

Efficacy and safety of benralizumab in patients with eosinophilic asthma: a meta-analysis of randomized placebo-controlled trials

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Abstract Benralizumab is a monoclonal antibody that targets interleukin-5 receptor α to deplete blood eosinophils and improve the clinical outcomes of allergic asthma. We conducted a meta-analysis to evaluate the safety and efficacy of different doses of benralizumab in patients with eosinophilic asthma. All randomized controlled trials involving benralizumab treatment for patients with eosinophilic asthma, which were searched in PubMed, Embase, and the Cochrane Library published until January 2017, as well as the rate of asthmatic exacerbation, pulmonary functionality, asthma control, quality of life scores, and adverse events were included. Randomized-effect models were used in the meta-analysis to calculate the pooled mean difference, relative risks, and 95% confidence intervals. Five studies involving 1951 patients were identified. Compared with the placebo, benralizumab treatment demonstrated significant improvements in the forced expiratory volume in 1 s (FEV1), Asthma Quality of Life Questionnaire scores, decreased asthmatic exacerbation and Asthma Control Questionnaire-6 (ACQ-6) scores. Benralizumab treatment was also not associated with increased adverse events. These findings indicated that benralizumab can be safely used to improve FEV1, enhance patient symptom control and quality of life, and reduce the risk of exacerbations and ACQ-6 scores in patients with eosinophilic asthma. Furthermore, our meta-analysis showed that benralizumab with 30 mg (every eight weeks) dosage can improve the health-related quality of life and appear to be more effective than 30 mg (every four weeks) dosage. Overall, data indicated that the optimal dosing regimen for benralizumab was possibly 30 mg (every eight weeks).

Keywords benralizumab; anti-interleukin-5; monoclonal antibody; eosinophilic asthma; meta-analysis

Introduction

Asthma is a chronic inflammatory airway disease that affects up to 334 million people worldwide and causes a high burden of disease and economic impact throughout the world [1]. According to the Global Initiative for Asthma guidelines, the primary treatment for asthma consists of daily inhaled corticosteroids combined with long-acting β_2 agonists [2]. However, some asthmatics suffer from inadequately controlled symptoms when undergoing this treatment, because they are either highly resistant to the inhaled drugs or they use them informally [2–4]. For some uncontrolled asthmatics, other drugs (e.g., slow-release theophylline, leukotriene-receptor antagonists, long-acting anticholinergics, and phosphodiester-

ase-4 inhibitors) can be used [2,4]. Currently, monoclonal antibodies have emerged as targeted therapy for asthma as an innovative approach [5].

Eosinophilic inflammatory infiltration plays an important role in the pathogenesis of asthma, and eosinophilic asthma accounts for approximately 50%–60% of the total asthma population [6]. One report demonstrated interleukin-5 (IL-5) to be the primary cytokine responsible for eosinophil production, survival, maturation, recruitment, activation, and secretion at sites of allergic inflammation [7]. Moreover, humanized monoclonal antibodies targeting IL-5 showed considerable potential in patients with eosinophilic asthma [5], and the novel anti-IL-5 agent, benralizumab, has been investigated for the treatment of asthma [8]. Benralizumab is a humanized afucosylated monoclonal antibody against the IL-5 receptor α , which exhibits enhanced effector function [9]. In addition, benralizumab has demonstrated enhanced eosinophil-depleting activity compared with neutralizing monoclonal antibodies directed against IL-5 [9]. However, effects of benralizumab therapy in asthmatics remain consistently

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incomplete. In the present study, we conducted a meta-analysis of randomized controlled trials (RCTs) to assess whether benralizumab is safe and effective in patients with eosinophilic asthma.

Research status of anti-interleukin-5 therapy for asthma

Recently, several studies showed that anti-IL-5 drugs have a clinically important effect on clinically relevant outcomes in patients with asthma [10–13]. Mepolizumab and reslizumab have been approved by the European Medicines Agency and the US Food and Drug Administration, respectively as an add-on treatment for severe asthma [14]. Benralizumab is a novel anti-IL-5 receptor α monoclonal antibody that selectively depletes eosinophils and basophils via enhancing antibody-dependent cell-mediated cytotoxicity [15]. Busse *et al.* [16] evaluated the safety profile, biological effects, and pharmacokinetic activity of benralizumab and found decreased airway, bone marrow, and peripheral blood eosinophil counts in conjunction with an acceptable safety profiles. Since then, several placebo-controlled clinical trials have evaluated the safety and efficacy of benralizumab as a treatment for patients with asthma [17]. Therefore, the safety and efficacy of benralizumab for the treatment of eosinophilic asthma should be evaluated by analyzing recent studies.

Specific steps of meta-analysis

We followed the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines [18]. A systematic search of PubMed, Embase, and the Cochrane Library published up until January 2017 using the search terms, such as “benralizumab,” “anti-interleukin-5,” or “anti-IL-5” and “eosinophilic asthma,” was conducted. In addition, a manual search of references from reports of clinical trials or review articles was performed to identify relevant trials. The search was performed without language restriction. Two authors independently selected the trials for inclusion. Trials published solely in abstract form were excluded given that the data cannot be fully analyzed. Any discrepancy was resolved by discussion and consensus between the two evaluating authors.

Studies that meet the following criteria were included: (1) adults and adolescents (12 years or older) with a diagnosis of eosinophilic asthma. Eosinophilic inflammation was selected by a sputum eosinophil count $\geq 3\%$ or an asthma-related peripheral blood eosinophil count ≥ 300 cells/ μ L [10]; (2) double-blind, randomized, and placebo-controlled studies; (3) treatment intervention

consisted of benralizumab monoclonal antibody therapy compared with a placebo, regardless of the different drug names and doses; and (4) the outcome measures included forced expiratory volume in 1 s (FEV1), Asthma Control Questionnaire (ACQ), Asthma Quality of Life Questionnaire (AQLQ), as well as rate of asthmatic exacerbation and adverse events. Data retrieved from the articles included the following: first author, year of publication, benralizumab doses used, numbers of patients, duration of study periods, and outcome measures. Standardized data extraction forms were used. We assessed the methodological quality of the included trials and the risk of bias using the Cochrane risk-of-bias tool [19].

