 4.5 \pm 3.40 ng/ml in those receiving belimumab), followed by patients with disease remission induced by oral cyclophosphamide (mean \pm SD BLYS levels 1.7 \pm 2.04 ng/ml in those receiving placebo versus 1.9 \pm 1.70 ng/ml in those receiving belimumab), and were lowest in those with disease remission induced by IV cyclophosphamide (mean \pm SD BLYS levels 1.1 \pm 1.23 ng/ml in those receiving placebo versus 0.8 \pm 0.34 ng/ml in those receiving belimumab)

(see Supplementary Table 1, available on the *Arthritis & Rheumatology* web site at <http://onlinelibrary.wiley.com/doi/10.1002/art.40802/abstract>).

Efficacy. For the primary end point, time to first PSE (BVAS score of ≥ 6 , presence of at least 1 predefined major BVAS item, or the receipt of prohibited medications for any reason), there was no statistically significant difference between the belimumab group and the placebo group (adjusted hazard ratio [HR] 1.07, 95% confidence interval [95% CI] 0.44–2.59; $P = 0.884$). Treatment with belimumab did not reduce the risk of a PSE in the overall study population (see Supplementary Figure 1, available on the *Arthritis & Rheumatology* web site at <http://onlinelibrary.wiley.com/doi/10.1002/art.40802/abstract>). Overall, 21 PSEs were recorded during the study (11 patients in the placebo group, 10 patients in the belimumab group) (Table 2). The median time to first PSE was

Table 2. Summary of relapses in the total intent-to-treat population and by induction regimen in the double-blind phase*

	Placebo, no./total (%)	Belimumab 10 mg/kg		
		No./total (%)	HR (95% CI)	<i>P</i>
Total population				
PSE	11/52 (21.2)†	10/53 (18.9)‡	1.07 (0.44–2.59)	0.884
Vasculitis relapse	8/52 (15.4)	6/53 (11.3)	0.88 (0.29–2.65)	0.821
Cyclophosphamide induction regimen				
PSE	7/39 (17.9)	9/39 (23.1)	–	–
Vasculitis relapse	5/39 (12.8)	6/39 (15.4)	–	–
Rituximab induction regimen				
PSE	4/13 (30.8)	1/14 (7.1)	–	–
Vasculitis relapse	3/13 (23.1)	0	–	–

* The hazard ratio (HR) with 95% confidence interval (95% CI) was calculated in the total intent-to-treat population for the risk of experiencing a protocol-specified event (PSE) or vasculitis relapse in the belimumab group relative to the placebo group. PSE was defined as a Birmingham Vasculitis Activity Score (BVAS) of ≥ 6 or presence of a major BVAS item or receipt of a prohibited medication for any reason, resulting in treatment failure. Vasculitis relapse was defined as a BVAS score of ≥ 6 or presence of a major BVAS item or receipt of a prohibited medication for vasculitis activity, resulting in treatment failure.

† Two patients were not receiving placebo at the time of the PSE, of whom 1 received the final placebo dose 2 months prior to the PSE (not vasculitis relapse) and 1 received the final placebo dose 4 months prior to the PSE (vasculitis relapse).

‡ One patient received the final belimumab dose 7 months prior to the PSE (vasculitis relapse).

