ORIGINAL ARTICLE

Oral Glucocorticoid–Sparing Effect of Benralizumab in Severe Asthma

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ABSTRACT

BACKGROUND

Many patients with severe asthma rely on oral glucocorticoids to manage their disease. We investigated whether benralizumab, a monoclonal antibody directed against the alpha subunit of the interleukin-5 receptor that significantly reduces the incidence of asthma exacerbations, was also effective as an oral glucocorticoid–sparing therapy in patients relying on oral glucocorticoids to manage severe asthma associated with eosinophilia.

METHODS

In a 28-week randomized, controlled trial, we assessed the effects of benralizumab (at a dose of 30 mg administered subcutaneously either every 4 weeks or every 8 weeks [with the first three doses administered every 4 weeks]) versus placebo on the reduction in the oral glucocorticoid dose while asthma control was maintained in adult patients with severe asthma. The primary end point was the percentage change in the oral glucocorticoid dose from baseline to week 28. Annual asthma exacerbation rates, lung function, symptoms, and safety were assessed.

RESULTS

Of 369 patients enrolled, 220 underwent randomization and started receiving benralizumab or placebo. The two benralizumab dosing regimens significantly reduced the median final oral glucocorticoid doses from baseline by 75%, as compared with a reduction of 25% in the oral glucocorticoid doses in the placebo group ($P<0.001$ for both comparisons). The odds of a reduction in the oral glucocorticoid dose were more than 4 times as high with benralizumab as with placebo. Among the secondary outcomes, benralizumab administered every 4 weeks resulted in an annual exacerbation rate that was 55% lower than the rate with placebo (marginal rate, 0.83 vs. 1.83, $P=0.003$), and benralizumab administered every 8 weeks resulted in an annual exacerbation rate that was 70% lower than the rate with placebo (marginal rate, 0.54 vs. 1.83, $P<0.001$). At 28 weeks, there was no significant effect of either benralizumab regimen on the forced expiratory volume in 1 second (FEV_1), as compared with placebo. The effects on various measures of asthma symptoms were mixed, with some showing significant changes in favor of benralizumab and others not showing significant changes. Frequencies of adverse events were similar between each benralizumab group and the placebo group.

CONCLUSIONS

Benralizumab showed significant, clinically relevant benefits, as compared with placebo, on oral glucocorticoid use and exacerbation rates. These effects occurred without a sustained effect on the FEV_1. (Funded by AstraZeneca; ZONDA ClinicalTrials.gov number, NCT02075255.)

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*A complete list of the investigators in the ZONDA trial is provided in the Supplementary Appendix, available at NEJM.org.

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Asthma is a common chronic inflammatory disease of the airways that affects an estimated 315 million persons worldwide.[1] Approximately 5 to 10% of persons with asthma have a severe form of disease that is usually managed with high-dose inhaled glucocorticoids and bronchodilators.[2,3] Within this group, 32 to 45% of persons rely on frequent or maintenance use of oral glucocorticoid therapy.[4,5] Oral glucocorticoid therapy adversely affects health-related quality of life,[6] and effective alternative therapies without severe adverse effects are needed.

Eosinophilic inflammation is a key part of asthma, and increased numbers of circulating and airway eosinophils are accompanied by more frequent asthma exacerbations and declines in lung function.[7-9] Glucocorticoids are thought to act by reducing the number of inflammatory cells, including eosinophils, in airways.[10] Mepolizumab and reslizumab are monoclonal antibodies that are directed against interleukin-5, a cytokine involved in the eosinophil life cycle.[11] Mepolizumab and reslizumab have both been approved as add-on therapies to treat asthma exacerbations and control symptoms in patients who have severe asthma with an eosinophilic phenotype.[12,13] Treatment with mepolizumab also provides a glucocorticoid-sparing effect.[14,15]

Benralizumab is a humanized, afucosylated (engineered to eliminate fucose sugars from the oligosaccharides in the Fc region) monoclonal antibody directed against the alpha subunit of the interleukin-5 receptor that induces direct, rapid, and nearly complete depletion of eosinophils by means of natural killer cell–mediated antibody-dependent cellular cytotoxic effects.[16] In the ZONDA trial, we assessed the effect of benralizumab, as compared with that of placebo, on the reduction in the oral glucocorticoid dose while asthma control was maintained in adult patients who had severe asthma with persistent blood eosinophilia despite receipt of treatment with high-dose inhaled glucocorticoids, long-acting β_2-agonists (LABAs), and oral glucocorticoids.

METHODS

TRIAL DESIGN

This randomized, double-blind, parallel-group, placebo-controlled trial comprised an enrollment visit, a run-in phase that included stabilization of the oral glucocorticoid dose, a randomized intervention period, and a follow-up visit (Fig. 1). The intervention period consisted of the following: an induction phase, during which patients continued receiving their oral glucocorticoid dose as established during the run-in phase; a dose-reduction phase, during which the oral glucocorticoid dose was reduced at regular intervals; and a dose-maintenance phase, during which the reduced oral glucocorticoid dose was maintained or, in patients in whom oral glucocorticoid therapy was discontinued, no further oral glucocorticoids were received.

