

Reslizumab Compared with Benralizumab in Patients with Eosinophilic Asthma: A Systematic Literature Review and Network Meta-Analysis



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What is already known about this topic? Reslizumab and benralizumab have each demonstrated significant efficacy compared with placebo for the treatment of severe asthma of the eosinophilic phenotype.

What does this article add to our knowledge? Based on an indirect comparison, reslizumab may have greater efficacy compared with benralizumab in a subgroup of patients with Global Initiative for Asthma step 4/5, blood eosinophil levels of greater than or equal to either 300 or 400 cells/mL, and 2 or more exacerbations in the previous year.

How does this study impact current management guidelines? In the absence of head-to-head data, indirect comparisons help clinicians to choose from among reasonable treatment options the agent most likely to produce the best outcome for the individual patient.

BACKGROUND: The interaction of IL-5 with its receptor on eosinophils increases the activation and maintenance of eosinophils; blocking this interaction reduces asthma symptoms in patients with the eosinophilic phenotype. Reslizumab, which binds to IL-5, and benralizumab, which targets the IL-5 receptor α subunit, have not been compared in head-to-head trials.

OBJECTIVE: To indirectly compare reslizumab with benralizumab in similar patient populations using a network meta-analysis.

METHODS: A systematic literature review was conducted and a network meta-analysis was performed on eligible studies using the Markov Chain Monte-Carlo simulation method and a Bayesian statistical framework.

RESULTS: Eleven studies were identified, 4 of which evaluated clinically relevant doses and had outcomes at similar time points. To control for population differences, subgroups were selected for the base-case efficacy analysis: a benralizumab subgroup with blood eosinophil levels of greater than or equal to 300 cells/ μ L ($n = 1537$) and a reslizumab subgroup in Global Initiative for

Asthma step 4/5 with 2 or more previous exacerbations and greater than or equal to 400 eosinophils/ μ L ($n = 318$). Safety was analyzed in the full population ($N = 3462$). Reslizumab significantly improved Asthma Control Questionnaire (ACQ) and Asthma Quality of Life Questionnaire (AQLQ) scores compared with benralizumab once every 4 weeks and there were reasonably high posterior probabilities that reslizumab is superior to benralizumab once every 4 weeks and once every 8 weeks for ACQ score, AQLQ score, FEV₁, and clinical asthma exacerbations. **CONCLUSIONS:** This indirect comparison suggests that reslizumab may be more efficacious than benralizumab in patients with eosinophilic asthma in Global Initiative for Asthma step 4/5 with elevated blood eosinophil levels (benralizumab, $\geq 300/\mu$ L; reslizumab, $\geq 400/\mu$ L) and 2 or more exacerbations in the previous year. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:122-30)

Key words: Indirect comparison; IL-5; mAbs; Eosinophil; Asthma

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speaker for Boston Scientific, Genentech, and Teva Pharmaceuticals; has received compensation for industry-sponsored studies from Teva Pharmaceuticals, GlaxoSmithKline, Sanofi-Aventis, Vectura, Boehringer Ingelheim, Invion, AstraZeneca, Gilead, Novartis, and Chiesi; serves as a speaker for Boehringer Ingelheim and AstraZeneca; receives royalties from Elsevier, serves as a member of the Data Safety Monitoring Committee of GlaxoSmithKline; and has received grant money from the National Institutes of Health. The rest of the authors declare that they have no relevant conflicts of interest.

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Abbreviations used

ACQ- Asthma Control Questionnaire
AQLQ- Asthma Quality of Life Questionnaire
Crl- credible interval
GINA- Global Initiative for Asthma
ICS- inhaled corticosteroid
Q4W- once every 4 weeks
Q8W- once every 8 weeks

INTRODUCTION

Asthma represents a major health burden, affecting an estimated 235 million individuals worldwide.¹ Approximately 5% to 10% of patients with asthma have severe disease that does not respond to treatment with high-dose inhaled corticosteroids (ICSs) and long-acting β_2 -antagonists.² Eosinophils have been implicated in the pathogenesis of certain forms of asthma, and airway eosinophilia appears to be related to asthma exacerbations.³ Airway infiltration by eosinophils and elevated blood eosinophil counts (eosinophilia) have been associated with poor asthma control, worsening symptoms, and impaired lung function.^{4,5} One of the major drivers of the activation and maintenance of eosinophils is the cytokine IL-5.⁶ Consequently, IL-5 and its receptor on eosinophils are targets for intervention in patients with severe asthma with an eosinophilic phenotype.

Current treatment guidelines recommend adding a biologic therapy that targets the activity of IL-5 for patients with severe, uncontrolled asthma with eosinophilia (Global Initiative for Asthma [GINA] step 5).⁷ Two humanized anti-IL-5 mAbs are currently available for treating patients with severe eosinophilic asthma: mepolizumab, which was approved in the United States and Europe in 2015,^{8,9} and reslizumab, which was approved in the United States and Europe in 2016 on the basis of data in patients with severe asthma and greater than or equal to 400 cells/ μ L.^{10,11} Both of these agents bind to IL-5, sequestering the cytokine, which results in reduced survival and activity of eosinophils.^{8,10} A third mAb targeted against the effects of IL-5, benralizumab, was recently approved.¹² In contrast to mepolizumab and reslizumab, benralizumab targets the α -subunit of the IL-5 receptor on eosinophils and basophils, blocking interaction with IL-5.¹² This interaction with the IL-5 receptor on eosinophils results in eosinophil apoptosis and depletion via antibody-dependent cell-mediated cytotoxicity.¹³