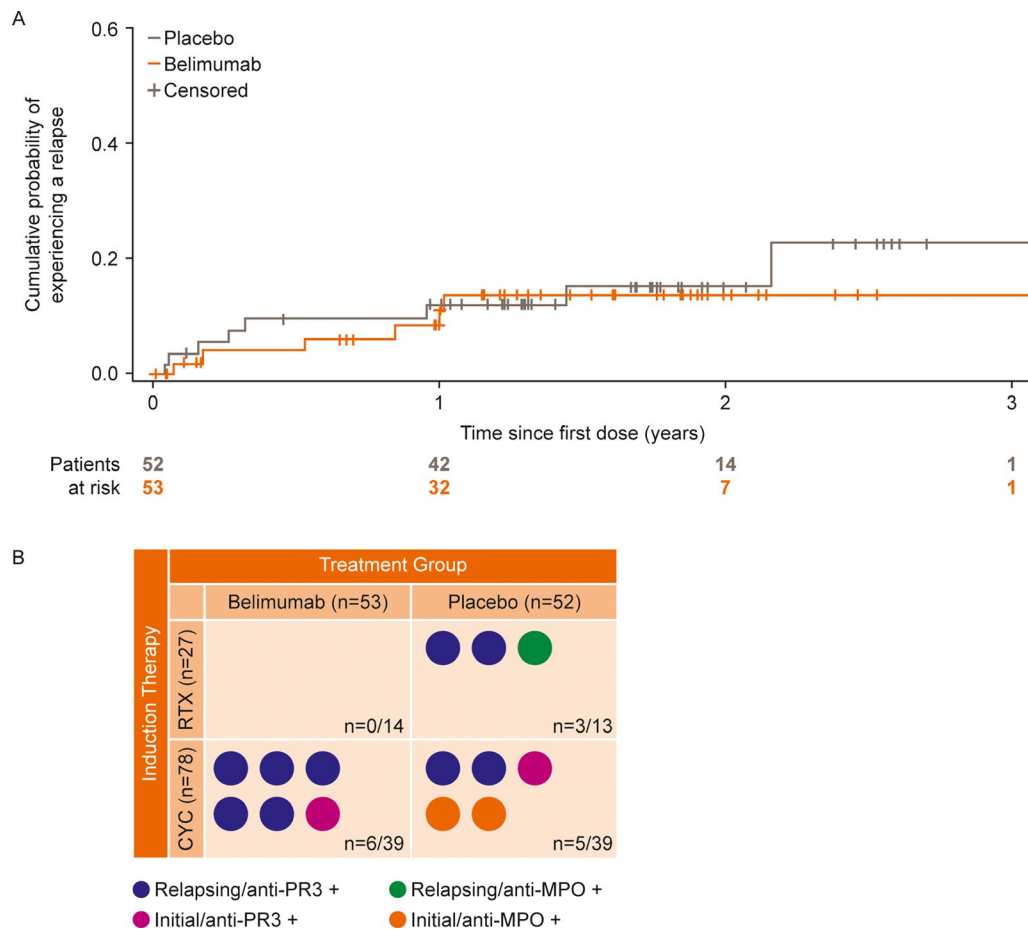


Figure 3. **A**, Kaplan-Meier plot of time to first vasculitis relapse in each treatment group. Vasculitis relapse was defined as a Birmingham Vasculitis Activity Score (BVAS) of ≥ 6 , presence of a major BVAS item, or receipt of a prohibited medication for vasculitis. **B**, Occurrence of vasculitis relapse, as defined in **A**, in patients according to disease status at screening (initial versus relapsing disease). RTX = rituximab; CYC = cyclophosphamide; PR3 = proteinase 3; MPO = myeloperoxidase.

95 days (range 15–789 days) in patients receiving placebo and 162 days (range 1–371 days) in patients receiving belimumab.

The secondary end point of time to first major relapse was not summarized, due to the limited number of major relapses that occurred during the study (none in the placebo group, 1 in the belimumab group). No absolute changes from baseline in the total VDI score were observed in the placebo group, with only minimal changes being seen in the belimumab group (mean \pm SD change in VDI in year 1, week 48, 0.0 ± 0.15 in the placebo group and 0.1 ± 0.38 in the belimumab group; in year 2, week 24, 0.0 ± 0.00 in the placebo group and 0.2 ± 0.50 in the belimumab group). The majority of patients in both treatment groups were in remission at the year 1 week 48 and year 2 week 28 time points, as well as across visits during the double-blind phase (see Supplementary Table 2, available on the *Arthritis & Rheumatology* web site at <http://onlinelibrary.wiley.com/doi/10.1002/art.40802/abstract>).