All the patients had been treated continuously with oral glucocorticoids for 6 months or more before enrollment and were receiving oral prednisone or prednisolone at trial entry. Patients who were receiving any other oral glucocorticoid at enrollment were switched to an equivalent dose of oral prednisone or prednisolone. During the run-in phase, the oral glucocorticoid dose was adjusted to the minimum dose that could be received without loss of asthma control (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). No additional asthma-controller medication was initiated unless it was used for the treatment of exacerbations (medication was provided by the trial investigators).

After the run-in phase, patients underwent randomization at week 0 (baseline) to receive benralizumab or placebo and then entered the 4-week induction phase, during which the oral glucocorticoid dose established in the run-in phase was maintained. In the subsequent dose-reduction phase (weeks 4 to 24), the daily oral glucocorticoid dose was reduced every 4 weeks by 2.5 to 5.0 mg (Table S2 in the Supplementary Appendix). Only patients who had an oral glucocorticoid dose of 12.5 mg or less per day at the end of the run-in phase (baseline) were eligible for a 100% dose reduction (discontinuation of oral glucocorticoid therapy). If the criteria for dose reduction were not met, the oral glucocorticoid dose was returned to a previous level, which was maintained until the end of the trial. If a patient's asthma worsened during the maintenance phase (weeks 24 to 28), the final dose was deemed to be one adjustment increment greater than the dose at which the worsening started.

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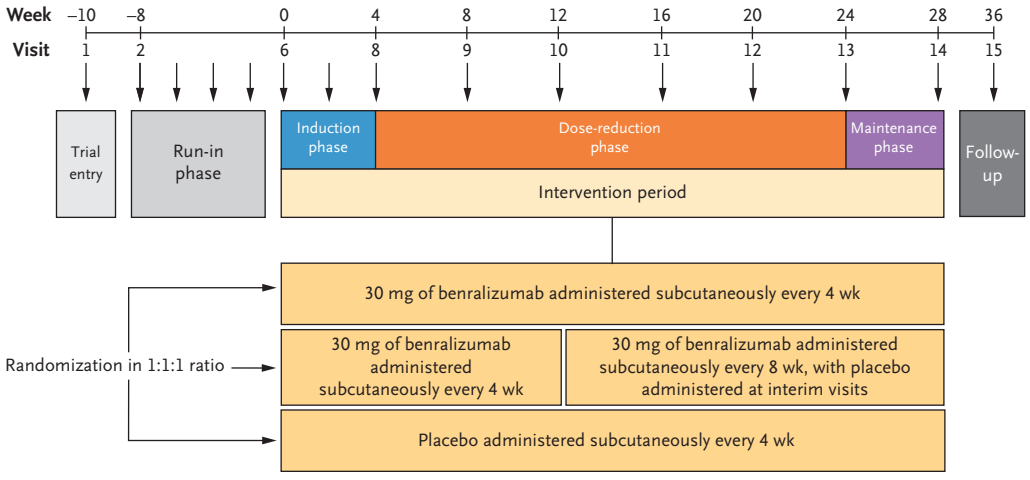

Figure 1. Trial Design.

Patients entering the run-in phase had their oral glucocorticoid dose reduced until the minimum effective dose without loss of asthma control was reached. All the patients then underwent randomization and entered the induction phase, during which the dose established in the run-in phase was maintained. The oral glucocorticoid dose was further reduced, every 4 weeks, in the intervention period from weeks 4 to 24. The oral glucocorticoid dose that was reached at week 24, or the complete discontinuation of oral glucocorticoid therapy, was maintained until week 28. The last dose of benralizumab or placebo was administered at the week 24 visit.

TRIAL OVERSIGHT

The trial was designed by AstraZeneca in collaboration with the first author. Trial data were collected by the clinical investigators and analyzed by employees of AstraZeneca. The first author and two of the authors who are employees of the sponsor vouch for the accuracy and completeness of the data and analyses and for the fidelity of the trial to the protocol (available at NEJM.org). All the authors reviewed the data. Writing and editing assistance, including preparation of a draft manuscript under the direction and guidance of the authors, incorporation of author feedback, and manuscript submission, was provided by Endpoint Medical Communications (funded by the sponsor) and the sponsor. The independent ethics committees of the trial centers or the central institutional review boards approved the trial protocol. The statistical analysis plan is available with the protocol. The trial was conducted in accordance with the principles of the Declaration of Helsinki, and all the patients provided written informed consent.

PATIENTS

Adults were eligible to participate in the trial if they had a blood eosinophil count of 150 cells or more per cubic millimeter and had asthma that had been treated with medium-dose to high-dose inhaled glucocorticoid and LABA therapy for at least 12 months before enrollment and treated with high-dose inhaled glucocorticoid and LABA therapy for at least 6 months before enrollment. Patients had been receiving oral glucocorticoid therapy for at least 6 continuous months directly before enrollment (equivalent to a prednisolone or prednisone dose of 7.5 to 40.0 mg per day). The full eligibility criteria are provided in Section 2 in the Supplementary Appendix.