In phase 3 trials in patients with severe, uncontrolled eosinophilic asthma, reslizumab, mepolizumab, and benralizumab have been shown to improve lung function and symptom control and reduce exacerbations, in comparison with placebo, as an add-on therapy to best standard of care.¹⁴⁻¹⁹ However, there is little evidence to guide clinicians in choosing among IL-5 and IL-5 receptor-targeted agents. Head-to-head clinical trials provide the highest level of evidence comparing 2 interventions, but are often long in duration, difficult to implement, and very expensive. An accepted method for comparing agents evaluated in different trials, but in similar populations, is a network meta-analysis.²⁰ Such analyses are conducted using published guidelines to ensure the quality of the analyses and minimize the risk of bias.^{20,21} A previously reported network meta-analysis compared mepolizumab, reslizumab, and benralizumab, but

TABLE 1. Population, Intervention, Comparator, Outcome, and Study type (PICOS) framework

PICOS	Description
Population	Patients with severe eosinophilic asthma
Intervention	Reslizumab (in addition to best standard of care)
Comparator	• Best standard of care and/or placebo • Benralizumab (in addition to best standard of care)
Outcomes	• Incidence of exacerbations and clinically significant exacerbations (include those requiring unscheduled contact with health care professionals or hospitalization) • Asthma control (ie, overall change from baseline in FEV₁, change from baseline in FVC, change in ACQ score from baseline) • Quality of life (change in AQLQ score from baseline, change in ASUI score) • Use of oral corticosteroids; patient and clinical evaluation of response; lung function; mortality; time to discontinuation; adverse effects of treatment
Study type	Randomized clinical trials

ASUI, Asthma Symptom Utility Index; FVC, forced vital capacity.

data available at the time of the analysis were insufficient to compare benralizumab with mepolizumab or reslizumab because the phase 3 benralizumab studies had not yet been published.²² The aim of this study was to indirectly compare the efficacy and safety of reslizumab and benralizumab in patient populations with similar characteristics.

METHODS

Systematic literature review

A systematic literature review was performed on August 12, 2016, using Medline (PubMed), Embase, and the Cochrane library. Search terms were developed using a combination of MeSH/EMTREE terms and free-text terms to capture the relevant population, outcomes, and study type according to the populations, interventions, comparisons, outcomes, and study types (Table 1). Additional hand searches were performed on June 1, 2017, for conference abstracts on databases not indexed in Embase (eg, European Respiratory Society, American Thoracic Society, and British Thoracic Society), for clinical trials (Clinicaltrials.gov), and for health technology assessment submissions.

To select studies for the network meta-analysis, titles and abstracts of articles were reviewed by 2 analysts, one as primary screener and the other to check the quality of the screening process. The analysts were not blinded to each other's assessments. Full-text articles were reviewed to assess eligibility according to prespecified inclusion/exclusion criteria. Any discrepancies in the screening were resolved by discussion with a third, neutral person. Trials assessing at least 2 treatments at clinically relevant doses were eligible for inclusion in the network meta-analysis. Publications not reporting any outcomes related to efficacy or safety were excluded. Only randomized, controlled trials in English were analyzed.

Efficacy and safety data were extracted from selected publications. Efficacy outcomes included the rate of clinical asthma exacerbations, change from baseline in FEV₁, change from baseline in Asthma Control Questionnaire (ACQ) score, and change from baseline in the Asthma Quality of Life Questionnaire (AQLQ) score. The base-case analysis for the ACQ end point considered only the 6-item ACQ.

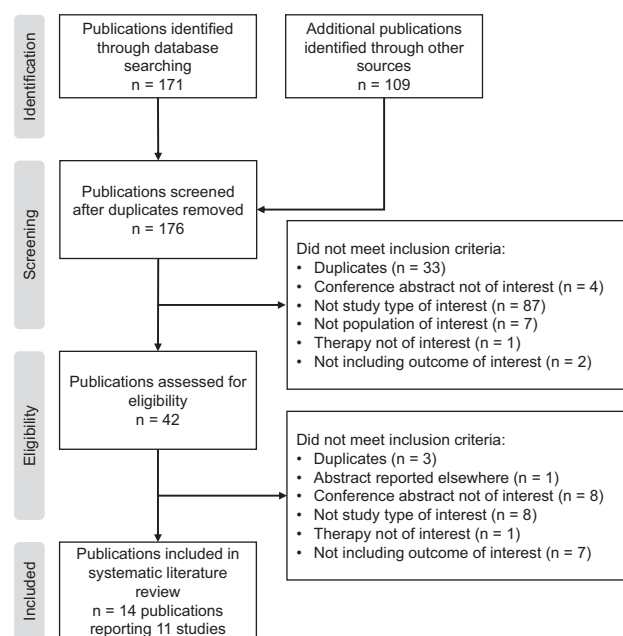


FIGURE 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA): Diagram of publications identified through the systematic literature review.

Clinical asthma exacerbations were defined as per individual studies (see the Results section) and expressed as events per patient-year of exposure, to adjust for differences in observation time between studies. Safety outcomes included proportions of patients with at least 1 adverse event (all grades), proportions of patients with at least 1 serious adverse event, proportions of patients with at least 1 treatment-related adverse event, and discontinuations due to adverse events.

It should be noted that eligible studies did not provide any direct comparisons between reslizumab and benralizumab; only indirect comparisons across the studies could be made.