The data analysis was performed to treat, and all the participants were included to minimize bias. We calculated the mean differences (MD) or standardized mean differences (SMD) with 95% confidence intervals (CIs) for continuous outcome relative risks (RRs) with 95% CIs for dichotomous outcomes. SMDs were used when studies reported different units or scales for the outcome. Heterogeneity was measured using the I^2 statistic. $I^2 > 50\%$ indicated significant heterogeneity [20]. Fixed-effect models were used if the heterogeneity between studies was nonsignificant, otherwise random effects were used. As a priori subgroup analysis, we explored the influence of different dosage of benralizumab. A P value less than 0.05 was statistically significant. All analyses were performed using Review Manager, version 5.3 (Nordic Cochrane Centre).

Characteristics and quality of the individual studies

The study selection process is outlined in Fig. 1. We included 47 potentially relevant studies that were obtained from the search results. After removing the duplicates and screening the abstracts and full text, five trials ($N = 1951$ patients) met the entry criteria [14,21–24]. All studies were multi-center double-blind RCTs. The duration of treatment ranged from 8 to 56 weeks and the follow-up period ranged from 20 to 56 weeks. The participants received intravenous or subcutaneous injections of benralizumab in one study [21], whereas the patients only received subcutaneous injections of benralizumab in the remaining four studies. To reduce the possible bias, we analyzed the effects of subcutaneous benralizumab on all the above outcomes in this meta-analysis. Outcome reporting was highly variable as FEV1 was reported in liters in three trials [14,22,24] and percent of predicted value in one study [23]. The characteristics of the five selected studies are listed in Table 1.

All five studies included in the meta-analysis exhibited a low risk of bias (Fig. 2). All the included studies were double-blinded and used random sequence generation except for one [21]. All the outcome data in the included

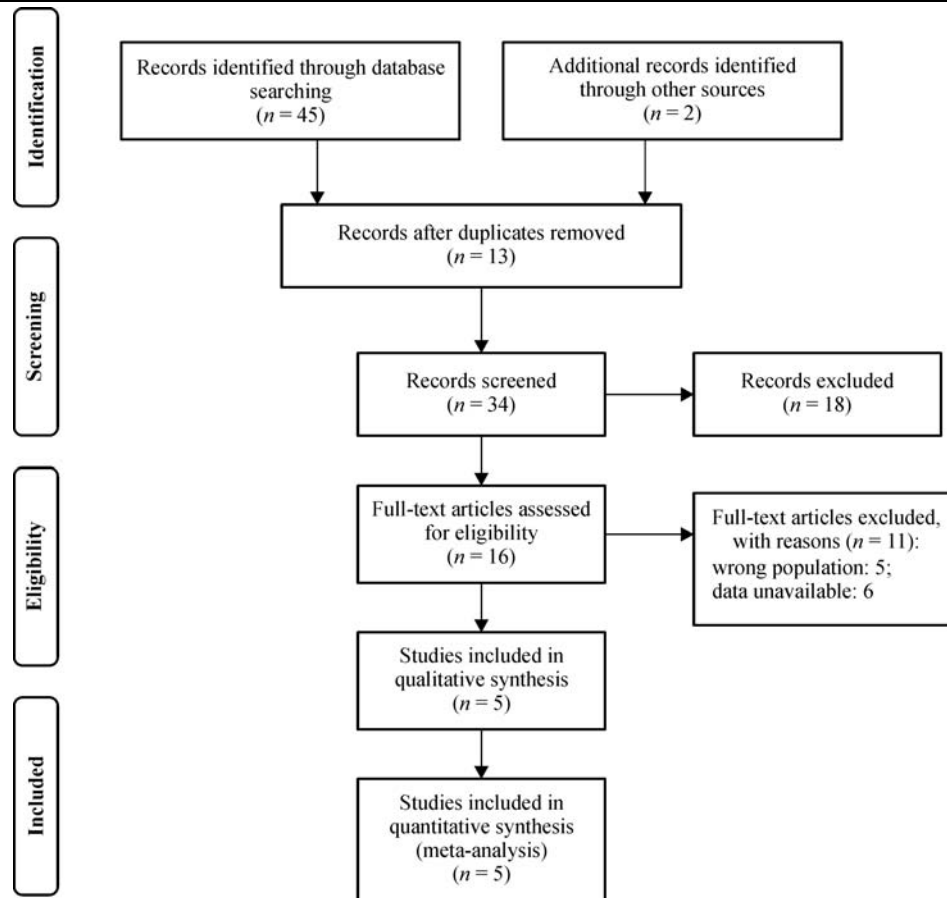


Fig. 1 Flow chart identifying the studies included in the analysis.