INTERVENTIONS

Patients received subcutaneous injections of benralizumab at a dose of 30 mg every 4 weeks, benralizumab at a dose of 30 mg administered every 4 weeks for the first three doses and then every 8 weeks (with placebo administered at the 4-week interim visits; hereafter referred to as the group that received benralizumab every 8 weeks), or placebo administered every 4 weeks. All the trial agents were provided by AstraZeneca. Patients underwent randomization in a 1:1:1 ratio, with the use of an interactive Web- or voice-response system, and were stratified according to eosinophil count (≥150 to <300 cells per cubic

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millimeter vs. ≥300 cells per cubic millimeter) and country. Investigators and patients were unaware of the trial-group assignments. Patients continued their prescribed high-dose inhaled glucocorticoid and LABA therapies, as well as any other asthma-controller medications aside from oral glucocorticoid therapy (including leukotriene modifiers, long-acting muscarinic antagonists, and theophylline), in an unchanged fashion throughout the trial. Short-acting β_2-agonists were permitted as rescue medications.

ASSESSMENTS AND PROCEDURES

Worsening of asthma was defined as new or increased asthma symptoms or clinical signs that were troubling to the patient or were related to an electronic Asthma Daily Diary alert (see the Supplementary Appendix). An asthma exacerbation was defined as worsening of asthma that led to a temporary increase in the systemic glucocorticoid dose for at least 3 days to treat the symptoms, an emergency department visit resulting from asthma that led to treatment with a systemic glucocorticoid in addition to the patient's regular maintenance medications, or an inpatient hospitalization because of asthma.

Patients recorded their lung-function measurements (using an electronic handheld spirometer) and asthma symptoms in the Asthma Daily Diary. Patients used the diary to complete the Asthma Control Questionnaire 6 (ACQ-6)[17] and the Asthma Quality of Life Questionnaire (standardized) for persons 12 years of age or older (AQLQ[S]+12).[18] The total asthma symptom score (a composite of morning assessments of asthma symptoms, nighttime awakenings, and rescue medication use and an evening assessment of activity impairment) is assessed on a scale from 0 to 6, with higher scores indicating a greater symptom burden. The ACQ-6 is scored on a scale from 0 to 6, with lower numbers indicating better control of asthma), and the AQLQ(S)+12 is scored on a scale from 1 to 7, with higher scores indicating better asthma-related quality of life. Score changes of 0.5 or more points were considered to be clinically meaningful for the ACQ-6 and AQLQ(S)+12. Blood and induced sputum (from a subgroup of patients) were obtained for the analysis of eosinophils.[19] Adverse events were monitored throughout the trial. These procedures are described fully in Section 3 in the Supplementary Appendix.

END POINTS

The primary end point was the percentage reduction in the oral glucocorticoid dose from baseline (randomization at week 0) to the final dose at the end of the maintenance phase (week 28) while asthma control was maintained. Secondary end points included the percentages of patients who had a reduction in the average daily oral glucocorticoid dose of 25% or more, of 50% or more, or of 100% (discontinuation of oral glucocorticoid therapy) from baseline to end of the maintenance phase and the percentage of patients with an average final oral glucocorticoid dose of 5.0 mg or less per day while asthma control was maintained.

Additional end points included the annual asthma exacerbation rate, the time to the first asthma exacerbation, the percentage of patients with at least one asthma exacerbation (including exacerbations associated with emergency department visits or hospitalization), the forced expiratory volume in 1 second (FEV_1) before bronchodilation, the total asthma symptom score, the ACQ-6 score, and the AQLQ(S)+12 score. Exploratory end points were used to investigate the effect of blood and sputum eosinophilia on the efficacy of the trial drug. Safety end points included frequencies of adverse events.

STATISTICAL ANALYSIS

We estimated that 70 patients per group would be required for the trial to detect a difference in the primary end point between each benralizumab group and the placebo group with 86% power by means of a Wilcoxon rank-sum test with a two-sided level of 5%. Our estimation was based on simulations that used data from the Steroid Reduction with Mepolizumab Study (SIRIUS), which yielded a median percentage reduction from baseline of 50% in the glucocorticoid dose in the active-treatment group, as compared with no reduction in the placebo group.[14] We aimed for approximately 60 patients with a blood eosinophil count of at least 150 cells to less than 300 cells per cubic millimeter and 150 patients with a blood eosinophil count of 300 cells or more per cubic millimeter to undergo randomization. Efficacy analyses were conducted with an intention-to-treat approach in the full analysis set.

For the primary end point, benralizumab was compared with placebo by means of a Wilcoxon rank-sum test. To control the overall type I error

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rate, we accounted for multiple comparisons by means of the Hochberg procedure. A sensitivity analysis for the assessment of the primary end point was conducted with a proportional-odds model, with controls for trial group, geographic region (Asia, Central Europe and Eastern Europe, Western Europe and Turkey, North America, and the rest of world), and baseline oral glucocorticoid dose.