Construction of the evidence network

Comparability of the trials was assessed on the basis of the following baseline characteristics: number of previous exacerbations, blood eosinophil counts, severity of asthma, and use of oral corticosteroids and/or ICSs. If trial populations were not directly comparable because of differences in these baseline characteristics, the base-case analysis selected a patient subgroup to provide similar patient populations for analysis. For continuous variables (FEV₁, ACQ score, and AQLQ score), the input was the absolute difference in mean (SE) change from baseline between treatment arms. For binary outcomes, including all safety end points, the input was the number of events and the total number of patients in each treatment arm. For rate of exacerbations, counts over a certain time period were used (which could vary with different trials), with the total number of patient-years used as the denominator. Missing data were imputed using standard methods.²³

Statistical analysis

For the modeling of binary outcomes, it was assumed that the number of events in each treatment arm follows a binomial likelihood where parameters were the probability of events under each treatment and the number of patients in each arm. Because the probabilities can vary only between 0 and 1, a transformation was

used to map these probabilities into a continuous measure. For a binomial likelihood, the standard link function was the logit, which is based on the assumption of the linearity of treatment effects. Based on National Institute for Health and Care Excellence recommendations,²⁴ rates of clinically significant exacerbations were modeled using a Poisson likelihood and a log link, where the number of person-years at risk was used rather than the number of patients at risk. A heterogeneity assessment was conducted on all clinical end points to validate the similarity assumption.

A Bayesian hierarchical model, which preserves the randomization of each trial, was used for the network meta-analysis.²⁵ The network meta-analysis was performed with WinBUGS V1.4, using the Markov Chain Monte-Carlo simulation method and a Bayesian statistical framework. A random- or fixed-effects model was selected for each outcome, depending on which model provided the best fit. For trials comparing more than 2 interventions, we adjusted for correlation between treatment effects in the same trial using a conditional distribution formulation of the multivariate normal distribution. An estimate of the rate ratio, odds ratio, or differences among treatments was modeled and reported with the credible interval (CrI). Statistical significance was declared when the 95% CrI excluded 0 for values expressed as a difference or 1 for rate ratio or odds ratio values. The posterior probability (Pr) that an intervention is superior to the comparator was expressed as a percentage, according to Bayesian inference conventions. The interpretation of results was complemented by reporting treatment rankings on the basis of the surface under the cumulative ranking curve. Surface under the cumulative ranking is a numeric representation of a therapy's overall ranking, shown as a number ranging from 0% to 100%.²⁶ Values closer to 100% represent a higher probability that a therapy is in one of the top ranks, whereas values closer to 0% represent a higher probability that a therapy is in one of the bottom ranks.²⁶ Details on the Bayesian hierarchical model prior and posterior distributions for the analysis of clinical asthma exacerbation rates are shown in Figure E1 in this article's Online Repository at www.jaci-inpractice.org.

RESULTS

Systematic literature review

A total of 176 publications were screened, following the removal of duplicates from database searches, hand searching, and clinical study reports (data on file, Teva Pharmaceuticals, Frazer, Pa) from the manufacturer of reslizumab (Figure 1). After assessment for eligibility, the narrative review identified 11 randomized controlled clinical studies (Table II).^{15-19,27-31}

All studies evaluated reslizumab or benralizumab as add-on therapy. Concomitant maintenance therapy, such as the administration of ICSs and/or long-acting β_2 -antagonists, was allowed. Eight studies reported results on asthma exacerbation rates, of which 7 reported it as a primary end point. Asthma exacerbations were reported differently across studies (ie, rates of exacerbations at time point, time to exacerbation, number of events, or exacerbation of active treatment arms vs a comparator arm). Across trials, blood eosinophil levels ranged from 168 to 815.4 cells/ μ L and the mean number of exacerbations in the previous year ranged from 1.9 to 3.1. In the reslizumab studies, baseline blood eosinophil levels of greater than or equal to 400 cells/ μ L was a criterion for inclusion and patients were reported to be in GINA steps 3 to 5.¹⁵ Benralizumab trials did not report the severity of asthma; however, for the CALIMA¹⁸ and