Table 1 Characteristics of the randomized controlled trials included in the meta-analysis

Reference	Study design	No. of subjects (treatment /placebo)	Age (year)	Doses of benralizumab used	Routine	Treatment duration	Outcomes	Follow-up
Laviolette <i>et al.</i> , 2013 [21] ^a	mRCT	4/5	18–65	100 mg Q4W	SC	8 weeks	Blood, sputum eosinophils; adverse events	20 weeks
Castro <i>et al.</i> , 2014 [22] ^b	mRCT	244/80	18–75	2, 20, 100 mg Q8W	SC	52 weeks	Blood eosinophils; asthma exacerbations; FEV1	52 weeks
Park <i>et al.</i> , 2016 [23] ^b	mRCT	60/21	20–75	2, 20, 100 mg Q8W	SC	40 weeks	Blood eosinophils; asthma exacerbations; FEV1; PEF; ACQ-6	52 weeks
FitzGerald <i>et al.</i> , 2016 [24] ^b	mRCT	480/248	12–75	30 mg Q4W or 30 mg Q8W	SC	56 weeks	Asthma exacerbations; FEV1; ACQ-6; AQLQ	56 weeks
Bleecker <i>et al.</i> , 2016 [14] ^a	mRCT	542/267	12–75	30 mg Q4W or 30 mg Q8W	SC	48 weeks	Asthma exacerbations; FEV1; ACQ-6; AQLQ	48 weeks

^aWe only included 100 mg benralizumab in cohort 2. ^bWe only included patients with baseline blood eosinophils ≥ 300 cells/ μ L. mRCT, multicenter RCT; Q4W, every four weeks; Q8W, every eight weeks; SC, subcutaneous injections; FEV1, forced expiratory volume in 1 s; PEF, peak expiratory flow; ACQ, Asthma Control Questionnaire; AQLQ, the Asthma Quality of Life Questionnaire.

studies were reported. The funnel plot provided a qualitative estimation of the publication bias associated with the studies, and no evidence of bias was found (Fig. 3).

Efficacy and safety of benralizumab in eosinophilic asthmatics

We described and analyzed the efficacy and safety of

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Bleecker ER 2016	+	+	+	+	+	+	+
Castro 2014	+	+	+	+	+	+	+
FitzGerald JM 2016	+	+	+	+	+	+	+
Laviolette 2013	?	+	+	?	+	+	+
Park HS 2016	+	+	+	+	+	+	+

Fig. 2 Risk of bias summary of the included studies.

benralizumab in eosinophilic asthmatics from the following five aspects.

Asthma exacerbations

Two studies involving 1537 participants were identified to describe the effect of benralizumab on eosinophilic asthma exacerbation [14,24]. Our analysis revealed that benralizumab significantly decreased the risk of exacerbation compared with placebo ($RR = 0.59$, 95% CI: 0.52 – 0.68, $P < 0.00001$) (Fig. 4), with modest heterogeneity ($I^2 = 30\%$). Analyses of the different benralizumab dosing regimens showed that no difference exists between a dose of 30 mg every four weeks (Q4W) and 30 mg every eight weeks (Q8W; first three doses given four weeks apart) in significantly lower exacerbation rates ($RR = 0.59$, 95% CI: 0.49–0.71; $RR = 0.59$, 95% CI: 0.49–0.72, respectively).

Forced expiratory volume in 1 s (FEV1)

Four studies assessed the effects of benralizumab treatment and different doses of benralizumab on FEV1 [14,22–24]. Overall, the pooled effect of benralizumab on FEV1 was significant ($SMD = 0.24$, 95% CI: 0.16–0.32, $P < 0.00001$), with minimal heterogeneity ($I^2 = 3\%$) (Fig. 5). Analyses of different benralizumab doses revealed that 100 mg Q8W was the most effective dose and significantly improved FEV1 ($SMD = 0.47$, 95% CI: 0.20–

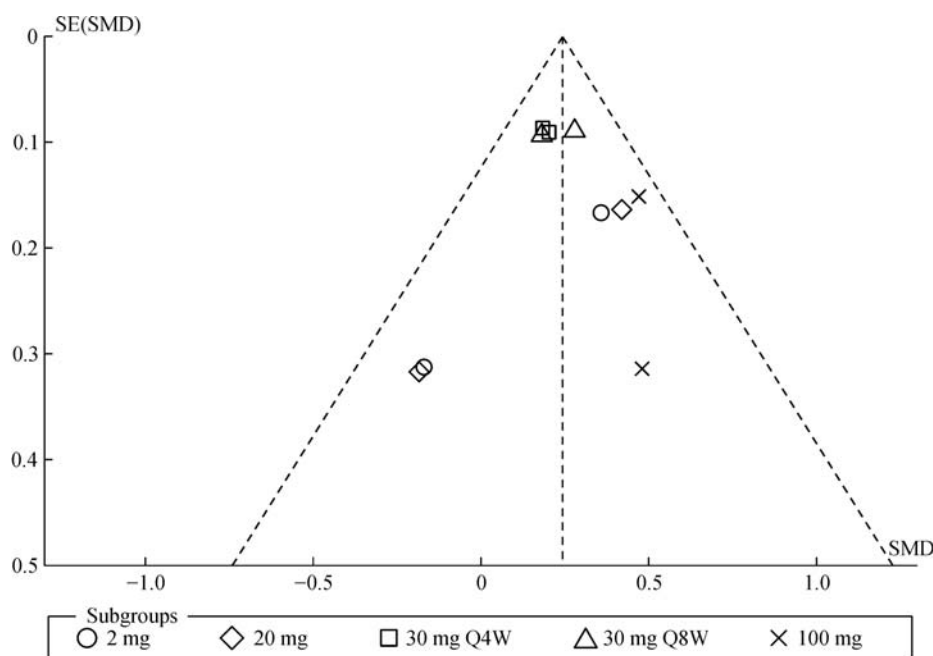


Fig. 3 Funnel plot of the five studies that evaluated the effect of benralizumab on FEV1.