We used a Cochran–Mantel–Haenszel test, with adjustment for geographic region, to analyze secondary end points regarding reductions in the oral glucocorticoid dose. A negative binomial model, with adjustment for trial group, geographic region, and number of exacerbations in the previous year, with an offset term of the logarithm of the follow-up time was used to calculate annual exacerbation rates in the trial groups. Treatment effects were described with the use of rate ratios. Details of the models that were used to analyze other secondary end points are described in Section 5 in the Supplementary Appendix. The trial was not powered to assess secondary end points. The analyses of the secondary end points were not controlled for multiple comparisons and are presented with nominal P values. Results for exploratory variables were analyzed with the use of descriptive statistics according to trial group, unless otherwise indicated. Data were analyzed with the use of SAS software, version 9.2 (SAS Institute).

RESULTS

PATIENTS

From April 2014 through November 2015, a total of 369 patients were recruited and entered screening (Fig. S1 in the Supplementary Appendix). Of these, 98 patients did not enter the run-in phase for the adjustment of the oral glucocorticoid dose, most commonly because they did not fulfill the eligibility criteria (84 patients). An additional 51 patients did not complete the run-in phase, most commonly because they did not meet the eligibility criteria (35 patients). A total of 220 patients underwent randomization and started the intervention phase. A total of 11 patients did not complete the trial, including 5 who withdrew of their own decision. All the patients who underwent randomization were included in the full analysis set. Table 1 provides details about the characteristics of the patients at baseline (additional information is provided in Table S3 in the Supplementary Appendix).

PRIMARY OUTCOME

With respect to the prespecified primary outcome, the median reduction from baseline in the final oral glucocorticoid dose was 75% in patients who received either of the benralizumab regimens, as compared with a reduction of 25% in the patients who received placebo (P<0.001 for both comparisons) (Table 2 and Fig. 2A). A total of 24 patients (33%) who received benralizumab every 4 weeks and 27 patients (37%) who received benralizumab every 8 weeks had a reduction of 90% or more from baseline in their final oral glucocorticoid dose, as compared with 9 patients (12%) who received placebo (Table 2). More patients in the group that received benralizumab every 4 weeks and in the group that received benralizumab every 8 weeks than in the group that received placebo had a reduction of 75% or more from baseline (38 patients [53%] and 37 patients [51%], respectively, vs. 15 patients [20%]); similar results were observed with respect to a reduction of 50% or more (48 patients [67%] and 48 patients [66%], respectively, vs. 28 patients [37%]). The odds of a reduction in the oral glucocorticoid dose were 4.09 times (95% confidence interval [CI], 2.22 to 7.57) as high with benralizumab administered every 4 weeks as with placebo (P<0.001) and 4.12 times (95% CI, 2.22 to 7.63) as high with benralizumab administered every 8 weeks as with placebo (P<0.001) (Table 2).

SECONDARY AND EXPLORATORY OUTCOMES

In patients who received benralizumab, all the secondary end points related to reduction in the oral glucocorticoid dose were met. These end points included cessation of oral glucocorticoid therapy: 56% of the eligible patients who received benralizumab every 4 weeks and 52% of those who received benralizumab every 8 weeks had a 100% reduction from baseline in the final oral glucocorticoid dose, as compared with 19% of those who received placebo. The odds of cessation of oral glucocorticoid therapy were 5.23 times (95% CI, 1.92 to 14.21) as high with benralizumab administered every 4 weeks as with placebo (P<0.001) and 4.19 times (95% CI, 1.58 to 11.12) as high with benralizumab administered every 8 weeks as with placebo (P=0.002) (Table 2).

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Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Placebo (N=75)	Benralizumab, Every 4 Wk (N=72)	Benralizumab, Every 8 Wk (N=73)
Age — yr	49.9±11.7	50.2±12.0	52.9±10.1
Female sex — no. (%)	48 (64)	40 (56)	47 (64)
Body-mass index†	28.7±5.2	29.8±6.8	30.2±6.5
Median smoking history (range) — pack-yr	6.0 (1 to 9)	5.5 (2 to 9)	5.0 (1 to 8)
Median time since asthma diagnosis (range) — yr	10.5 (1.1 to 54.5)	13.3 (1.2 to 52.3)	16.3 (1.3 to 53.0)
Median oral glucocorticoid dose (range) — mg/day			
At trial entry‡	10.0 (7.5 to 40.0)	10.0 (7.5 to 40.0)	10.0 (7.5 to 40.0)
At end of run-in phase	10.0 (7.5 to 40.0)	10.0 (7.5 to 40.0)	10.0 (7.5 to 40.0)
Mean inhaled glucocorticoid dose (range) — μg/day	1232 (250 to 5000)	1033 (250 to 3750)	1192 (100 to 3250)
Leukotriene-receptor antagonist — no. (%)	25 (33)	28 (39)	29 (40)
No. of exacerbations in previous 12 mo	2.5±1.8	2.8±2.0	3.1±2.8
FEV_1 before bronchodilation			
Value — liters	1.931±0.662	1.850±0.741	1.754±0.635
Percent of predicted normal value	62.0±16.5	57.4±18.0	59.0±17.9
FEV_1:FVC ratio before bronchodilation — %	62±13	59±13	59±12
Median percent reversibility of FEV_1 (range)§	16.4 (–5.4 to 93.4)	18.2 (–3.0 to 126.0)	22.6 (–3.4 to 88.0)
Total asthma symptom score¶	2.4±1.0	2.5±1.0	2.3±1.1
ACQ-6 score‖	2.7±1.0	2.6±1.1	2.4±1.2
AQLQ(S)+12 score**	4.1±1.1	4.2±1.1	4.4±1.2
Blood eosinophil count			
Median count (range) — cells/mm^3††	535 (160 to 4550)	462 (160 to 1740)	437 (154 to 2140)
Distribution — no. (%)			
≥150 to <300 cells/mm^3	11 (15)	10 (14)	12 (16)
≥300 cells/mm^3	64 (85)	62 (86)	61 (84)