A total of 8 (15.4%) of 52 patients in the placebo group and 6 (11.3%) of 53 patients in the belimumab group experienced a vasculitis relapse (BVAS score ≥ 6 , presence of a predefined major

BVAS item, or the receipt of prohibited medications for the treatment of vasculitis) (Table 2). No statistically significant difference between the belimumab and placebo groups was identified for time to first vasculitis relapse (adjusted HR 0.88, 95% CI 0.29–2.65; $P = 0.821$) (Figure 3A). The median time to first vasculitis relapse was 105.5 days (range 15–789 days) in the placebo group and 251.0 days (range 25–371 days) in the belimumab group.

Among patients who experienced a PSE, 3 (27.3%) of 11 in the placebo group and 4 (40.0%) of 10 in the belimumab group did not qualify as having a vasculitis relapse (see Supplementary Table 3, available on the *Arthritis & Rheumatology* web site at <http://onlinelibrary.wiley.com/doi/10.1002/art.40802/abstract>).

In the placebo group, the vasculitis relapses ($n = 8$) were evenly distributed across the different induction regimens (3 of 13 having received rituximab; 5 of 39 having received cyclophosphamide) and ANCA types (5 of 40 with PR3-ANCA; 3 of 12 with MPO-ANCA), and occurred regardless of disease status at screening (3 of 24 with initial diagnosis; 5 of 28 with relapsing disease) (Table 2 and Figure 3B).

In the belimumab group, all vasculitis relapses ($n = 6$) occurred following induction of disease remission with cyclophosphamide in patients with PR3-ANCA; all but 1 patient had relapsing disease at screening (1 of 19 with initial diagnosis; 5 of 34 with relapsing disease) (Table 2 and Figure 3B). No vasculitis relapses (0 of 14) occurred in the belimumab group following the induction of remission with rituximab, compared with 3 of 13 relapses in the placebo group (Table 2).

Overall, vasculitis relapses ($n = 14$) were reported to occur in 11 of 81 PR3-ANCA-positive patients and in 3 of 24 MPO-ANCA-positive patients (Figure 3B). Relapse of vasculitis occurred irrespective of disease state at the time of induction (4 of 43 with initial diagnosis; 10 of 62 with relapsing disease) (Figure 3B).

Biomarker analysis. *B cells.* Summaries of the data revealed that the induction regimen did affect B cell populations at baseline. Levels of B cells were at or below the lower limit of quantification for patients with rituximab-induced remission. Patients with cyclophosphamide-induced remission also demonstrated notably low baseline B cell (CD19+) counts, the lowest occurring following oral administration of cyclophosphamide (IV cyclophosphamide, median 59.0 cells/mm³ [interquartile range (IQR) 20.5–97.0] in the placebo group versus median 50.0 cells/mm³ [IQR 27.0–80.0] in the belimumab group; oral cyclophosphamide, median 16.0 cells/mm³ [IQR 12.0–139.0] in the placebo group versus median 25.0 [IQR 10.0–105.0] in the belimumab group). Patients with cyclophosphamide-induced disease remission also exhibited a rapid increase in the number of circulating memory B cells (CD20+/CD27+) following belimumab treatment, which gradually returned to baseline levels, whereas no major changes in circulating memory B cells occurred in the placebo group (see Supplementary Figure 2, available on the *Arthritis & Rheumatology* web site at <http://onlinelibrary.wiley.com/doi/10.1002/art.40802/abstract>), which is consistent with the pharmacodynamic effects of belimumab on memory B cells previously observed in patients with systemic lupus erythematosus.

Belimumab had no impact on the proportion of naive (CD20+CD27-) B cells compared with placebo following cyclophosphamide induction. The number of patients with rituximab-induced remission who had quantifiable B cell data was low, with partial reconstitution occurring in only a minority of patients (2 of 13 in the placebo group; 4 of 14 in the belimumab group). Reconstitutions did not translate into vasculitis relapses.

Serum immunoglobulins. Overall, serum IgG levels declined noticeably in the belimumab group compared with the placebo group, the latter of which showed an increase in serum IgG levels, suggesting that belimumab affects antibody-secreting cells (see Supplementary Figure 3, available on the *Arthritis & Rheumatology* web site at <http://onlinelibrary.wiley.com/doi/10.1002/art.40802/abstract>). The mean percentage change from baseline in serum IgG levels at year 1, week 48 was 9.0% in the placebo group and -3.5% in the belimumab group. By year

2, week 24, the mean percentage change from baseline had reached 20.7% in placebo patients and was -0.9% in the belimumab group.

