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Efficacy and Safety of Belimumab and Azathioprine for Maintenance of Remission in ANCA-Associated Vasculitis: A Randomized Controlled Study

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ABSTRACT (250 words)

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

***Methods*.** This double-blind, placebo-controlled, multicenter study (BEL115466/NCT01663623) randomized (1:1) patients (≥18 years) with AAV following remission induction with rituximab/cyclophosphamide and glucocorticoids. Patients received azathioprine 2 mg/kg/day, oral glucocorticoids, and placebo/intravenous belimumab 10 mg/kg. Primary endpoint was time to first protocol-specified event (PSE), defined as Birmingham Vasculitis Activity Score (BVAS) ≥6, ≥1 major BVAS item, or receipt of prohibited medication (adjusted for ANCA type [proteinase 3 (PR3)/myeloperoxidase (MPO)], disease stage at induction, and induction regimen). Vasculitis relapse was defined as PSE BVAS activity, or receipt of prohibited medications for vasculitis. Changes in treatment practice led to study truncation from 300 to ~100 patients.

***Results*.** The intention-to-treat population totaled 105 patients (placebo, 52 [40 PR3-ANCA; 12 MPO-ANCA]; belimumab, 53 [41 PR3-ANCA; 12 MPO-ANCA]: induced by rituximab, 27; cyclophosphamide, 78. Compared with placebo, belimumab did not reduce PSE risk (adjusted HR=1.07; 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); overall PSE rate was low (placebo, 11/52 [21.2%]; belimumab 10/53 [18.9%]). Vasculitis relapse in the placebo group (n=8) occurred independently of induction regimen/disease stage, or ANCA type. All vasculitis relapses in the belimumab group (n=6) were in cyclophosphamide-induced, anti-PR3-ANCA-associated patients. Adverse events occurred in 49/53 belimumab (92.5%) and 43/52 placebo (82.7%) recipients, with no new safety concerns.

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

Keywords: ANCA-Associated Vasculitis, B-Lymphocyte, Randomized Trial, Vasculitis

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 disease pathogenesis of AAV (1,2).

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 to 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 immunoglobulin G1λ (IgG1λ) monoclonal antibody against BLyS, is licensed for adults with active, autoantibody-associated systemic lupus erythematosus, 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 with either rituximab or cyclophosphamide, with glucocorticoids, tested within a randomized controlled trial setting.

PATIENTS AND METHODS

Study design

This double-blind, placebo controlled, multicenter, multinational study (GlaxoSmithKline study BEL115466; clinicaltrials.gov identifier, NCT01663623; EudraCT number, 2011-004569-33) (23) randomized (1:1) patients with GPA or MPA to receive 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 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 to treatment allocation at all times. The randomization schedule was produced by the company Human Genome Sciences (HGS) and subjects were stratified by ANCA Type (anti-PR3 vs. anti-MPO), disease stage at induction (initial vs. relapsing) and induction regimen (IV CYC vs. oral CYC vs. rituximab). Subjects were assigned to their treatment group via an interactive web response system (IWRS) 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 at Days 0, 14, 28, and every 28 days thereafter until either study completion or relapse. BREVAS was originally a Phase III study investigating the maintenance or remission in 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 randomized, leading to variable durations of treatment. The sample size was reduced from ~300 to ~100 patients.

Institutional review board approval and ethical considerations

This study was reviewed and approved by the appropriate ethics committee or institutional review board in accordance with the International Conference for Harmonization of Technical Requirements for Pharmaceuticals for Human Use, Good Clinical Practice guidelines, the ethical 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 ≥18 years old, with a clinical diagnosis of GPA or MPA according to the 2012 Chapel Hill definitions (25), and tested positive for proteinase 3 (PR3-) or myeloperoxidase (MPO-) ANCA (current or historical). 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 induction regimens: a single course of rituximab (375 mg/m^2/week for 4 weeks), plus high-dose glucocorticoids (HDGCS); or two doses of IV rituximab (1 g) separated by a 2-week interval, plus HDGCS; or oral cyclophosphamide (2 mg/kg/day); or pulses of IV cyclophosphamide (15 mg/kg) administered 2 weeks apart for three doses followed by further pulses every 3 weeks, plus HDGCS. Additionally, patients were in remission at Day 0 (Birmingham Vasculitis Activity Score [BVAS] version 3 [v.3] = 0) and receiving glucocorticoids (presented as prednisone-equivalent doses) at ≤10 mg/day (on two 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 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 or five half-lives of the agent (whichever was longest) of Day 0; any acute or chronic infections requiring hospitalization (within 60 days of Day 0) and/or the administration 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.