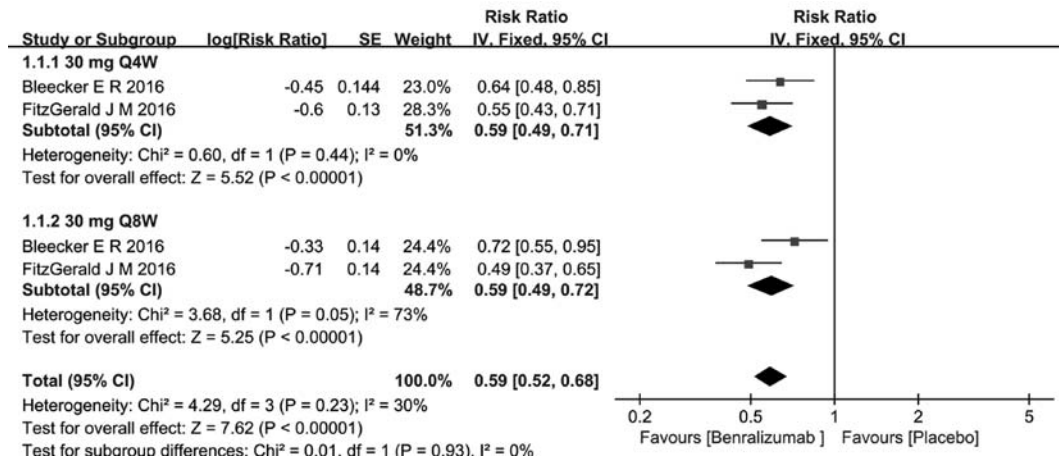


Fig. 4 Forest plot of the effect of benralizumab treatment on asthma exacerbations versus the placebo. Fixed-effect model. SE, standard error; IV, inverse variance; CI, confidence interval.

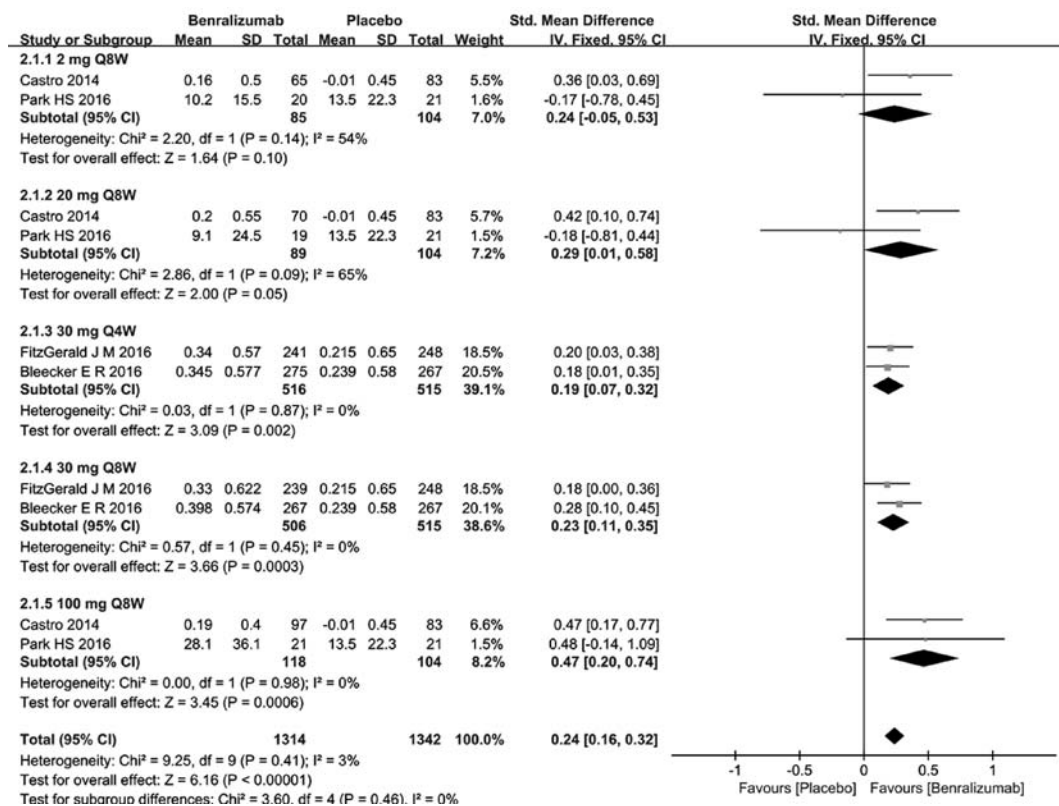


Fig. 5 Effect of benralizumab treatment versus the placebo on FEV1. SD, standard deviation; IV, inverse variance; CI, confidence interval; Std. Mean Difference, standardized mean difference.

0.74, $P = 0.0006$), without significant heterogeneity ($I^2 = 0\%$). Benralizumab at doses of 2 and 20 mg Q8W had no significant effect on FEV1 (SMD = 0.24, 95% CI: -0.05 to 0.53, $P = 0.1$; SMD = 0.29, 95% CI: 0.01–0.58, $P =$

0.05, respectively). In the 30 mg subgroup, 30 mg benralizumab Q8W appeared to be more effective than 30 mg Q4W (SMD = 0.23, 95% CI: 0.11–0.35, $P = 0.0003$; SMD = 0.19, 95% CI: 0.07–0.32, $P = 0.002$, respectively).

Asthma Control Questionnaire (ACQ)

Four trials reported the ACQ-6 scores in association with benralizumab treatment [14,22–24]. All benralizumab doses were associated with a significant reduction in the ACQ-6 scores. The pooled analysis demonstrated that benralizumab was associated with a significant decrease in ACQ-6 scores (MD = −0.25, 95% CI: −0.32 to −0.17, $P < 0.00001$) (Fig. 6). Moreover, this finding was statistically homogeneous ($I^2 = 0\%$). Among the different doses, 100 mg benralizumab Q8W was the most effective dose (MD = −0.44, 95% CI: −0.75 to −0.14, $P = 0.005$). Benralizumab at 2 and 20 mg doses, as well as 30 mg Q8W were less effective (MD = −0.36, 95% CI: −0.67 to −0.06, $P = 0.02$; MD = −0.32, 95% CI: −0.63 to −0.01, $P = 0.04$; MD = −0.27, 95% CI: −0.39 to −0.16, $P < 0.00001$). In the 30 mg subgroup, 30 mg benralizumab Q8W was more effective than 30 mg Q4W (MD = −0.17, 95% CI: −0.28 to −0.06, $P = 0.004$).