* Plus–minus values are means ±SD. Patients were randomly assigned to receive benralizumab either every 4 weeks or every 4 weeks for the first three doses and then every 8 weeks (with placebo administered at the 4-week interim visits; referred to as the group that received benralizumab every 8 weeks), or placebo. Data on the demographic characteristics of the patients, lung-function variables after bronchodilation, asthma (including smoking) history, and local blood eosinophil counts were collected at visit 1, which occurred 10 weeks before the induction phase began. Data on other clinical characteristics were collected at multiple time points from visit 1 to visit 6 (the start of the induction phase). The last recorded value before randomization served as the baseline measurement. Details about the characteristics at baseline are provided in Table S3 in the Supplementary Appendix. FEV_1 denotes forced expiratory volume in 1 second, and FVC forced vital capacity.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ Patients who were taking an oral glucocorticoid other than prednisone or prednisolone at enrollment were switched to an equivalent dose of prednisone or prednisolone at trial entry.

§ The percentage reversibility of the FEV_1 was calculated with the use of FEV_1 values obtained before and after bronchodilation at baseline as follows: ([postbronchodilation FEV_1 – prebronchodilation FEV_1] ÷ prebronchodilation FEV_1) × 100.

¶ The total asthma symptom score is a composite of morning assessments of asthma symptoms, nighttime awakenings, and rescue medication use and an evening assessment of activity impairment. Scores range from 0 to 6, and higher scores indicate a greater symptom burden.

‖ The Asthma Control Questionnaire 6 (ACQ-6)[17] is a six-item questionnaire to assess daytime and nighttime symptoms and rescue use of short-term β_2-agonists. Scores range from 0 to 6, and lower scores indicate better control. Score changes of 0.5 or more points were considered to be clinically meaningful.

** The Asthma Quality of Life Questionnaire (standardized) for persons 12 years of age or older (AQLQ[S]+12)[18] is a 32-item questionnaire to assess asthma-related quality of life. Scores range from 1 to 7, and higher scores indicate better asthma-related quality of life. Score changes of 0.5 or more points were considered to be clinically meaningful.

†† Patients were stratified at randomization according to the local laboratory baseline blood eosinophil count that was defined as the result obtained at visit 1.

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Table 2. Primary and Secondary Outcomes.

Outcome	Placebo (N=75)	Benralizumab, Every 4 Wk (N=72)	Benralizumab, Every 8 Wk (N=73)
Primary outcome			
Median oral glucocorticoid dose (range) — mg/day*			
At baseline	10.0 (7.5 to 40.0)	10.0 (7.5 to 40.0)	10.0 (7.5 to 40.0)
At final visit	10.0 (0.0 to 40.0)	5.0 (0.0 to 45.0)	5.0 (0.0 to 30.0)
Median reduction from baseline (range) — % of baseline value†	25.0 (–150 to 100)	75.0 (–100 to 100)	75.0 (–50 to 100)
P value†	—	<0.001	<0.001
Reduction from baseline in final oral glucocorticoid dose — no. (%)			
≥90%	9 (12)	24 (33)	27 (37)
≥75%	15 (20)	38 (53)	37 (51)
≥50%	28 (37)	48 (67)	48 (66)
>0%	40 (53)	55 (76)	58 (79)
Any increase or no change in dose	35 (47)	17 (24)	15 (21)
Analysis of percentage reduction from baseline in oral glucocorticoid dose			
Odds ratio (95% CI)	—	4.09 (2.22 to 7.57)	4.12 (2.22 to 7.63)
P value	—	<0.001	<0.001
Secondary outcomes			
Reduction from baseline in final oral glucocorticoid dose, according to percentage reduction			
100% Reduction — no./total no. (%)‡	8/42 (19)	22/39 (56)	22/42 (52)
Odds ratio (95% CI)	—	5.23 (1.92 to 14.21)	4.19 (1.58 to 11.12)
P value	—	<0.001	0.002
≥50% Reduction — no. (%)	28 (37)	48 (67)	48 (66)
Odds ratio (95% CI)	—	3.59 (1.79 to 7.22)	3.03 (1.57 to 5.86)
P value	—	<0.001	<0.001
≥25% Reduction — no. (%)	38 (51)	54 (75)	57 (78)
Odds ratio (95% CI)	—	2.89 (1.45 to 5.79)	3.25 (1.62 to 6.52)
P value	—	0.002	<0.001
Final oral glucocorticoid dose of ≤5.0 mg/day — no. (%)§	25 (33)	44 (61)	43 (59)
Odds ratio (95% CI)	—	3.16 (1.60 to 6.23)	2.74 (1.41 to 5.31)
P value	—	<0.001	0.002