TABLE II. Studies identified through the systematic literature review

Trial	Intervention assessed	Phase	Study design	Intervention groups	Outcomes assessed	Timing of assessment
Castro et al, ²⁷ 2011	Reslizumab	2	Double-blind, parallel-group, randomized, placebo-controlled	Reslizumab 3.0 mg/kg Q4W (n = 53); placebo (n = 53)	Blood eosinophil, ACQ score, FEV ₁ , asthma exacerbations	Week 15
Castro et al, ¹⁵ 2015 (Study 3082)*	Reslizumab	3	Double-blind, parallel-group, randomized, placebo-controlled	Reslizumab 3.0 mg/kg Q4W (n = 245); placebo (n = 244)	Blood eosinophil, ACQ score, FEV ₁ , asthma exacerbations, AQLQ score, rescue SABAs	Weeks 16 and 52
Corren et al, ¹⁶ 2016 (Study 3084)	Reslizumab	3	Double-blind, parallel-group, randomized, placebo-controlled	Reslizumab 3.0 mg/kg Q4W (n = 395); placebo (n = 97)	Blood eosinophil, ACQ score, FEV ₁ , rescue SABAs	Week 16
Bjerner et al, ¹⁷ 2016 (Study 3081)	Reslizumab	3	Double-blind, parallel-group, randomized, placebo-controlled	Reslizumab 0.3 mg/kg Q4W (n = 104) or 3.0 mg/kg Q4W (n = 106); placebo (n = 105)	Blood eosinophil, ACQ score, FEV ₁ , FVC, ASUI score, AQLQ score	Week 16
Castro et al, ¹⁵ 2015 (Study 3083)	Reslizumab	3	Double-blind, parallel-group, randomized, placebo-controlled	Reslizumab 3.0 mg/kg Q4W (n = 232); placebo (n = 232)	Asthma exacerbations, blood eosinophils, SABA use, ACQ score, AQLQ score, ASUI score, FEV ₁	Weeks 16 and 52
FitzGerald et al, ¹⁸ 2016 (CALIMA)*	Benralizumab	3	Double-blind, randomized, parallel-group, placebo-controlled	Benralizumab 30 mg Q4W (n = 425) or 30 mg Q8W (Q4W for the first 3 doses; n = 441); placebo (n = 440)	ACQ score, FEV ₁ , asthma exacerbations, AQLQ score	Week 56
Bleecker et al, ¹⁹ 2016 (SIROCCO)*	Benralizumab	3	Double-blind, randomized, parallel-group, placebo-controlled	Benralizumab 30 mg Q4W (n = 400) or 30 mg Q8W (Q4W for the first 3 doses; n = 398); placebo (n = 407)	ACQ score, FEV ₁ , asthma exacerbations, AQLQ score	Week 48
Castro et al, ²⁸ 2014	Benralizumab	2b	Double-blind, randomized, parallel-group, placebo-controlled, dose-ranging	Benralizumab 2 mg (n = 81), 20 mg (n = 81), or 100 mg (n = 222) Q4W for the first 3 doses and then Q8W; placebo (n = 222)	Blood eosinophils, asthma exacerbations, FEV ₁ , AQLQ score	Week 52
Park et al, ²⁹ 2016	Benralizumab	2a	Double-blind, randomized, parallel-group, placebo-controlled	Benralizumab 2 mg (n = 27), 20 mg (n = 26), or 100 mg (n = 26) Q4W for the first 3 doses and then Q8W; placebo (n=27)	Blood eosinophil, ACQ score, FEV ₁ , asthma exacerbations, PEF, FeNO	Week 52
Nowak et al, 2015 ³⁰	Benralizumab	2	Double-blind, randomized, parallel-group, placebo-controlled, single-dose	Benralizumab 0.3 mg/kg (n = 36) or 1.0 mg/kg (n = 36); placebo (n = 38)	Blood eosinophil, ACQ score, FEV ₁ , asthma exacerbations, AQLQ score	Weeks 12 or 24
Nair et al, 2017 ³¹ (ZONDA)	Benralizumab	3	Double-blind, randomized, parallel-group, placebo-controlled	Benralizumab 30 mg Q4W (n = 72) or Q8W (Q4W for the first 3 doses; n = 73); placebo (n = 75)	Reduction in glucocorticoid dose, asthma exacerbations, FEV ₁	Week 28

ASUI, Asthma Symptom Utility Index; FeNO, fractional exhaled nitric oxide; PEF, peak expiratory flow; SABA, short-acting beta-agonist.

*Included in network meta-analysis.

SIROCCO¹⁹ studies, data on baseline medication use (ie, ICS/long-acting β_2 -antagonist and additional oral medications, as well as high-dose ICS [>500 $\mu\text{g}/\text{d}$]) generally aligned with the GINA criteria used to define severe persistent asthma (step 4/5).⁷

All studies identified were of high quality according to criteria published by the Centre for Reviews and Dissemination³² and randomization was appropriate; there was no significant imbalance between treatment arms within each study. Studies were generally balanced with respect to age, sex, baseline FEV₁ levels, and baseline AQLQ scores; however, differences in inclusion criteria resulted in imbalances between the patient populations in which reslizumab and benralizumab were assessed. The reslizumab trials enrolled patients with blood eosinophil levels of greater than or equal to 400 cells/ μL who experienced at least 1 previous exacerbation, whereas benralizumab studies enrolled patients who had a lower blood eosinophil threshold of greater than or equal to 150 cells/ μL and who had experienced at least 2 previous exacerbations. In addition, reslizumab trials included patients in GINA steps 3 through 5; whereas benralizumab trials did not report GINA stage, but baseline medications suggest patients were in GINA step 4/5.

Network of evidence

The network of evidence was designed to compare clinically relevant doses at similar time points. A pharmacokinetic study³³ identified subcutaneous benralizumab 30 mg every 4 weeks (Q4W) or every 8 weeks (Q8W) as regimens that would be carried forward for phase 3 development. Because these doses were approved by regulatory authorities, other doses and regimens were considered clinically irrelevant and were excluded. Of the 11 studies identified in the systematic literature review, 3 were excluded because they reported only on benralizumab doses that were not clinically relevant.²⁶⁻³⁰ The pivotal benralizumab studies evaluated outcomes at weeks 48¹⁸ or 56¹⁹; therefore, the 3 reslizumab studies that did not include an assessment at a time point of approximately 1 year were excluded.^{16,17,27} Finally, 1 benralizumab study was excluded because its design and primary outcome measure (reduction in glucocorticoid dose) were considered to be too dissimilar from the other studies in the network for meaningful comparison.³¹ The remaining 4 studies (reported in 3 publications) were included in the evidence network.^{15,18,19}

Because of the differing inclusion criteria among the reslizumab and benralizumab studies, subgroups were used for the base-case efficacy analysis. Both benralizumab studies reported data for a subgroup with blood eosinophil levels of greater than or equal to 300 cells/ μL (combined $n = 1537$; median blood eosinophils = 460–490 cells/ μL).^{18,19} To generate a comparable reslizumab subgroup, data for the subgroup in GINA step 4/5 and with 2 or more previous exacerbations ($n = 318$; median blood eosinophils = 500 cells/ μL) were obtained from study data provided by the manufacturer. A sensitivity analysis used the full population ($N = 3462$; reslizumab $n = 952$ and benralizumab $n = 2510$) to assess efficacy. Safety end points were analyzed using the full population. The final evidence network is shown in Figure 2.^{15,18,19}