OBJECTIVE

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 induction regimen.

Efficacy endpoints and assessments

Efficacy assessments and measures of disease severity were performed according to the BVAS and Vasculitis Damage Index (VDI) scales. The primary endpoint was time to first protocol-specified event (PSE), which was defined as BVAS (v.3) ≥6, ≥1 pre-defined BVAS (v.3) major item, or the receipt of prohibited medications, for any reason, resulting in treatment failure as adjudicated by the sponsor (26,27). 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 ≥6, 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 endpoint was time from Day 0 to the first major relapse, defined as the occurrence of ≥1 major BVAS item. Efficacy assessments for clinical

disease activity (BVAS) were performed at screening and Day 0, followed by Week 2, Week 4, and every 4 weeks thereafter until study exit. Other efficacy endpoints included absolute change in VDI, and proportion of patients in remission (defined as BVAS = 0 and glucocorticoid dose ≤10 mg/day) at double-blind Week 48 of Year 1, double-blind Week 24 of Year 2 and 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 as experiencing a PSE from the day on which they were declared a treatment failure. Treatment with study agent was subsequently discontinued. Prohibited medications and therapies included: other immunomodulatory investigational agents, rituximab, cyclophosphamide, other immunosuppressive agents (exception: methotrexate for azathioprine intolerance), glucocorticoids for vasculitis (>10 mg/day), glucocorticoids for other reasons (>20 mg/day for >14 days or IV glucocorticoids pulses >125 mg), and plasmapheresis. Glucocorticoid doses were expressed as prednisone equivalents.

Safety assessments

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

Biomarker analysis

Biomarkers including ANCA (perinuclear-ANCA, cytoplasmic-ANCA, MPO-ANCA, and PR3-ANCA), serum complement (C3 and C4), 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 at Day 0 only.

Statistical analysis

Initially this study aimed to evaluate the superiority of belimumab compared with placebo in reducing the risk of relapse for patients with AAV that was in remission. However, after the sample size reduction, 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, adverse events (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 intention-to-treat (ITT) population, defined as all randomized patients who received at least one dose of study agent (belimumab or placebo). Patients who discontinued placebo or belimumab for reasons other than PSE were expected to continue on the study until they experienced a PSE or completed (whichever came first); these patients were included in evaluation of the primary endpoint. The primary efficacy endpoint, 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 (n), mean, standard deviation (SD), median, minimum (min), and maximum (max). Categorical variables were summarized using, frequency counts (n), and percentages.

RESULTS

Study population and patient demographics

Overall, 164 patients were screened and 106 randomized (belimumab n=54; placebo n=52), with 105 receiving ≥1 dose of study agent and being included in the ITT population. Patient disposition is summarized in **Figure 2.** Patient demographics were generally similar across

both treatment groups for the ITT population **(Table 1).** An imbalance was evident across the age categories; the proportion of elderly patients (≥65 years of age) was higher in the belimumab group (18/53 [34.0%]) than the placebo group (8/52 [15.4%]).

Baseline disease characteristics were generally balanced across treatment groups, except for the proportion of patients with relapsing disease, and disease duration at baseline **(Table 1).** All patients included in the ITT population were in remission at baseline (BVAS=0) and most had a VDI score greater than zero (83/105 [79.0%]; placebo, 40/52 [76.9%]; belimumab, 43/53 [81.1%]) **(Table 1)**. The median (range) VDI total score was 2.0 (0, 8) for patients in the placebo group and 3.0 (0, 11) for patients in the belimumab group. Median disease duration was longer in the placebo group (833 days) compared with the belimumab group (482 days). More patients included in the ITT population had been diagnosed with GPA (83/105; placebo, 41/52 [78.8%]; belimumab, 42/53 [79.2%]) than MPA (22/105; placebo, 11/52 [21.2%]; belimumab, 11/53 [20.8%]). The majority of patients (78/105 [74.3%]) had followed a cyclophosphamide induction regimen, while 27/105 (25.7%) received rituximab induction therapy, prior to the study **(Table 1)**.

