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Original

Meta-analysis of Low-versus High-dose Benralizumab in Adults with Uncontrolled Eosinophilic Asthma

Koichi ANDO*[1,2], Akihiko TANAKA[1], Takuya YOKOE[1], Tsukasa OHNISHI[1], Shin INOUE[2] and Hironori SAGARA[1]

Abstract: The aim of the present study was to assess the non-inferiority of low-dose benralizumab relative to high-dose benralizumab as a treatment option for uncontrolled eosinophilic asthma through a meta-analysis of efficacy and safety in randomized controlled trials (RCTs). PubMed, the Cochrane Library Database, and Scopus were searched to identify relevant articles. Outcome measures were a change in the Asthma Control Questionnaire-6 (ACQ-6) score and the exacerbation rate. In addition, the meta-analysis assessed the incidence of adverse events, injection site reactions, and pyrexia or influenza-like illness. Two RCTs with two doses of benralizumab (20 and 100 mg) and a placebo for the treatment of uncontrolled eosinophilic asthma met the criteria and were included in the present study. Non-inferiority of low-dose (20 mg) versus high-dose (100 mg) benralizumab was shown for the change in ACQ-6 score, exacerbation rate, and the incidence of adverse events, injection site reactions, and pyrexia or influenza-like illness. Although not significant, the incidence of pyrexia or influenza-like illness was lower in patients treated with low-dose benralizumab. These results suggest that low-dose (20 mg) benralizumab is effective for symptom control and reduction of exacerbation rate in uncontrolled eosinophilic asthma, with lower treatment costs.

Key words: benralizumab, dose comparison, meta-analysis, uncontrolled eosinophilic asthma

Introduction

The global use of inhaled corticosteroids (ICS) has contributed to a significant reduction in the frequency of hospitalization for acute exacerbation in patients with bronchial asthma[1,2]. However, there are still many patients with asthma that is not optimally controlled by a combination of drugs, including ICS and systemic glucocorticoids[3]. Therefore, there is an unmet medical need for additional treatment options for these patients[1-3].

There are two main subtypes of bronchial asthma, namely eosinophilic asthma and non-eosinophilic asthma, although the definition of the subtypes is still not standardized. Eosinophilic (eosinophil-mediated) asthma is relatively common, and most cases involve eosinophilic airway inflammation that is predominantly triggered by inhaled allergens or viral infections. Most cases

[1] *Department of Medicine, Division of Respiratory Medicine and Allergology, Showa University School of Medicine,* 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142-8666, Japan.
[2] *Showa University Dental Hospital Medical Clinic.*
* To whom corresponding should be addressed.

of non-eosinophilic asthma are based on neutrophilic airway inflammation, which may be triggered by environmental exposure to bacterial endotoxins, particulate air pollution, and ozone, as well as by viral infections.

Several drugs are available for the treatment of patients with severe eosinophilic asthma that is uncontrolled by high doses of ICS or two or more controller therapies[1]. Recent trials of anti-interleukin (IL)-5 agents in patients with severe asthma refractory to existing therapies and prominent sputum eosinophilia showed significant reductions in exacerbations[4, 5]. In patients with hypereosinophilic syndromes, IL-5 antagonism leads to significant reductions in the doses of systemic corticosteroids required while maintaining or improving blood eosinophil counts and symptoms[6]. Mepolizumab, a humanized monoclonal antibody against IL-5, selectively inhibits eosinophilic inflammation and contributes to reductions in both exacerbations and the requirement for systemic glucocorticoids[7–9].

Several randomized controlled trials (RCTs) have examined the effects of benralizumab, an anti-IL-5 receptor α monoclonal antibody, on uncontrolled eosinophilic asthma[10–12], with the results showing that a relatively high dose of benralizumab (100 mg) significantly reduces exacerbation rates and improves asthma symptoms and quality of life[10, 12]. A relatively low dose (20 mg) of benralizumab also reduces exacerbation rates in patients with uncontrolled eosinophilic asthma and has a lower incidence of adverse effects[10], but the non-inferiority of low- versus high-dose benralizumab remains untested. Therefore, the aim of the present study was to perform a non-inferiority trial to compare the efficacy and safety of low- versus high-dose benralizumab in patients with uncontrolled eosinophilic asthma through a meta-analysis of RCTs.