* The baseline oral glucocorticoid dose was the daily dose at which the patient's asthma was stabilized at randomization (after the run-in phase), and the final oral glucocorticoid dose was the final daily dose at week 28.

† Negative values indicate an increase in the final oral glucocorticoid dose from baseline. The P values were calculated with the use of a Wilcoxon rank-sum test.

‡ Patients with a baseline oral glucocorticoid dose of 12.5 mg or less per day at the end of the run-in phase were eligible for a 100% dose reduction (discontinuation of oral glucocorticoid therapy).

§ All the patients with a final oral glucocorticoid dose of 5.0 mg or less per day also had a reduction of at least 25% from baseline in the final oral glucocorticoid dose.

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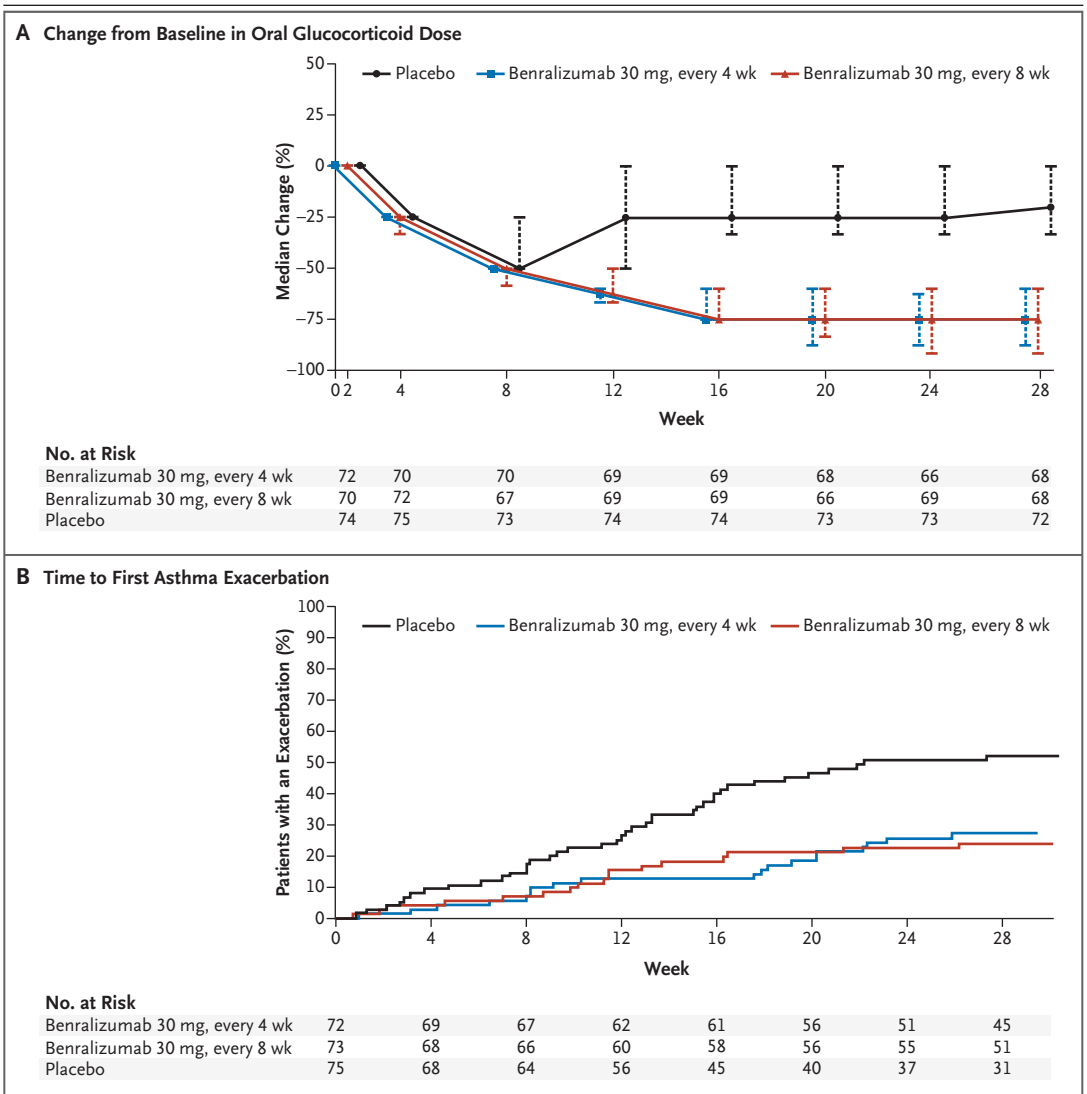

Figure 2. Change from Baseline in the Oral Glucocorticoid Dose and Asthma Exacerbations.