Similarly, reductions in the serum levels of both IgA and IgM were also observed in the belimumab group (for IgA, mean percentage reduction at year 1, week 48, -12.3%, and at year 2, week 24, -13.5%; for IgM, mean percentage reduction at year 1, week 48, -16.9%, and at year 2, week 24, -15.8%). In contrast, serum IgA and IgM levels were increased in the placebo group (for IgA, mean percentage increase at year 1, week 48, 7.2%, and at year 2, week 24, 6.6%; for IgM, mean percentage increase at year 1, week 48, 15.5%, and at year 2, week 24, 34.8%) (see Supplementary Figures 4 and 5, available on the *Arthritis & Rheumatology* web site at <http://onlinelibrary.wiley.com/doi/10.1002/art.40802/abstract>).

ANCA status. The numbers of patients found to be ANCA positive, as measured by immunoassay, at any time post-baseline were similar between the groups (32 [64.0%] of 50 patients receiving placebo; 30 [61.2%] of 49 patients receiving belimumab). No trends in change in ANCA status over time were observed, regardless of induction regimen. Review of individual patient data showed no apparent trends between ANCA titers and AAV relapse (data not shown).

Safety. A greater proportion of patients in the belimumab group compared with the placebo group reported at least 1 AE at any time post-baseline (92.5% of patients in the belimumab group versus 82.7% of patients in the placebo group) (Table 3). The highest incidence of AEs overall was in the “infections and infestations” system organ class (57.7% of patients receiving placebo versus 56.6% of patients receiving belimumab). Infections were the most common type of AE irrespective of induction regimen. An imbalance, however, was identified among patients with disease remission induced with rituximab, in whom infections occurred to a greater extent in the belimumab group compared with the placebo group. In this subset, 9 patients (69.2%) in the placebo group reported developing 21 infections, while in the belimumab group, 14 patients (100.0%) reported developing 50 infections (3 serious infections) (Table 3). No specific events were identified as driving this imbalance.

Serious AEs occurred to a similar extent in both treatment groups (30.8% in the placebo group versus 34.0% in the belimumab group). The highest incidence of serious AEs was in the “infections and infestations” system organ class (7.7% in the placebo group versus 7.5% in the belimumab group) (Table 3). Overall, 7 patients (13.5%) in the placebo group and 9 (17.0%) in the belimumab group experienced AEs leading to study drug discontinuation, and 1 death, attributable to ischemic stroke considered by the investigator to be unrelated to the study drug, occurred in a patient in the belimumab group; the patient was not receiving belimumab at the time of death (Table 3).

Table 3. Summary of adverse events at any time post-baseline in the total intent-to-treat population and by induction regimen during the double-blind phase*