Methods

Publication search and inclusion criteria

Searches were performed in MEDLINE (PubMed), Scopus, and the Cochrane Library Database (up to June 2016) using the term "benralizumab". No restrictions were imposed on the search language. Studies were considered eligible for inclusion in the present study if they met the following criteria: (i) an RCT that assessed the clinical efficacy of benralizumab in uncontrolled eosinophilic asthma; (ii) inclusion of the exacerbation rate and Asthma Control Questionnaire-6 (ACQ-6) scores in the outcome measures; and (iii) a minimum of three comparison groups (high-dose benralizumab, low-dose benralizumab, and placebo). In addition, the reference lists of the studies identified were searched for other relevant publications.

ACQ-6 score

The ACQ-6 is a simple questionnaire that is used to measure the adequacy of asthma control and changes in asthma control that occur spontaneously or as a result of treatment. The ACQ-6 has a multidimensional construction for assessment of symptoms (five items, self-administered), rescue bronchodilator use (one item, self-administered), and forced expiratory volume in 1 second ($FEV_{1.0}$) expressed as a percentage of the forced vital capacity (FEV 1 %; one item, completed by clinic staff). Scores range from 0 (total control) to 6 (severe lack of control)[13, 14].

Definitions of uncontrolled eosinophilic asthma

The ELEN index is a proprietary mathematical algorithm that uses blood absolute eosinophil, neutrophil, and lymphocyte cell counts to classify patients with asthma as having $< 2\%$ or $\geq 2\%$ sputum eosinophils, without the need for sputum collection[15]. The decision rule for assignment to eosinophilic or non-eosinophilic groups is as follows: if Score 1 (score for sputum eosinophils $<$ 2.0%) $\leq$ Score 2 (score for sputum eosinophils $\geq$ 2.0%), assign the subject to the eosinophilic group; otherwise, assign the subject to the non-eosinophilic group. Scores 1 and 2 are calculated using the following equations[12]:

Score 1 = −9.5243 + [70.0975 × blood eosinophils / blood lymphocytes] − [3.7790 × ln (blood eosinophils / blood neutrophils)]

Score 2 = −14.5853 + [101.2198 × blood eosinophils / blood lymphocytes] − [3.9567 × ln (blood eosinophils / blood neutrophils)]

In both studies included in the present meta-analysis[10, 12], subtypes of bronchial asthma were determined on the basis of the ELEN index. If Score 1 $\leq$ Score 2, patients were considered to be eligible for inclusion in the studies. Therefore, the present meta-analysis is specific to patients with eosinophilic asthma.

The common definition of uncontrolled asthma in the two studies was a documented history of two to six exacerbations needing treatment with systemic corticosteroids in the past year, a morning prebronchodilator $FEV_{1.0}$ of 40% or higher but less than 90% predicted, and an ACQ-6 score of 1.5 or higher.

Quality assessment and statistical analysis

The methodological quality of the trials included in the present analysis was evaluated using the Jadad score, which assesses studies on the basis of their description of randomization, blinding, and dropout[16]. Statistical heterogeneity among RCTs was assessed using the I^2 statistic, which measures the degree of heterogeneity in outcome measures among studies by calculating the percentage of the total variation across studies[17]. Random-effect[18] and fixed[19] models were used in the presence and absence of statistical heterogeneity, respectively.