Among patients receiving maintenance therapy at baseline (placebo, 51; belimumab, 52), 46/51 (90.2%; placebo group) and 47/52 (90.4%; belimumab group) were treated with azathioprine; the remaining 5 patients in each group received methotrexate due to known tolerability issues **(Table 1)**. In both treatment groups, mean (SD) baseline levels of BLyS were highest in rituximab-induced patients (placebo, 4.5 [4.00] ng/mL; belimumab, 4.5 [3.40] ng/mL), followed by those induced with oral cyclophosphamide (placebo, 1.7 [2.04] ng/mL; belimumab, 1.9 [1.70] ng/mL), and were lowest in those induced with IV

cyclophosphamide (placebo, 1.1 [1.23] ng/mL; belimumab, 0.8 [0.34] ng/mL) **(Supplementary Table 1).**

Efficacy

For the primary endpoint, time to first PSE (BVAS [v.3] ≥6, a predefined BVAS [v.3] major item, or the receipt of prohibited medications for any reason), there was no statistically significant difference between the belimumab and placebo groups (adjusted hazard ratio 1.07; 95% CI: 0.44, 2.59; p=0.884). Belimumab did not reduce the risk of PSE in the overall study population (**Supplementary Figure 1).** Overall, 21 PSEs were recorded during the study (placebo, n=11; belimumab, n=10) **(Table 2)**. The median (range) time to first PSE was 95 (15, 789) days for patients in the placebo group and 162 (1, 371) days for patients in the belimumab group. The secondary endpoint of time to first major relapse was not summarized due to the limited number of major relapses during the study (placebo, 0; belimumab, 1). No absolute mean (SD) changes in VDI total score from baseline were observed in the placebo group, with only minimal changes being seen in the belimumab group (Year 1, Week 48: placebo, 0.0 [0.15]; belimumab, 0.1 [0.38]; Year 2, Week 24: placebo, 0.0 [0.00], belimumab, 0.2 [0.50]). The majority of patients in both treatment groups were in remission at Year 1 Week 48 and Year 2 Week 28, and across visits, during the double-blind phase (**Supplementary Table 2**)**.**

A total of 8/52 (15.4%) patients in the placebo group and 6/53 (11.3%) patients in the belimumab group experienced a vasculitis relapse (BVAS ≥6, a pre-defined BVAS major 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 hazard ratio 0.88; 95% CI: 0.29, 2.65; p=0.821) **(Figure 3a)**. Median (range) time to first vasculitis relapse was 105.5 (15, 789) days in the placebo group and 251.0 (25, 371) days in the belimumab group**.**

Among patients who experienced a PSE, 3/11 (27.3%) in the placebo group and 4/10 (40.0%) in the belimumab group did not qualify as having a vasculitis relapse **(Supplementary Table 3)**.

In the placebo group, the vasculitis relapses (n=8) were evenly distributed across different induction regimens (rituximab, 3/13; cyclophosphamide, 5/39), ANCA types (PR3-ANCA, 5/40; MPO-ANCA, 3/12), and occurred regardless of disease status at screening (initial diagnosis, 3/24; relapsing disease, 5/28) (**Table 2; Figure 3b).** In the belimumab group, all vasculitis relapses (n=6) occurred following cyclophosphamide induction in patients with PR3-ANCA; all but one patient had relapsing disease at screening (initial diagnosis, 1/19; relapsing disease, 5/34) **(Table 2; Figure 3b)**. Following the induction of remission with rituximab, there were no vasculitis relapses in the belimumab group (0/14), compared with 3/13 relapses in the placebo group **(Table 2)**.

Overall, vasculitis relapses (n=14) were reported in 11/81 PR3-ANCA patients and 3/24 MPO-ANCA patients **(Figure 3b)**. Relapse occurred irrespective of disease state at induction (initial diagnosis, 4/43; relapsing disease, 10/62) **(Figure 3b)**.