	Induction regimen							
	Total population		Intravenous cyclophosphamide		Oral cyclophosphamide		Rituximab	
	Placebo (n = 52)	Belimumab 10 mg/kg (n = 53)	Placebo (n = 24)	Belimumab 10 mg/kg (n = 21)	Placebo (n = 15)	Belimumab 10 mg/kg (n = 18)	Placebo (n = 13)	Belimumab 10 mg/kg (n = 14)
Any adverse event	43 (82.7)	49 (92.5)	17 (70.8)	20 (95.2)	13 (86.7)	15 (83.3)	13 (100.0)	14 (100.0)
Infections and infestations	30 (57.7)	30 (56.6)	11 (45.8)	8 (38.1)	10 (66.7)	8 (44.4)	9 (69.2)	14 (100.0)
Related adverse events	17 (32.7)	20 (37.7)	8 (33.3)	6 (28.6)	2 (13.3)	5 (27.8)	7 (53.8)	9 (64.3)
Serious adverse events	16 (30.8)	18 (34.0)	7 (29.2)	9 (42.9)	5 (33.3)	3 (16.7)	4 (30.8)	6 (42.9)
Infections and infestations	4 (7.7)	4 (7.5)	1 (4.2)	1 (4.8)	3 (20.0)	0	0	3 (21.4)
Injury, poisoning, and procedural complications	1 (1.9)	3 (5.7)	1 (4.2)	1 (4.8)	0	1 (5.6)	0	1 (7.1)
Blood and lymphatic system disorders	2 (3.8)	1 (1.9)	2 (8.3)	0	-	-	0	1 (7.1)
General disorders	2 (3.8)	1 (1.9)	2 (8.3)	0	-	-	-	-
Immune system disorders	0	3 (5.7)	0	2 (9.5)	-	-	0	1 (7.1)
Neoplasms benign, malignant, and unspecified	0	3 (5.7)	0	1 (4.8)	0	1 (5.6)	-	-
Respiratory, thoracic, and mediastinal disorders	2 (3.8)	1 (1.9)	0	1 (4.8)	1 (6.7)	0	1 (7.7)	0
Nervous system disorders	0	2 (3.8)	0	2 (9.5)	-	-	-	-
Severe adverse event	7 (13.5)	11 (20.8)	4 (16.7)	5 (23.8)	1 (6.7)	0	2 (15.4)	6 (42.9)
Any malignancies (including NMSC)	0	4 (7.5)	0	2 (9.5)	0	2 (11.1)	0	0
Adverse event leading to study agent discontinuation	7 (13.5)	9 (17.0)	3 (12.5)	6 (28.6)	1 (6.7)	1 (5.6)	3 (23.1)	2 (14.3)
Adverse event leading to study withdrawal	6 (11.5)	8 (15.1)	3 (12.5)	6 (28.6)	1 (6.7)	1 (5.6)	2 (15.4)	1 (7.1)
Death	0	1 (1.9)†	0	1 (4.8)	0	0	0	0

* Values are the number (%) of patients. NMSC = nonmelanoma skin cancer.

† Attributable to ischemic stroke, considered by the investigator to be unrelated to the study drug.

Malignancies occurred in 4 patients (7.5%) receiving belimumab; there were no malignancies in the placebo group (Table 3). Malignancies in the belimumab group were reported only among patients who received cyclophosphamide during the induction phase. This imbalance was predominantly driven by 3 patients having nonmelanoma skin cancer (all occurring in elderly patients age ≥ 65 years). The other malignancies were plasma cell myeloma (1 patient) and anal cancer (1 patient; this patient also had a nonmelanoma skin cancer). Furthermore, the higher proportion of elderly patients receiving belimumab (18 [34.0%] of 53) compared with those receiving placebo (8 [15.4%] of 52) may have confounded the results. Overall, no clinically meaningful differences between treatment groups, and no trends over time, were identified for any malignancies.

No trends of clinical concern and no clinically meaningful differences between treatment groups were observed for hematologic, clinical chemistry, serum IgG, or urinalysis values. None of the patients in the placebo group and 4 patients (7.5%) in the belimumab group exhibited a grade 3 IgG value (250–399 mg/dl) at any time post-baseline; no severe/serious infections or infections leading to treatment discontinuation were reported in these 4 patients. No patients in either treatment group had a grade 4 IgG value (< 250 mg/dl).

Pharmacokinetics. Belimumab levels close to the steady-state concentrations were reached early in the trial, and were maintained throughout the treatment period. The median peak concentration at week 2 was 297 $\mu\text{g/ml}$, which was similar to that at week 24 (325 $\mu\text{g/ml}$). Furthermore, the median trough concentrations at week 8 (90.9 $\mu\text{g/ml}$) were similar to those at week 48 (84.7 $\mu\text{g/ml}$).

DISCUSSION

This study investigated the safety and efficacy of belimumab, a monoclonal antibody that inhibits BLYS, in addition to standard of care, for the maintenance of remission in AAV following a standard induction regimen. This is also the first study to provide data related to the effect of sequential treatment with rituximab followed by belimumab in AAV.