Results of the efficacy analysis

Results of the base-case efficacy analysis are shown in Figure 3. Treatment rankings based on area under the surface under the

cumulative ranking curve for indirect comparisons between the treatments are presented in Table III. Reslizumab produced significantly greater improvement in asthma control, as measured by the 6-item ACQ, compared with benralizumab 30 mg Q4W ($\Delta = -0.37$; CrI, -0.63 to -0.10 ; Pr = 100%); statistical significance compared with benralizumab 30 mg Q8W was not reached. A sensitivity analysis using the 7-item ACQ had results that were similar to the base-case analysis. AQLQ scores increased (indicating greater health-related quality of life) significantly more with reslizumab than with benralizumab 30 mg Q4W ($\Delta = 0.32$; CrI, 0.03 to 0.60; Pr = 99%).

In the FEV₁ analysis, Pr was 92% that reslizumab would improve FEV₁ more than benralizumab Q8W and 96% compared with benralizumab Q4W with a magnitude of difference ranging from 0.09 to 0.11 L; these differences were not significant. Heterogeneity assessment of the inputs used in the analysis of FEV₁ revealed important differences among the studies with respect to change in FEV₁. In the 2 benralizumab studies, FEV₁ increased by 0.22 L and 0.24 L in the placebo arms. In the reslizumab studies, FEV₁ increased by 0.05 L and 0.18 L in the placebo arms.

Clinical asthma exacerbation rates were defined similarly across studies as a worsening of asthma that resulted in corticosteroid treatment, emergency department or urgent care, or hospitalization. In benralizumab studies, systemic corticosteroids for 3 or more days or a temporary increase in stable corticosteroids was considered evidence of exacerbation; Bleecker et al also included 1 corticosteroid injection as an exacerbation.^{18,19} Corticosteroid use criteria in reslizumab studies were any use of systemic corticosteroids in patients not already receiving them or a greater than or equal to 2-fold increase in dose for 3 or more days.¹⁵ There was no significant difference between reslizumab and benralizumab 30 mg Q4W or Q8W for clinical asthma exacerbations; the model estimated a Pr of 86% that reslizumab is superior to benralizumab 30 mg Q4W and Q8W. In the sensitivity analysis for efficacy using the overall study populations instead of subgroups, reslizumab was associated with a significantly greater reduction in clinically significant asthma exacerbations compared with either benralizumab dose. The rate ratio for reslizumab compared with benralizumab 30 mg Q4W was 0.73 (95% CI, 0.62–0.85) and compared with benralizumab 30 mg Q8W was 0.72 (95% CI, 0.61–0.84); Pr was 100% for both comparisons (Figure 4). Results for the other efficacy outcome measures were directionally consistent with the base-case efficacy analysis and the overall conclusions were not changed.

Results of the safety analysis

Adverse events leading to discontinuation were significantly less frequent with reslizumab than with either benralizumab dose (Pr = 99%; Figure 5). No significant difference was observed in the frequency of adverse events, treatment-related adverse events, or serious adverse events for reslizumab compared with either benralizumab regimen. For treatment-related and all-cause adverse events, Pr was 83% to 92% for a lower rate of adverse events with reslizumab compared with benralizumab Q4W or Q8W.

DISCUSSION

Results of this Bayesian network meta-analysis suggest that reslizumab may be more efficacious than benralizumab for patients in GINA step 4/5 with blood eosinophil levels of greater than or equal to 300 cells/ μL and 2 or more exacerbations in the

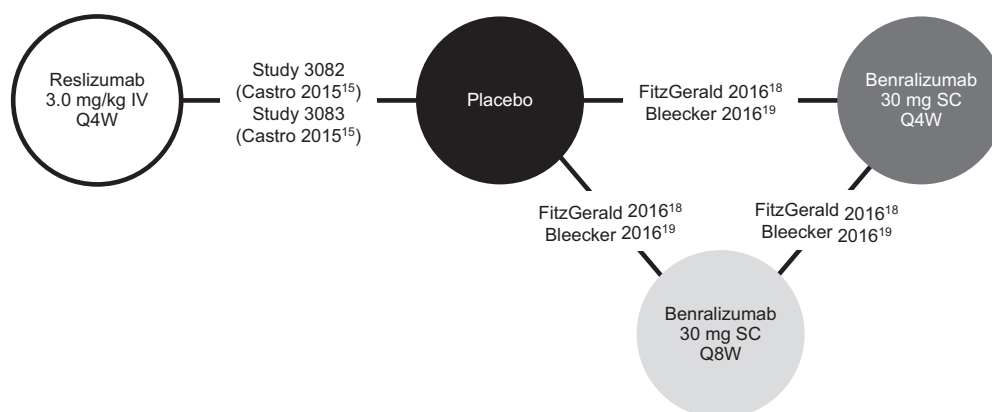


FIGURE 2. Global network of evidence. IV, Intravenous; SC, subcutaneous.