Biomarker analysis

B cells

Summaries of the data revealed that the induction regimen did affect B-cell populations at baseline. Levels were at or below the lower limit of quantification for rituximab-induced patients. Cyclophosphamide-induced patients also demonstrated notably low baseline B-cell counts (CD19+), the lowest occurring following oral administration (median (quartile 1, quartile 3) cells/mm^3; IV cyclophosphamide: placebo, 59.0 (20.5, 97.0); belimumab, 50.0 (27.0, 80.0); oral cyclophosphamide: placebo, 16.0 (12.0, 139.0); belimumab, 25.0 (10.0, 105,0)). Such cyclophosphamide-induced patients also exhibited a rapid increase in circulating memory B cells (CD20+/CD27+) following

belimumab treatment, before gradually returning to baseline levels; no major changes occurred in the placebo group, consistent with belimumab pharmacodynamic effects on memory B cells in SLE **(Supplementary Figure 2)**. Belimumab had no impact on the proportion of naïve (CD20+CD27−) B cells compared with placebo following cyclophosphamide induction. The number of rituximab-induced patients with quantifiable B-cell data was low, with partial reconstitution occurring in only a minority of patients (placebo, 2/13; belimumab, 4/14). Reconstitutions did not translate into vasculitis relapses.

Serum immunoglobulins

Overall serum IgG levels declined noticeably in the belimumab group compared with the placebo group where an increase was seen; suggesting that belimumab affects antibody-secreting cells **(Supplementary Figure 3)**. Mean percentage change from baseline at Year 1, Week 48, was 9.0% in the placebo group and −3.5% in the belimumab group. By Year 2, Week 24, mean percentage change from baseline had reached 20.7% for placebo patients and was −0.9% for the belimumab group. Mean percentage reductions in both IgA and IgM levels were also observed in the belimumab group (IgA: Year 1 Week 48, −12.3%; Year 2 Week 24, −13.5%; IgM: Year 1 Week 48, −16.9%; Year 2 Week 24, −15.8%) compared with increases in the placebo group (IgA: Year 1 Week 48, 7.2%; Year 2 Week 24, 6.6%; IgM: Year 1 Week 48, 15.5%; Year 2 Week 24, 34.8%) **(Supplementary Figures 4 and 5).**

ANCA status

Numbers of patients found to be ANCA positive at any time post baseline were similar between groups as measured by immunoassay (placebo, 32/50 [64.0%]; belimumab, 30/49 [61.2%]). 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 reported at least one AE at any time post baseline, compared with the placebo group (placebo, 82.7%; belimumab, 92.5%) **(Table 3)**. The highest incidence of AEs overall was in the "infections and infestations" system organ class (placebo, 57.7%; belimumab, 56.6%). Infections were the most common type of AE irrespective of induction regimen. An imbalance, however, was identified among patients induced with rituximab, in whom infections occurred to a greater extent in the belimumab group compared with the placebo group. Nine patients (69.2%) in the placebo group reported 21 infections; in the belimumab group, 14 patients (100.0%) reported 50 infections (3 serious) **(Table 3)**. No specific events were identified as driving this imbalance**.**

Serious AEs occurred to a similar extent in both treatment groups (placebo, 30.8%; belimumab, 34.0%;), the highest incidence was in the "infections and infestations" system organ class (placebo, 7.7%; belimumab 7.5%) **(Table 3)**. Overall, 7 (13.5%) patients in the placebo group and 9 (17.0%) in the belimumab group experienced AEs leading to study drug discontinuation, and one death due to ischemic stroke, considered by the investigator to be unrelated to study drug, occurred in the belimumab group; the patient was not receiving belimumab at the time of death **(Table 3).** Malignancies occurred in 4 (7.5%) patients 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 three nonmelanoma skin cancers (all occurring in elderly patients ≥65 years of age). The other malignancies were plasma cell myeloma (1 patient) and anal cancer (1 patient; this patient also had a nonmelanoma skin cancer). Additionally, the higher proportion of elderly patients receiving belimumab (18/53 [34.0%]), compared with those receiving placebo (8/52 [15.4%]) may have confounded the results. Overall, no clinically meaningful differences between treatments 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 hematological, clinical chemistry, IgG or urinalysis values. No patients in the placebo group, and 4 (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 four patients. No patients in either group had a Grade 4 IgG value (<250 mg/dL).