Differences between the low- and high-dose benralizumab groups are expressed as the weighted mean difference (WMD), relative risk (RR), and 95% confidence intervals (CI). The WMD and 95% CIs were used for comparisons of changes in ACQ-6 scores, exacerbation rate, and percentage changes in $FEV_{1.0}$, $FEV_{1.0}$ / predicted $FEV_{1.0}$, mean peak expiratory flow (PEF), and fractional exhaled nitric oxide (FeNO), whereas and RR and 95% CIs were used for comparisons of the incidence of adverse events, injection site reactions, and pyrexia or influenza-like illness. The incidence of pyrexia or influenza-like illness was estimated by adding the number of cases of pyrexia to those of influenza-like illness based on data described in the original publication. When only one trial investigated the effect of benralizumab (20 and 100 mg) for a particular outcome, only a non-inferiority test and comparison between low- and high-dose groups were conducted because a meta-analysis for these outcomes was not possible.

Non-inferiority for a change in ACQ-6 score, percentage changes in $FEV_{1.0}$, $FEV_{1.0}$ / predicted

$FEV_{1.0}$, mean PEF, and FeNO were defined as the lower 95% CI for WMD being no lower than −0.5, −0.2, −20.0, −20.0, and −30.0, respectively. Non-inferiority for exacerbation rate was defined as the upper 95% CI for WMD being no greater than 0.20. Non-inferiority for the incidence of adverse events, injection site reactions, and pyrexia or influenza-like illness was defined as the upper 95% CI for RR being no greater than 3.0. Comparison of these outcome measures between low- and high-dose groups was also conducted and $P < 0.05$ was taken to indicate a significant difference between groups. All analyses were performed using RevMan 5 ver. 5.3 for Windows (Cochrane Corporation, Oxford, UK).

Evaluation of publication bias

Publication bias occurs if the results of published studies differ systematically from those of unpublished studies. In the present meta-analysis, publication bias was investigated using a funnel plot in which the standard error of log of the odds ratio (OR) for each study was plotted against its OR[20]. A funnel plot is a scatter plot of the intervention effect estimated from individual studies against a measure of the size of each study. In common with forest plots, it is most common to plot the effect estimate on the horizontal scale and the measure of study size on the vertical axis. This is the opposite of conventional graphical displays for scatter plots, in which the outcome is plotted on the vertical axis and the covariate is plotted on the horizontal axis. Therefore, effects estimated from small studies will scatter more widely at the bottom of the graph, with the spread narrowing among larger studies. In the absence of bias, the plot should approximately resemble a symmetrical funnel. If there is bias, for example because smaller studies without significant effects remain unpublished, this will lead to an asymmetrical appearance of the funnel plot with a gap in a bottom corner of the graph. The asymmetry of the funnel plot was evaluated statistically in the present study using Begg's test[21–23].

Results

Article selection, Jadad score, and characteristics of eligible studies

The study selection process is shown in Fig. 1. Twelve relevant citations were retrieved from the databases, of which seven studies were not RCTs. Finally, two RCTs were included in the present meta-analysis[10, 12]. Both these articles had a Jadad score of 5 (Table 1), indicating that both articles were of high quality. The characteristics of the two studies on the efficacy of benralizumab for the treatment of uncontrolled asthma are given in Table 2. One study was performed in the US and the other was performed in South Korea and Japan.

Meta-analysis of the effects of benralizumab on ACQ-6 score

The two trials investigated the effects of low-dose (20 mg; 89 patients) and high-dose (100 mg; 118 patients) benralizumab on ACQ-6 scores. The degree of heterogeneity measured by the I^2 statistic was not significant, so the analysis was conducted using a fixed-effect model. This analysis showed the non-inferiority of low- versus high-dose benralizumab for a change in ACQ-6 score (WMD = 0.22, 95% CI −0.15, 0.59; Fig. 2A).