Asthma Quality of Life Questionnaire (AQLQ)

The quality of life was assessed in three studies with the use of AQLQ to assess the effect of treatment with

benralizumab [14,22,24]. The pooled analysis revealed that benralizumab significantly improved the AQLQ scores (MD = 0.22, 95% CI: 0.14–0.30, $P < 0.00001$) (Fig. 7). We found an improvement in the mean AQLQ score compared with the placebo in patients who received only 30 mg benralizumab. However, 30 mg benralizumab Q4W was less effective than 30 mg Q8W (MD = 0.17, 95% CI: 0.05–0.29, $P = 0.006$; MD = 0.28, 95% CI: 0.15–0.40, $P < 0.0001$, respectively). No statistically significant heterogeneity was observed between the studies ($I^2 = 0\%$).

Adverse events

All studies assessed adverse events, and benralizumab was well-tolerated. Adverse events were summarized for eosinophilic and non-eosinophilic participants combined in one study [22]. Therefore, only four studies can be pooled for the analysis. Based on the results of the meta-analysis, the overall incidence of adverse events was similar in both treatment and placebo groups (RR = 0.98, 95% CI: 0.93–1.02, $P = 0.34$) (Fig. 8). Statistical heterogeneity was not observed ($I^2 = 0\%$). The most common adverse events were as follows: nasopharyngitis,

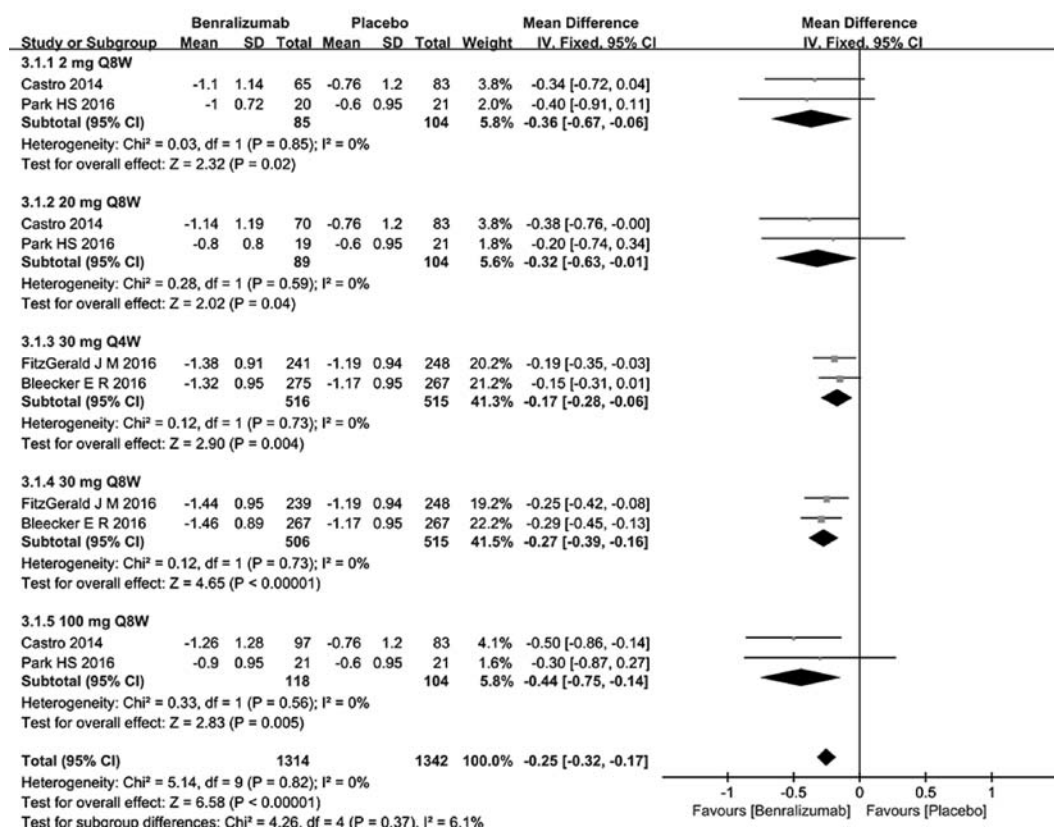


Fig. 6 Effect of benralizumab treatment versus the placebo on the ACQ-6 score. SD, standard deviation; IV, inverse variance; CI, confidence interval.