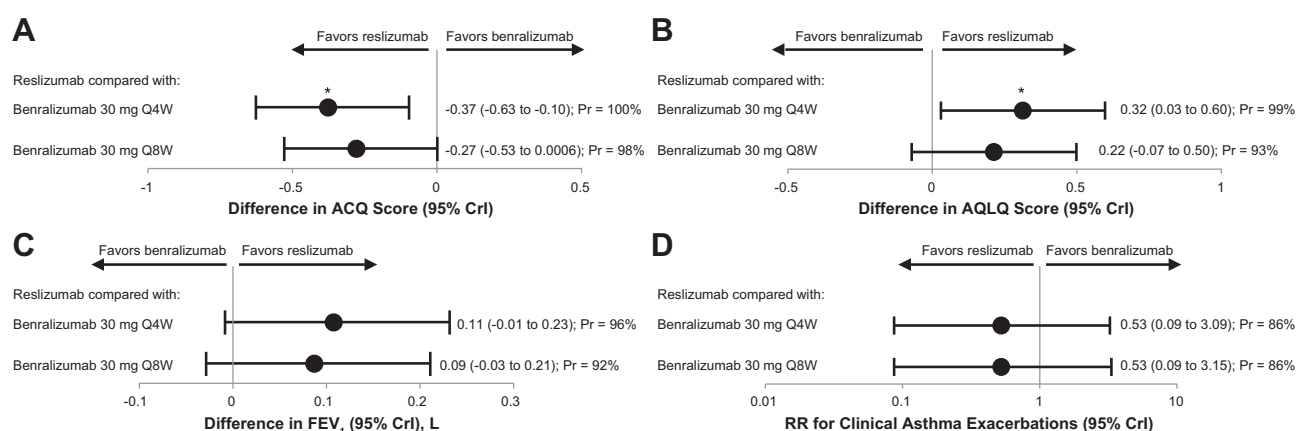


FIGURE 3. Results of the base-case efficacy analysis: A, ACQ scores. B, AQLQ scores. C, FEV₁. D, Clinical asthma exacerbations. Pr, Posterior probability; RR, rate ratio. *A statistically significant result.

TABLE III. Treatment rankings for efficacy outcomes based on SUCRA*

Regimen	Reduce clinical asthma exacerbations	Improve FEV ₁	Improve ACQ score	Improve AQLQ score
Reslizumab 3.0 mg/kg Q4W	First	First	First	First
Benralizumab 30 mg Q4W	Second	Second	Second	Second
Benralizumab 30 mg Q8W	Second	Third	Third	Third
Placebo	Fourth	Fourth	Fourth	Fourth

SUCRA, Surface under the cumulative ranking.

*Because this analysis involved indirect comparisons between individual studies, these results may have been influenced by differences in study populations and methodologies.

previous year. Although statistical significance was not reached for all efficacy outcomes in the base-case analysis, the posterior probabilities, which represent in Bayesian analysis a degree of belief in a hypothesis, were at least 86% for the superiority of reslizumab on clinical asthma exacerbation rates, FEV₁, ACQ scores, and AQLQ scores. Reslizumab was statistically superior in ACQ and AQLQ scores compared with benralizumab 30 mg Q4W; however, the differences in ACQ and AQLQ scores were small and did not achieve levels considered to be clinically meaningful (ie, minimal important difference). The safety analysis suggested, at a minimum, that reslizumab is no less tolerable than benralizumab. Reslizumab appeared to be associated with fewer discontinuations due to adverse events.

Given that results were indirectly compared across studies, this analysis had several limitations. An important limitation of this analysis was that it was not restricted to patients with blood eosinophil levels of greater than or equal to 400 cells/ μ L, on which the regulatory approval of reslizumab is based.^{9,10} Because the trial publications did not provide patient-level data that would allow further analysis by eosinophil levels, the results of this study were limited to benralizumab-treated and reslizumab-treated patients who had eosinophil levels of greater than or equal to 300 cells/ μ L and greater than or equal to 400 cells/ μ L, respectively. These differences in baseline blood eosinophil thresholds could have influenced response to anti-IL-5 therapy. Previous studies with reslizumab have shown greater

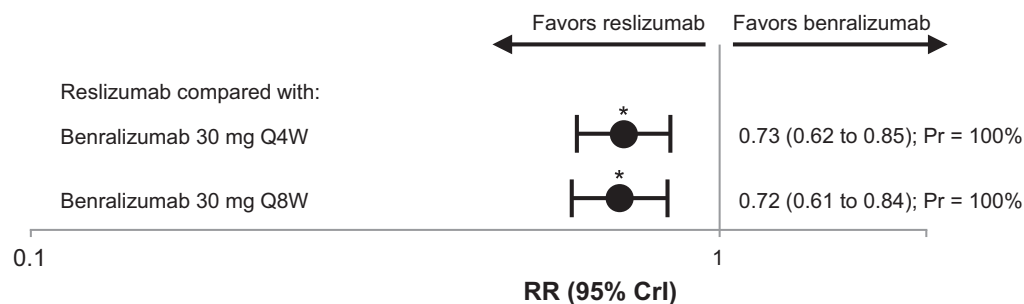


FIGURE 4. Sensitivity analysis for clinical asthma exacerbations (full study population). *Pr*, Posterior probability; *RR*, rate ratio. *A statistically significant result.