Panel A shows the median percentage change from baseline to week 28 in the oral glucocorticoid dose in patients who received benralizumab or placebo. Error bars represent 95% confidence intervals. Values are slightly offset from each other at each time point for clarity. Panel B is a Kaplan–Meier cumulative incidence curve for the time to the first exacerbation in patients who received benralizumab as compared with those who received placebo. Benralizumab administered every 4 weeks was associated with a longer time to the first exacerbation than was placebo (hazard ratio, 0.39; 95% confidence interval [CI], 0.22 to 0.66; P<0.001), and benralizumab administered every 8 weeks was also associated with a longer time to the first exacerbation than was placebo (hazard ratio, 0.32; 95% CI, 0.17 to 0.57; P<0.001).

Reductions in the oral glucocorticoid dose were observed regardless of the baseline oral glucocorticoid dose (Table S4 of the Supplementary Appendix).

For secondary end points related to asthma exacerbations, benralizumab administered every 4 weeks resulted in an annual asthma exacerbation rate that was 55% lower than the rate with

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placebo (marginal rate, 0.83 vs. 1.83; rate ratio, 0.45; 95% CI, 0.27 to 0.76; P=0.003), and benralizumab administered every 8 weeks resulted in an annual asthma exacerbation rate that was 70% lower than the rate with placebo (marginal rate, 0.54 vs. 1.83; rate ratio, 0.30; 95% CI, 0.17 to 0.53; P<0.001). The two benralizumab regimens were associated with lower odds of having at least one exacerbation than was placebo (odds ratio for benralizumab administered every 4 weeks vs. placebo, 0.32; 95% CI, 0.16 to 0.65; P=0.001; odds ratio for benralizumab administered every 8 weeks vs. placebo, 0.28; 95% CI, 0.14 to 0.56; P<0.001) and resulted in a longer time to the first exacerbation than placebo (Fig. 2B, and Fig. S2 in the Supplementary Appendix). Benralizumab that was administered every 8 weeks resulted in a marginal rate estimate of annual exacerbations associated with an emergency department visit or a hospitalization of 0.02 (95 CI, 0.00 to 0.18), as compared with a marginal rate estimate of annual exacerbations of 0.32 (95% CI, 0.16 to 0.65) in the placebo group. The rate with benralizumab was 93% lower than the rate with placebo (rate ratio, 0.07; 95% CI, 0.01 to 0.63; P=0.02). The differences between the group that received benralizumab every 4 weeks and the placebo group did not reach nominal significance for this end point (Table S5 in the Supplementary Appendix).

For secondary end points related to lung function, the FEV_1 before bronchodilation at week 20 was higher than that in the placebo group by 256 ml (95% CI, 109 to 403) in the group that received benralizumab every 4 weeks and by 222 ml (95% CI, 75 to 370) in the group that received benralizumab every 8 weeks; at this time the increase in each group was significantly larger than that with placebo. By 28 weeks, there was no longer a significant difference between either benralizumab group and the placebo group in the FEV_1 before bronchodilation (Fig. S3 in the Supplementary Appendix).

For secondary end points related to asthma control, symptoms, and asthma-related quality of life, the use of benralizumab every 8 weeks was associated with a decrease in the ACQ-6 score (indicating better asthma control) from baseline to the end of the maintenance phase that was 0.55 points (95% CI, 0.23 to 0.86) greater than the decrease with placebo (P=0.001) and with an increase in the AQLQ(S)+12 score (indicating better asthma-related quality of life) from baseline to the end of the maintenance phase that was 0.45 points (95% CI, 0.14 to 0.76) higher than the increase with placebo (P=0.004) (Figs. S4, S5, and S6 in the Supplementary Appendix). By contrast, the differences at week 28 between the group of patients who received benralizumab every 4 weeks and the placebo group with regard to the end points of the ACQ-6 score (least-squares mean difference, −0.24 points; 95% CI, −0.55 to 0.08; P=0.14) and the AQLQ(S)+12 score (least-squares mean difference, 0.23; 95% CI, −0.08 to 0.53; P=0.15) did not reach nominal significance. In addition, no significant differences were found between either benralizumab group and the placebo group with regard to changes from baseline to the end of the maintenance phase in total asthma symptoms. The results of exploratory analyses that were conducted to assess blood and sputum eosinophil counts and their potential associations with efficacy outcomes are described in Tables S6 and S7 and in Figures S7 through S10 in the Supplementary Appendix.

SAFETY AND ADVERSE EVENTS

A total of 166 patients (75%) had at least one adverse event during the intervention phase (Table 3). The most frequently reported adverse events were nasopharyngitis (in 17% of patients), worsening asthma (in 13%), and bronchitis (in 10%) (Table S8 in the Supplementary Appendix).