Pharmacokinetics

Belimumab levels close to steady-state concentration were reached early in the trial and maintained throughout the treatment period. Median peak concentration at Week 2 was 297 µg/mL, which was similar to that at Week 24 (325 µg/mL). Furthermore, median trough concentrations at Week 8 (90.9 µg/mL) were similar to those at Week 48 (84.7 µg/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 (RAVE and RITUXVAS) identified rituximab as non-inferior to cyclophosphamide; however, rituximab may be more effective for the treatment of relapsing disease (7,28). Additionally, EULAR/ERA-EDTA guidelines for the maintenance of remission in AAV recommend treatment with azathioprine, rituximab, methotrexate 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 (6,18,29). Increased BLyS 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 PSE (21/105 [20.0%]) and vasculitis relapse (14/105 [13.3%]) 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 (30). The use of prolonged azathioprine and oral glucocorticoids has been shown to reduce relapse rates in GPA/MPA (30). Belimumab plus maintenance therapy with azathioprine and oral glucocorticoids did not reduce the risk of PSE or vasculitis relapse in patients with AAV who were in remission.

No vasculitis relapses occurred in patients receiving rituximab for induction who were subsequently treated with belimumab (0/14). By contrast, 3/13 (23.1%) patients in the placebo groups who had been 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] + BLyS blockade [i.e., belimumab]) may be more efficacious than either therapy prescribed alone (31-34). 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 non-serious infections were balanced across treatment arms; however, an imbalance was observed for rituximab-induced patients. Infectious AEs in these patients were higher in the belimumab group compared with the placebo group, primarily driven by non-serious 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 than placebo.

Several limitations relating 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; and 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 azathioprine and low dose glucocorticoids for the maintenance of remission in AAV did not reduce the risk of 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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FIGURE LEGENDS AND TABLES

Figure 1. Study Design

BVAS - Birmingham Vasculitis Activity Score; IV - intravenous; PSE - protocol-specified event;

R – randomization.

Figure 2. Patient disposition

[a]Not all patients who withdrew due to lack of efficacy met PSE criteria (n=1 in the belimumab group and n=2 in the placebo group did not); and in some cases where patients experienced PSEs, the discontinuation reason was reported as an adverse event rather than lack of efficacy.

[b]Includes patients withdrawn from study; patients who discontinued placebo or belimumab continued in the study until relapse, study withdrawal or study completion.

[c]Patient decision, n=2; study termination (Italy), n=1; protocol deviation, n=1.

[d]Patient decision, n=3; study termination (Italy), n=1; protocol deviation, n=3; investigator decision, n=2.

AE - adverse event; BEL - belimumab; ITT- intention to treat; PBO - placebo; PSE - protocol-specified event.

Figure 3. (A) Kaplan–Meier plot of time to first vasculitis relapse[a]; (B) vasculitis relapse[a] by initial/relapsing disease at screening[b]

[a] Vasculitis relapse is defined as BVAS ≥6, or a major BVAS item, or receipt of a prohibited medications for vasculitis.

[b] 'Initial' and 'relapsing' refer to baseline disease status.

CYC - cyclophosphamide; MPO - myeloperoxidase; PR3 - proteinase 3; RTX - rituximab.

Table 1. Demographic and baseline characteristics in the intention-to-treat population)