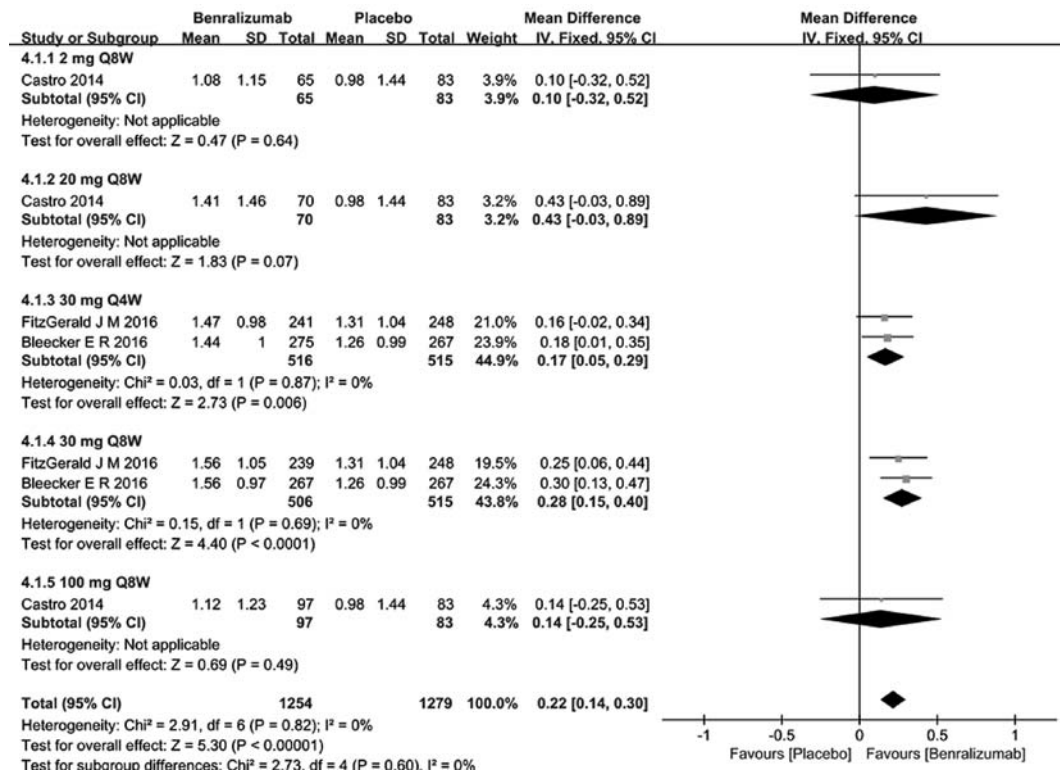


Fig. 7 Effect of benralizumab treatment versus the placebo on the AQLQ score. SD, standard derivation; IV, inverse variance; CI, confidence interval.

asthma worsening, upper respiratory tract infection, injection site reaction, and headache.

Discussion

Our meta-analysis was performed to investigate the safety and efficacy of different doses of benralizumab for the treatment of patients with eosinophilic asthma. Benralizumab decreased the asthmatic exacerbation, improved the FEV1 and AQLQ scores, reduced the ACQ scores, and exhibited a placebo-like safety profile. Furthermore, our findings suggest that the Q8W dosage can improve the health-related quality of life and appear to be more effective than the Q4W dosage, with 30 mg being the most effective reported dosage. To the best of our knowledge, this is the first meta-analysis of recent studies that have evaluated the efficacy and dosage of benralizumab for the treatment of eosinophilic asthma.

Our meta-analysis found that benralizumab significantly reduced the asthma exacerbations, improved the pulmonary function, and enhanced the symptom control for patients with moderate to severe asthma and eosinophilic inflammation. However, the mechanism of action of benralizumab differs from mepolizumab and reslizumab. The IL-5 receptor is a type I cytokine receptor that can recognize and respond to cytokines that have four α -helical

strands [25]. Upon binding to the IL-5 receptor, complex tyrosine kinases (e.g., JAK2 and Lyn) are activated, leading to an activation of intracellular signaling pathway. Benralizumab directly targets the eosinophil IL-5 receptor to induce eosinophil apoptosis and can circumvent the induction of increased cytokine production related to anticytokine antibodies [26]. Furthermore, a recent study retrospectively analyzed serum samples from two clinical trials and found that the concentrations of the eosinophil-resident cytotoxic granule proteins, eosinophil cationic protein, and eosinophil-derived neurotoxin were reduced following benralizumab treatment [27]. This result suggests that cytotoxic granule proteins are not released following eosinophil reduction [27].

Our study demonstrated that benralizumab significantly reduced the asthma exacerbations and improved the FEV1. This result might be due to the selection of a greater population with eosinophilic asthma. For instance, Castro *et al.* [22] evaluated the efficacy and safety of benralizumab in patients with eosinophilic and non-eosinophilic asthma. Patients in the subgroup had baseline blood eosinophils ≥ 300 cells/ μ L, and treatment with benralizumab was associated with greater improvements in lung function and quality of life compared with the placebo group [22]. In addition, Ortega *et al.* [28] reported that a blood eosinophil count greater than 150 cells/ μ L was