Current European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the induction of remission in AAV consist of treatment with a combination of glucocorticoids and either cyclophosphamide or rituximab (3). Two randomized controlled trials (the Rituximab in ANCA-Associated Vasculitis and Rituximab versus Cyclophosphamide in ANCA-Associated Vasculitis trials) identified rituximab as being non-inferior to cyclophosphamide; however, rituximab may be more effective for the treatment of relapsing disease (7,29). In addition, EULAR/ERA-EDTA guidelines for the maintenance of remission in AAV recommend treatment with azathioprine, rituximab, metho-

trexate, or mycophenolate mofetil (3). Full drug-free remission can be achieved in many patients with AAV; however, relapse is common and there is a need for better treatment regimens for the maintenance of remission (3,4,7).

As corroborated by results obtained during this study, BLYS levels are known to rise following therapy with rituximab (6,18,30). Increased BLYS levels may lead to autoreactive B cell reemergence, thus promoting relapse (18). Consequently, targeting BLYS via the action of belimumab may help to prolong remission following induction of remission with rituximab for AAV.

The overall rate of a PSE (21 [20.0%] of 105 patients) and vasculitis relapse (14 [13.3%] of 105 patients) in the current study was low compared with that reported in the literature (4,7). The majority of patients remained in remission throughout the double-blind phase; this may have been influenced by their ongoing treatment with azathioprine and glucocorticoids (31). The use of prolonged treatment with azathioprine and oral glucocorticoids has been shown to reduce relapse rates in GPA and MPA (31). Belimumab plus maintenance therapy with azathioprine and oral glucocorticoids did not reduce the risk of a PSE or vasculitis relapse in patients with AAV who were in remission.

No vasculitis relapses (0 of 14) occurred in patients receiving rituximab for induction of disease remission who were subsequently treated with belimumab. In contrast, 3 (23.1%) of 13 patients in the placebo group with disease remission induced with rituximab did experience a vasculitis relapse. This finding in a small subgroup of patients warrants further investigation and is consistent with data from preclinical models and case studies suggesting that dual B cell–targeted immunotherapy (B cell depletion [i.e., rituximab] plus BLYS blockade [i.e., belimumab]) may be more efficacious than either therapy prescribed alone (32–35). However, it should be noted that both the sample size and the number of events in the current study were small.

No new safety signals were identified for belimumab. Serious and nonserious infections were balanced across treatment arms; however, an imbalance was observed for patients with rituximab-induced remission. Infectious AEs in these patients were higher in the belimumab group compared with the placebo group, primarily driven by nonserious events. Furthermore, no differences in Ig-related toxicity were observed in this study. The imbalance in malignancy events observed between treatment groups and induction regimens may have been related to the greater proportion of elderly patients receiving belimumab compared with those receiving placebo.

Several limitations related to the study should be considered. First, a number of recruitment difficulties, primarily relating to the advancement of standard of care treatment options, including the licensing of rituximab for the treatment of AAV, led to truncation of the intended sample size from ~ 300 to ~ 100 patients. Furthermore, evidence for the superior efficacy of rituximab as a therapy for the maintenance of remission, compared with azathioprine, was communicated

after the study started (4). Consequently, the study consists of a small sample size with reduced power for the primary outcome analysis; caution is therefore required in interpretation of the results. Future studies regarding the maintenance of remission in AAV with belimumab as monotherapy may increase the ability of the trial to detect potential treatment benefit.

In conclusion, the addition of belimumab to a regimen of azathioprine with low-dose glucocorticoids for the maintenance of remission in AAV did not reduce the risk of a PSE or vasculitis relapse. However, patients with rituximab-induced remission who were subsequently treated with belimumab exhibited no vasculitis relapses. This observation warrants further investigation.

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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. Merkel 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. Jayne, Luqmani, Ji, Roth, Merkel.

Acquisition of data. Blockmans, Luqmani, Moiseev.

Analysis and interpretation of data. Jayne, Luqmani, Moiseev, Ji, Green, Hall, Roth, Henderson, Merkel.

ROLE OF THE STUDY SPONSOR

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APPENDIX A: BREVAS STUDY COLLABORATORS

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