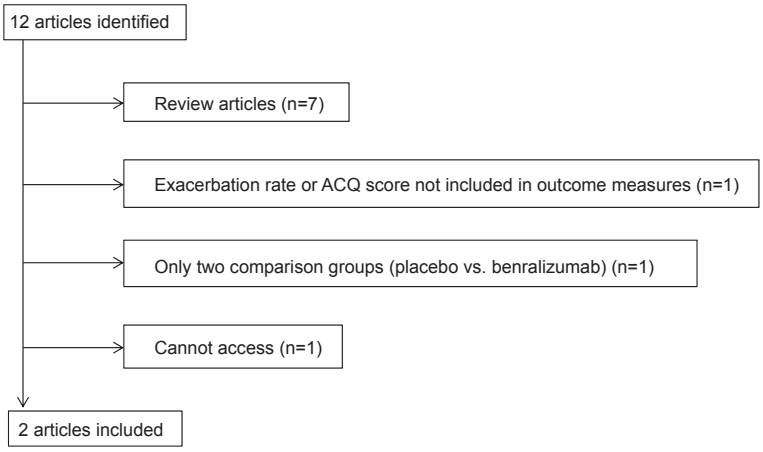

Fig. 1. Flow diagram of the study selection process. ACQ, Asthma Control Questionnaire-6.

Table 1. Jadad quality scores for the randomized controlled trials included in the meta-analysis

Study	Factors and Jadad score			
	Randomization	Blinding	Withdrawal or drop-out	Total Jadad score
Castro *et al*[12]	2	2	1	5
Park *et al*[10]	2	2	1	5

Table 2. Characteristics of the studies included in the meta-analysis

Study	Year of publication	Type of study	Country	No. patients	Criteria	Drugs	Dosage	Duration
Castro *et al*[12]	2014	RCT	USA	609	Adults with two to six exacerbations in the past year	Placebo or benralizumab 2, 20, or 100 mg	Every 4 weeks for the first three doses, then every 8 weeks for 1 year	1 year
Park *et al*[10]	2016	RCT	South Korea and Japan	106	Adults with two to six exacerbations in the past year	Placebo or benralizumab 2, 20, or 100 mg	Weeks 0 (Day 1), 4, 8, 16, 24, 32, and 40	52 weeks

RCT, randomized controlled trial.

Exacerbation rate and percentage changes in $FEV_{1.0}$, $FEV_{1.0}$/predicted $FEV_{1.0}$, and mean PEF

Only one trial investigated the effects of benralizumab (20 and 100 mg) on exacerbation rate and percentage changes in $FEV_{1.0}$, $FEV_{1.0}$/predicted $FEV_{1.0}$, and mean PEF[10, 12]. Therefore, meta-analyses could not be performed for these outcomes, and only a non-inferiority test and a comparison were performed between the low- and high-dose groups. Non-inferiority of low- ver-

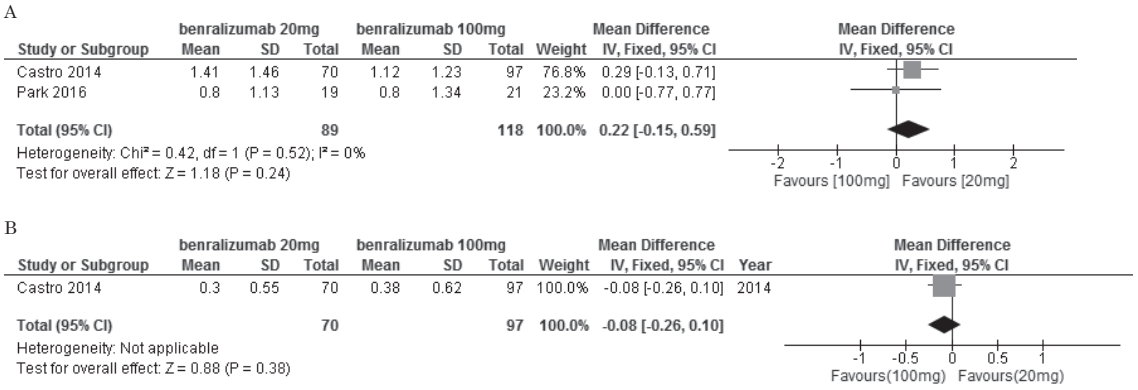

Fig. 2. Forest plots for (A) Asthma Control Questionnaire-6 (ACQ-6) scores and (B) exacerbation rate in the two studies included in the present meta-analysis, namely those of Park *et al*[10] and Castro *et al*[12] WMD, weighted mean difference; CI, confidence interval.