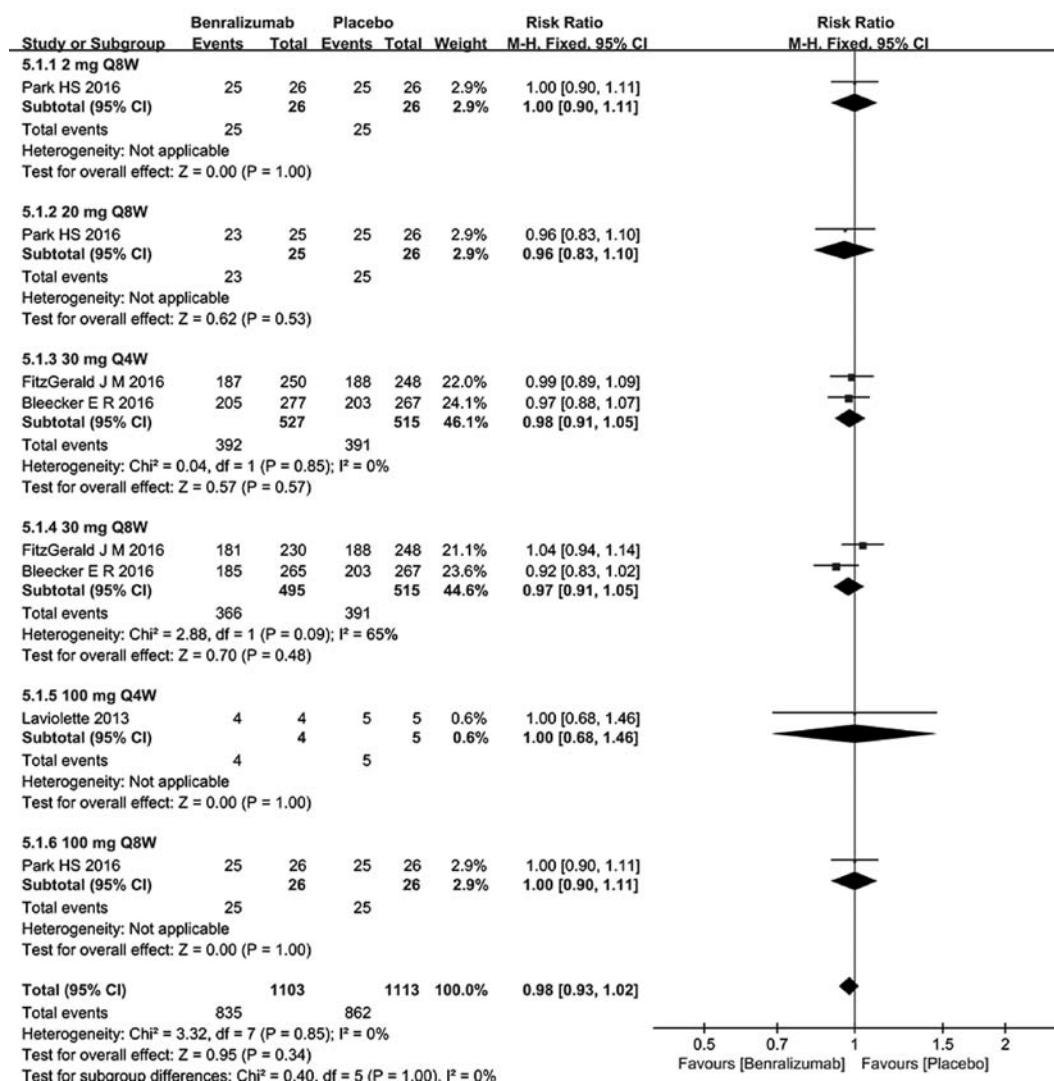


Fig. 8 Forest plot of the effect of benralizumab treatment on adverse events versus the placebo. M-H, Mantel-Haenszel; CI, confidence interval.

sufficient to select for patients who had significant reductions in symptom exacerbations following mepolizumab treatment compared with the placebo. This finding suggested that blood eosinophil counts might also be a reliable and simple biomarker for patient selection associated with positive clinical responses to benralizumab treatment.

A phase IIb dose-ranging study found that in 20 and 100 mg dosages, benralizumab reduced the asthma exacerbations in patients with uncontrolled asthma and eosinophilia (>300 cells/ μ L) [23]. Furthermore, a global meta-analysis revealed that benralizumab with 20 mg dosage appeared to be excellent alternative for severe asthmatics [29]. However, the regimen consisting of two doses was not associated with a significant improvement in the AQLQ scores. According to an exposure-response analysis and

overall risk assessment, a subcutaneous administration of 30 mg benralizumab Q8W appeared to be the optimum benralizumab dosing regimens [30]. Two subsequent phase 3 studies identified the two optimal benralizumab dosing regimens. Both studies indicated that 30 mg benralizumab Q4W and Q8W significantly reduced the annual rate of asthma exacerbations, improved the lung function, and enhanced the patient quality of life [14,24]. Consistent with these two trials, our analysis found that the 30 mg Q8W dose was more efficacious than the 30 mg Q4W dosage; however, both dosing regimens improved the ACQ-6 and AQLQ. The small improvements in the ACQ-6 and AQLQ scores are lower than the clinical minimally important difference of 0.5 units [22,31]. Therefore, the clinical benefit of these small improvements is uncertain.

A similar percentage of patients who received benralizumab or the placebo reported adverse events in all included studies. The pooled analysis also indicated that benralizumab was well-tolerated. Few adverse events were considered to be drug-related, and discontinuations due to benralizumab were uncommon.

Our study has several limitations. First, given the small number of studies included in the meta-analysis, our ability to draw conclusions is limited. Second, the subgroups were small, with only one to three studies in each subgroup, which may influence our results. Third, although these studies shared many common issues, substantial heterogeneities were observed across the studies (e.g., the type of patients included, study design, follow-up duration, and definitions of asthma exacerbation).

Conclusions

In conclusion, this meta-analysis indicated that benralizumab can be safely used to improve the FEV1 and AQLQ scores, reduced the asthmatic exacerbations, and improved the ACQ-6 scores. A benralizumab dose of 30 mg Q8W appears to be the optimal treatment regimen for adults with uncontrolled eosinophilic asthma. Further trials are required to further investigate the safety and efficacy of benralizumab in eosinophilic asthma, as well as the threshold eosinophil count that results in significant therapeutic improvement following benralizumab treatment.

Compliance with ethics guidelines

Ting Liu, Faping Wang, Geng Wang, and Hui Mao declare no conflict of interest. This manuscript does not involve any research protocols requiring approval by any relevant institutional review boards or ethics committees.