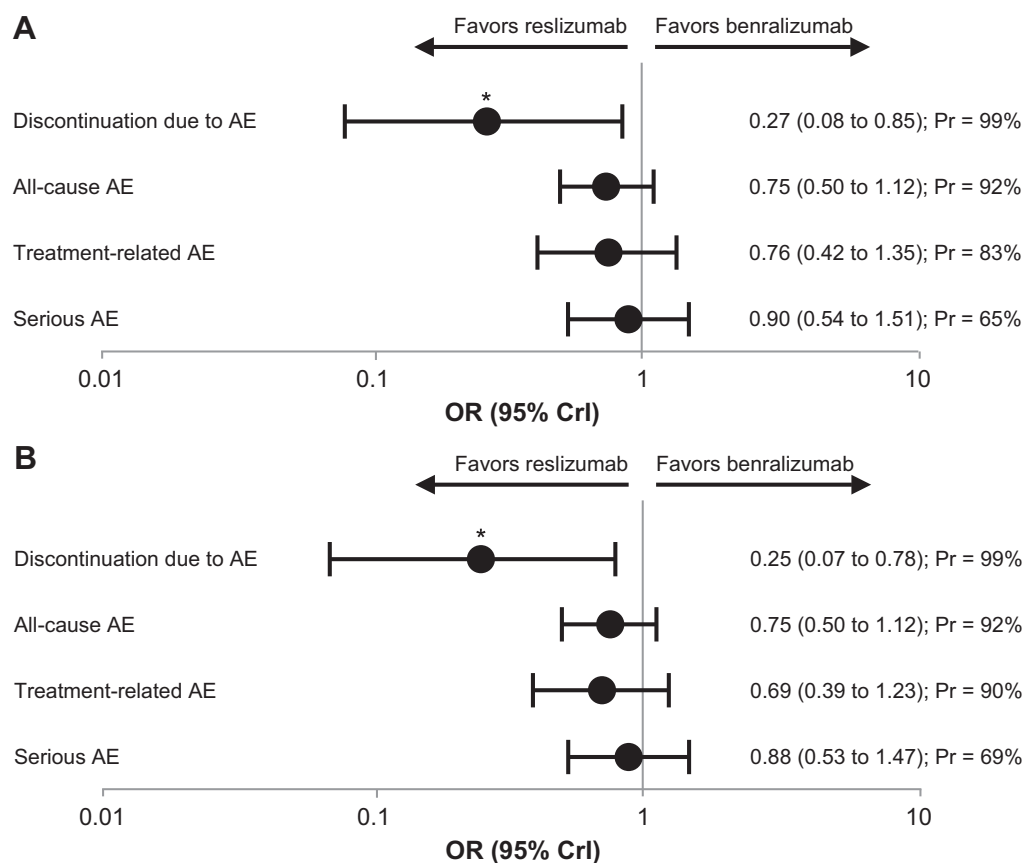


FIGURE 5. Results of the safety analysis for reslizumab compared with benralizumab 30 mg Q4W (A) and for reslizumab compared with benralizumab 30 mg Q8W (B). Reslizumab results in this figure are from data on file (Teva Pharmaceuticals, Frazer, Pa). *AE*, Adverse event; *OR*, odds ratio; *Pr*, Posterior probability. *A statistically significant result.

treatment response in patients with baseline blood eosinophils of greater than or equal to 400 cells/ μ L compared with patients with baseline levels below this threshold.¹⁶ It should also be noted that a higher enrollment eosinophil threshold is associated with a greater risk for exacerbations.³⁴ The greater risk for exacerbations could lead to a greater likelihood of benefit from an intervention. Although differences in enrollment eosinophil thresholds between studies could have influenced exacerbation rates in our analysis, the sensitivity analysis for asthma exacerbations in which the overall study population was used

demonstrated favorable results for reslizumab despite a lower baseline rate of exacerbations (potentially less exacerbation-prone) in the previous 12 months in the reslizumab studies compared with the benralizumab studies. Although the reslizumab and benralizumab cohorts differed with respect to the lower bound of blood eosinophils, the median values were comparable across reslizumab and benralizumab cohorts (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). Mean baseline exacerbations were slightly higher in the reslizumab studies, but we consider that the

statistical adjustment in the model was sufficient to control for this variability. Nonetheless, there remains a possibility that observed or unobserved differences between the study populations may have biased the results. Other limitations include those inherent to all indirect comparisons, chiefly the possibility that uncontrolled differences, study populations, and/or methodology among the studies influenced the results. Heterogeneity among studies was observed, particularly in FEV₁ results. In this study, because a subgroup analysis was required to ensure similar populations for comparison, the smaller sample size reduced the statistical power of the analysis, potentially contributing to lack of statistical significance for several measures that favored reslizumab with high probabilities. Furthermore, because the base-case efficacy analysis compared a narrower population than that assessed in the pivotal studies of either agent, the results may not be generalizable to a population with fewer than 2 previous exacerbations per year and blood eosinophil levels of less than 300 or less than 400 cells/ μ L. However, the use of subgroups reduced the risk of bias associated with differences in the study populations. Finally, posterior probabilities are sensitive to the assumptions and details of the model and should be interpreted with caution.

When multiple agents targeting the same pathway have demonstrated effectiveness, as is the case for IL-5–targeted therapy in eosinophilic asthma, head-to-head comparisons become prohibitively difficult and expensive. Yet, clinicians still need some basis for rationally selecting the most appropriate therapeutic options for their patients. Network meta-analysis allows indirect comparison of interventions in the absence of head-to-head data. The Bayesian statistical framework used in the present study simulates the way clinicians routinely make decisions, based on available information. This principle has been discussed most often in the context of diagnosis,³⁵ but may reasonably apply to treatment selection as well. In Bayesian inference, the posterior probability is interpreted as a degree of belief or certainty in the result, in contrast to the arbitrary either/or determined by a *P* value of greater than or less than .05.

The current study generally supports and extends the findings of previous indirect comparisons. An indirect comparison of mepolizumab, reslizumab, and benralizumab, using similar methods, suggested that reslizumab 3 mg/kg Q4W had the highest probability of effectiveness for reducing exacerbation rates.²² That analysis included the approved dose of mepolizumab, 100 mg Q4W, but available benralizumab data included only those doses that were not carried forward in the phase 3 program³³ and, consequently, are irrelevant to the practicing clinician. The present study, therefore, focused on the indirect comparison of reslizumab and benralizumab at clinically relevant doses.