A total of 28 patients (13%) had at least one serious adverse event (Table 3). Worsening asthma was the most common serious adverse event (in 7 patients). A total of 3 patients discontinued their assigned regimen because of serious adverse events. Two patients in the group that received benralizumab every 8 weeks discontinued benralizumab: 1 because of pneumonia and 1 because of cardiac failure. One patient in the placebo group discontinued placebo because of pericarditis.

Two patients in the group that received benralizumab every 8 weeks died during the trial (Table 3). The causes of death were acute cardiac failure (the patient had hypertension and coronary artery disease at trial entry) and pneumonia (atrial fibrillation while the patient was in the hospital; this patient had concurrent hypercholesterolemia, hypertension, angina pectoris, con-

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Table 3. Summary of Adverse Events.*

Event	Placebo (N=75)	Benralizumab, Every 4 Wk (N=72)	Benralizumab, Every 8 Wk (N=73)
		number of patients (percent)	
Adverse event	62 (83)	49 (68)	55 (75)
Adverse event leading to discontinuation of trial regimen	2 (3)	0	3 (4)
Serious adverse event	14 (19)	7 (10)	7 (10)
Serious adverse event unrelated to asthma exacerbation†	11 (15)	6 (8)	6 (8)
Death	0	0	2 (3)
Injection-site reaction	2 (3)	2 (3)	0
Hypersensitivity	1 (1)	1 (1)	2 (3)
Urticaria	1 (1)	0	1 (1)

* Data on adverse events that occurred during the period from the receipt of the first dose of the trial regimen (week 0) to the visit at the end of the trial (week 28) are provided. Complete details of adverse events are provided in Table S8 in the Supplementary Appendix.
† Patients who had only the serious adverse events of worsening asthma or status asthmaticus were excluded from these totals.

gestive heart failure, dyslipidemia, and a history of atrial fibrillation at trial entry). Details are provided in Section 6 in the Supplementary Appendix.

Antidrug antibodies were positive in 12 of 145 patients (8%) who received benralizumab, 10 of whom had neutralizing antibody–positive status (Table S9 in the Supplementary Appendix). Among patients with a positive antidrug-antibody response, 1 of 5 patients in the group that received benralizumab every 4 weeks and 3 of 7 patients in the group that received benralizumab every 8 weeks had an increase from baseline in the blood eosinophil count (Table S10 in the Supplementary Appendix).

DISCUSSION

In this trial involving patients who relied on oral glucocorticoid therapy to control their asthma, benralizumab significantly reduced the oral glucocorticoid dose, while asthma control was maintained, in patients who had severe asthma, were receiving high-dose inhaled glucocorticoid and LABA, and had an elevated blood eosinophil count. The likelihood of a reduction in the oral glucocorticoid dose was more than 4 times as high with benralizumab as with placebo, and one half the eligible patients (those receiving a baseline prednisone dose of ≤12.5 mg per day) who were receiving benralizumab stopped the oral glucocorticoid therapy completely. In addition to clinically relevant dose reductions or the discontinuation of oral glucocorticoid therapy, patients receiving benralizumab had substantially lower rates of asthma exacerbations than did patients receiving placebo, as well as lower rates of exacerbation-related hospital visits.

The FEV_1 did not significantly increase over the entire 28-week trial period with benralizumab versus placebo. However, it did not decline, either, despite a reduction of 75% in the prednisone dose in each benralizumab group.

Targeting of the alpha subunit of the interleukin-5 receptor with benralizumab has potential advantages over existing anti–interleukin-5 therapies. By targeting the interleukin receptor rather than the cytokine, luminal depletion of eosinophils can occur,[16] which may be related to greater clinical efficacy. In addition, this approach avoids the potential for autoimmune-mediated worsening of asthma, which has been reported with low-dose anti–interleukin-5 therapy.[20]

This trial has limitations. Although we computed annualized exacerbation rates, benralizumab or placebo was administered only for 28

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weeks, and longer-term studies involving patients with oral glucocorticoid–dependent asthma would be necessary before definitive conclusions could be drawn about the long-term efficacy and safety of benralizumab in this group of patients, who had undergone a reduction in the oral glucocorticoid dose.

It was unclear why approximately 20% of patients did not have any reduction in the oral glucocorticoid dose with benralizumab. In a preliminary analysis (data not shown), the baseline blood eosinophil counts in patients who did not have a response were similar to those in patients who had the greatest reductions in their final oral glucocorticoid doses. Perhaps the presence of blood eosinophilia may not identify the eosinophil as a key effector cell in some patients. Future studies may aim to investigate the characteristics of patients that are indicative of a response to benralizumab, to assess the long-term safety and efficacy of eosinophil depletion (as opposed to normalization of eosinophil counts), and to determine the effects of benralizumab on other cells that may express the interleukin-5 receptor.

In conclusion, in patients with severe eosinophilic asthma who received benralizumab subcutaneously every 8 weeks, the use of maintenance oral glucocorticoid therapy could be reduced while asthma control was maintained. No significant effect on FEV_1 was observed at the end of the trial.

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