References

- Global Asthma Network. The Global Asthma Report 2014. Auckland, New Zealand: Global Asthma Network, 2014. Available: http://www.globalasthmareport.org/resources/Global_Asthma_Report_2014.pdf
- McIvor RA. Emerging therapeutic options for the treatment of patients with symptomatic asthma. *Ann Allergy Asthma Immunol* 2015; 115(4): 265–271.e5
- Torrego A, Solà I, Munoz AM, Roqué I Figuls M, Yepes-Núñez JJ, Alonso-Coello P, Plaza V. Bronchial thermoplasty for moderate or severe persistent asthma in adults. *Cochrane Database Syst Rev* 2014; (3): CD009910
- Chung KF. Targeting the interleukin pathway in the treatment of asthma. *Lancet* 2015; 386(9998): 1086–1096
- Mitchell PD, El-Gammal AI, O'Byrne PM. Emerging monoclonal antibodies as targeted innovative therapeutic approaches to asthma. *Clin Pharmacol Ther* 2016; 99(1): 38–48
- Aleman F, Lim HF, Nair P. Eosinophilic endotype of asthma. *Immunol Allergy Clin North Am* 2016; 36(3): 559–568
- Cardet JC, Israel E. Update on reslizumab for eosinophilic asthma. *Expert Opin Biol Ther* 2015; 15(10): 1531–1539
- Khorasanizadeh M, Eskian M, Assa'ad AH, Camargo CA Jr, Rezaei N. Efficacy and safety of benralizumab, a monoclonal antibody against IL-5R α , in uncontrolled eosinophilic asthma. *Int Rev Immunol* 2016; 35(4): 294–311
- Wu Y, Li JJ, Kim HJ, Liu X, Liu W, Akhgar A, Bowen MA, Spitz S, Jiang XR, Roskos LK, White WI. A neutralizing antibody assay based on a reporter of antibody-dependent cell-mediated cytotoxicity. *AAPS J* 2015; 17(6): 1417–1426
- Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, Ortega H, Chané P. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet* 2012; 380(9842): 651–659
- Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Keene ON, Yancey SW, Ortega HG, Pavord ID; SIRIUS Investigators. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med* 2014; 371(13): 1189–1197
- Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, Humbert M, Katz LE, Keene ON, Yancey SW, Chané P; MENSA Investigators. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med* 2014; 371(13): 1198–1207
- Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusselle GG, Bardin P, Murphy K, Maspero JF, O'Brien C, Korn S. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet Respir Med* 2015; 3(5): 355–366
- Bleecker ER, FitzGerald JM, Chané P, Papi A, Weinstein SF, Barker P, Sproule S, Gilmartin G, Aurivillius M, Werkström V, Goldman M; SIROCCO study investigators. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β_2 -agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet* 2016; 388(10056): 2115–2127
- Ghazi A, Trikha A, Calhoun WJ. Benralizumab—a humanized mAb to IL-5R α with enhanced antibody-dependent cell-mediated cytotoxicity—a novel approach for the treatment of asthma. *Expert Opin Biol Ther* 2012; 12(1): 113–118
- Busse WW, Katial R, Gossage D, Sari S, Wang B, Kolbeck R, Coyle AJ, Koike M, Spitalny GL, Kiener PA, Geba GP, Molino NA. Safety profile, pharmacokinetics, and biologic activity of MEDI-563, an anti-IL-5 receptor alpha antibody, in a phase I study of subjects with mild asthma. *J Allergy Clin Immunol* 2010; 125(6): 1237–1244.e2
- Menzella F, Lusuardi M, Galeone C, Facciolo N, Zucchi L. The clinical profile of benralizumab in the management of severe eosinophilic asthma. *Ther Adv Respir Dis* 2016; 10(6): 534–548
- Higgins J, Green S. *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1. 0. The Cochrane Collaboration, 2011
- Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savović J, Schulz KF, Weeks L, Sterne JA; Cochrane Bias

- Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; 343: d5928
20. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; 327(7414): 557–560
 21. Laviolette M, Gossage DL, Gauvreau G, Leigh R, Olivenstein R, Katial R, Busse WW, Wenzel S, Wu Y, Datta V, Kolbeck R, Molfino NA. Effects of benralizumab on airway eosinophils in asthmatic patients with sputum eosinophilia. *J Allergy Clin Immunol* 2013; 132(5): 1086–1096.e5
 22. Castro M, Wenzel SE, Bleecker ER, Pizzichini E, Kuna P, Busse WW, Gossage DL, Ward CK, Wu Y, Wang B, Khatry DB, van der Merwe R, Kolbeck R, Molfino NA, Raible DG. Benralizumab, an anti-interleukin 5 receptor α monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study. *Lancet Respir Med* 2014; 2(11): 879–890
 23. Park HS, Kim MK, Imai N, Nakanishi T, Adachi M, Ohta K, Tohda Y; Asian Benralizumab Study Group. A phase 2a study of benralizumab for patients with eosinophilic asthma in South Korea and Japan. *Int Arch Allergy Immunol* 2016; 169(3): 135–145
 24. Fitzgerald JM, Bleecker ER, Nair P, Korn S, Ohta K, Lommatzsch M, Ferguson GT, Busse WW, Barker P, Sproule S, Gilmartin G, Werkström V, Aurivillius M, Goldman M; CALIMA study investigators. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2016; 388 (10056): 2128–2141
 25. Hilvering B, Xue L, Pavord ID. Evidence for the efficacy and safety of anti-interleukin-5 treatment in the management of refractory eosinophilic asthma. *Ther Adv Respir Dis* 2015; 9(4): 135–145
 26. Rudulier CD, Larché M, Moldaver D. Treatment with anti-cytokine monoclonal antibodies can potentiate the target cytokine rather than neutralize its activity. *Allergy* 2016; 71(3): 283–285
 27. Pham TH, Damera G, Newbold P, Ranade K. Reductions in eosinophil biomarkers by benralizumab in patients with asthma. *Respir Med* 2016; 111: 21–29
 28. Ortega HG, Yancey SW, Mayer B, Gunsoy NB, Keene ON, Bleecker ER, Brightling CE, Pavord ID. Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies. *Lancet Respir Med* 2016; 4(7): 549–556
 29. Cabon Y, Molinari N, Marin G, Vachier I, Gamez AS, Chanez P, Bourdin A. Comparison of anti-interleukin-5 therapies in patients with severe asthma: global and indirect meta-analyses of randomized placebo-controlled trials. *Clin Exp Allergy* 2017; 47(1): 129–138
 30. Wang B, Yan L, Hutmacher M, White W, Ward CK, Nielsen J, Wu Y, Goldman M, Raible DG, Roskos L. Exposure-response analysis for determination of benralizumab optimal dosing regimen in adults with asthma. *Am J Respir Crit Care Med* 2014; 189: A1324
 31. Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific Quality of Life Questionnaire. *J Clin Epidemiol* 1994; 47(1): 81–87