There are several potential explanations, not mutually exclusive, for the apparent efficacy and tolerability differences observed in indirect comparisons of IL-5 and IL-5 receptor–targeted antibodies. Other than the methodological risks discussed above, these differences might be related to the mechanisms of action, route of administration, and/or dosing. Although reslizumab and mepolizumab bind and sequester IL-5, benralizumab interacts directly with the IL-5 receptor to deplete eosinophils by apoptosis.¹³ The clinical significance of this mechanistic difference has not been studied. Eosinophils are active in innate immunity and also have immunomodulatory roles,³⁶ and the long-term effects of eosinophil depletion are unknown. With respect to route of administration and dosing,

reslizumab is administered intravenously with weight-based dosing,^{10,11,15} whereas, in pivotal trials, benralizumab was given subcutaneously with a fixed dose of 30 mg irrespective of body size.^{18,19} Although weight-based and fixed dosing often result in similar exposure to mAbs,³⁷ and the benralizumab dosing regimen was supported by pharmacokinetic modeling,^{32,38} given normal interpatient variability, these differences could have an effect on the efficacy and/or tolerability for some patients.

In conclusion, although analyses are limited by differences in study designs, this indirect comparison of reslizumab with benralizumab suggests that reslizumab may be more efficacious in patients with eosinophilic asthma in GINA step 4/5 with elevated blood eosinophil levels (≥ 300 cells/ μ L for benralizumab and ≥ 400 cells/ μ L for reslizumab) and 2 or more exacerbations in the previous year, and has similar tolerability. Further study is needed to confirm these results and to explain the observed differences in efficacy and tolerability.

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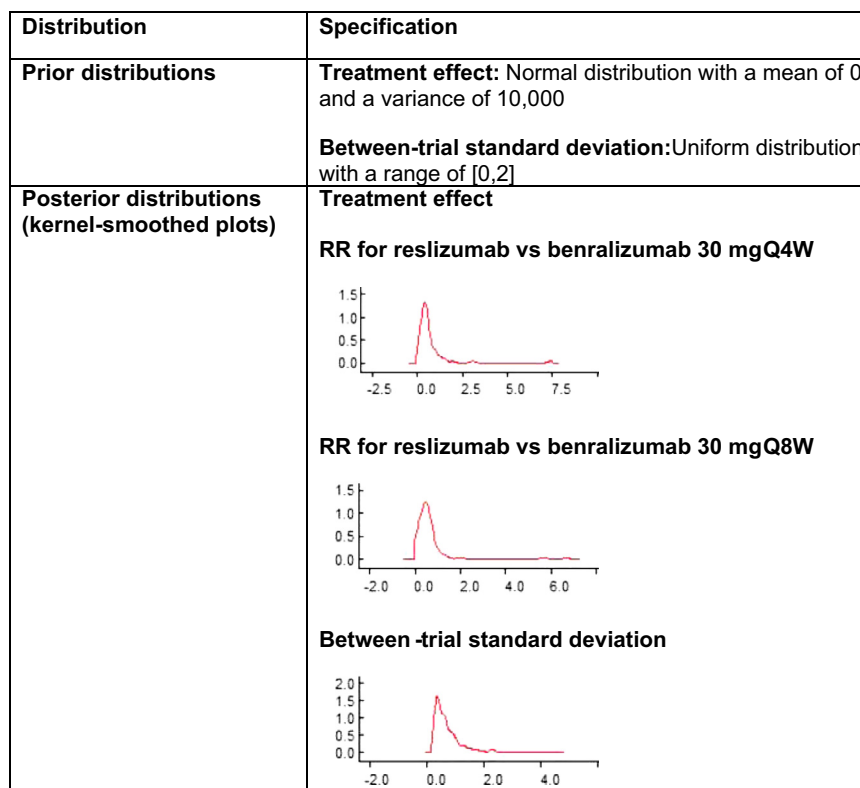


FIGURE E1. This figure shows details of the Bayesian hierarchical model prior and posterior distributions (clinical asthma exacerbation rates – base-case analysis, random effects model). *RR*, rate ratio.

TABLE E1. Baseline eosinophil levels and exacerbations in the patient cohorts included in the network meta-analysis

Patient cohort	Baseline eosinophils, median (range)	Baseline exacerbations (no. of exacerbations in previous 12 mo), mean $\pm$ SD
Pooled reslizumab subgroups: GINA steps 4/5 and ≥ 2 exacerbations		
Placebo (n = 162)	550 (0*-7400)	3.5 $\pm$ 2.3
Reslizumab (n = 156)	500 (0*-9700)	3.3 $\pm$ 2.0
Bleecker et al ¹⁹ (SIROCCO): subgroup with eosinophil level of >300 cells/ μ L		
Placebo (n = 267)	500 (300-2690)	3.1 $\pm$ 2.0
Benralizumab 30 mg Q4W (n = 275)	500 (300-3440)	3.0 $\pm$ 2.0
Benralizumab 30 mg Q8W (n = 267)	500 (300-3100)	2.8 $\pm$ 1.5
FitzGerald et al ¹⁸ (CALIMA): subgroup with eosinophil level of >300 cells/ μ L		
Placebo (n = 248)	510 (300-4494)	2.8 $\pm$ 1.7
Benralizumab 30 mg Q4W (n = 241)	500 (300-2420)	2.8 $\pm$ 1.7
Benralizumab 30 mg Q8W (n = 239)	500 (300-2600)	2.7 $\pm$ 1.3

*Although an eosinophil level of ≥ 400 cells/ μ L was required at screening, lower levels at baseline/randomization were allowed.