	Placebo (n=52)	Belimumab 10 mg/kg (n=53)
Sex, n (%)		
Female	25 (48.1)	26 (49.1)
Race, n (%)		
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
Mean age, years (SD)	54 (14)	56 (14)
Age group, n (%)		
<65 years	44 (84.6)	35 (66.0)
≥65 years	8 (15.4)	18 (34.0)
Disease classification, n (%)		
GPA	41 (78.8)	42 (79.2)
MPA	11 (21.2)	11 (20.8)
BVAS total, median (min, max)[a]	0 (0, 0)	0 (0, 0)
ANCA type, n (%)[b]		
PR3-ANCA	40 (76.9)	41 (77.4)
MPO-ANCA	12 (23.1)	12 (22.6)
ANCA positivity at baseline[c]		
n	50	49
Yes, n (%)	22 (44.0)	24 (49.0)
Induction regimen, n (%)		
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, n (%)		
Initial diagnosis	24 (46.2)	19 (35.8)
Relapsing disease	28 (53.8)	34 (64.2)
Median disease duration, days (min, max)	833 (107, 5445)	482 (3, 7538)
Previous cyclophosphamide use		
n	45	47
Yes, n (%)	34 (75.6)	35 (74.5)
Cumulative lifetime exposure to cyclophosphamide (where known, g)[d]		
n	34	35
Median (min, max)	11 (4, 355)	10 (1, 149)
Any damage on Vasculitis Damage Index items, n (%)		
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)

	Placebo (n=52)	Belimumab 10 mg/kg (n=53)
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)
Maintenance therapy		
n	51	52
Azathioprine, n (%)	46 (90.2)	47 (90.4)
Methotrexate, n (%)	5 (9.8)	5 (9.6)
Average Daily Prednisone dose (mg/day)[e]		
Mean (SD)	7.47 (2.198)	7.18 (2.818)

[a]All organ system scores were 0 at baseline.

[b]Historical diagnosis (all patients must have been positive for ANCA at some stage prior to screening).

[c]Determined by immunoassay.

[d]Outliers are due to previous and prolonged receipt of oral cyclophosphamide.

[e]Glucocorticoid dose converted to prednisone-equivalent daily dose, averaged over 7 days up to but not including Day 0.

ANCA - antineutrophil cytoplasmic antibody; BVAS - Birmingham Vasculitis Activity Score; GPA - Granulomatosis with polyangiitis; IV - intravenous; max - maximum; min - minimum; MPA - microscopic polyangiitis; MPO - myeloperoxidase; PR3 - proteinase 3; SD - standard deviation.

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

	Number of patients with relapse, n (%)	Placebo (n=52)	Belimumab 10 mg/kg (n=53)
Total population	PSE[a]	11 (21.2)[b]	10 (18.9)[c]
	HR (95% CI), p-value	1.07 (0.44, 2.59), p=0.884	
	Vasculitis relapse[d]	8 (15.4)	6 (11.3)
	HR (95% CI), p-value	0.88 (0.29,2.65), p=0.821	
Cyclophosphamide induction regimen	**Number of patients, n (%)**	**n=39**	**n=39**
	PSE[a]	7 (17.9)	9 (23.1)
	Vasculitis relapse[d]	5 (12.8)	6 (15.4)
Rituximab induction regimen	**Number of patients, n (%)**	**n=13**	**n=14**
	PSE[a]	4 (30.8)	1 (7.1)
	Vasculitis relapse[b]	3 (23.1)	0

[a]PSE is defined as BVAS ≥6 OR a major BVAS item OR receipt of a prohibited medication for any reason resulting in treatment failure.

[b]Two patients were not receiving placebo at the time of PSE; one patient received the final placebo dose 2 months prior to PSE (not vasculitis relapse); one patient received the final placebo dose 4 months prior to PSE (vasculitis relapse).

[c]One patient received the final belimumab dose 7 months prior to PSE (vasculitis relapse).[d]Vasculitis relapse is defined as BVAS ≥6 OR a major BVAS item OR receipt of a prohibited medication for vasculitis activity resulting in treatment failure.

BVAS - Birmingham Vasculitis Activity Score; CI - confidence interval; HR - hazard ratio; PSE - protocol-specified event.

Any time post baseline (incidence ≥2 for the ITT)	Number (%) of patients							
	Total ITT		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)**
Malignancies								
Any malignancies (including NMSC)	0	4 (7.5)	0	2 (9.5)	0	2 (11.1)	0	0

Any time post baseline (incidence ≥2 for the ITT)	Number (%) of patients							
	Total ITT		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)
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)[a]	0	1 (4.8)	0	0	0	0

[a]Ischemic stroke, considered by the investigator to be unrelated to study drug.

ITT - intention to treat; NMSC - nonmelanoma skin cancer.