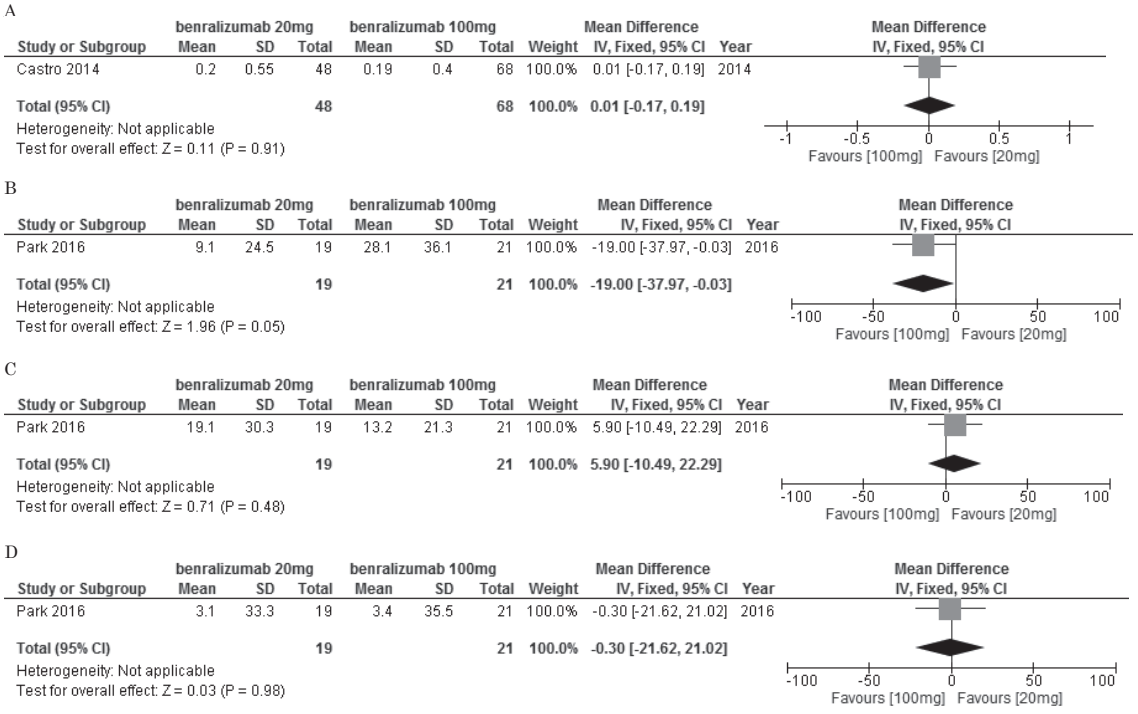

Fig. 3. Forest plots for percentage changes in (A) forced expiratory volume in one second ($FEV_{1.0}$), (B) $FEV_{1.0}$ / predicted $FEV_{1.0}$, (C) mean peak expiratory flow (PEF), and (D) fractional exhaled nitric oxide (FeNO) in the studies of Park *et al*[10] and Castro *et al*[12] WMD, weighted mean difference; CI, confidence interval.

sus high-dose benralizumab was shown for exacerbation rate (WMD = −0.08, 95% CI −0.26, 0.10; Fig. 2B), percentage change in $FEV_{1.0}$, (WMD = 0.01, 95% CI −0.17, 0.19; Fig. 3A), percentage change in mean PEF (WMD = 5.90, 95% CI −10.49, 22.29; Fig. 3C), and percentage change in FeNO (WMD = −0.30, 95% CI −21.61, 21.02; Fig. 3D). The WMD for the percentage change in $FEV_{1.0}$ / predicted $FEV_{1.0}$ was −19.0 (95% CI −37.97, −0.03). The lower CI was lower than

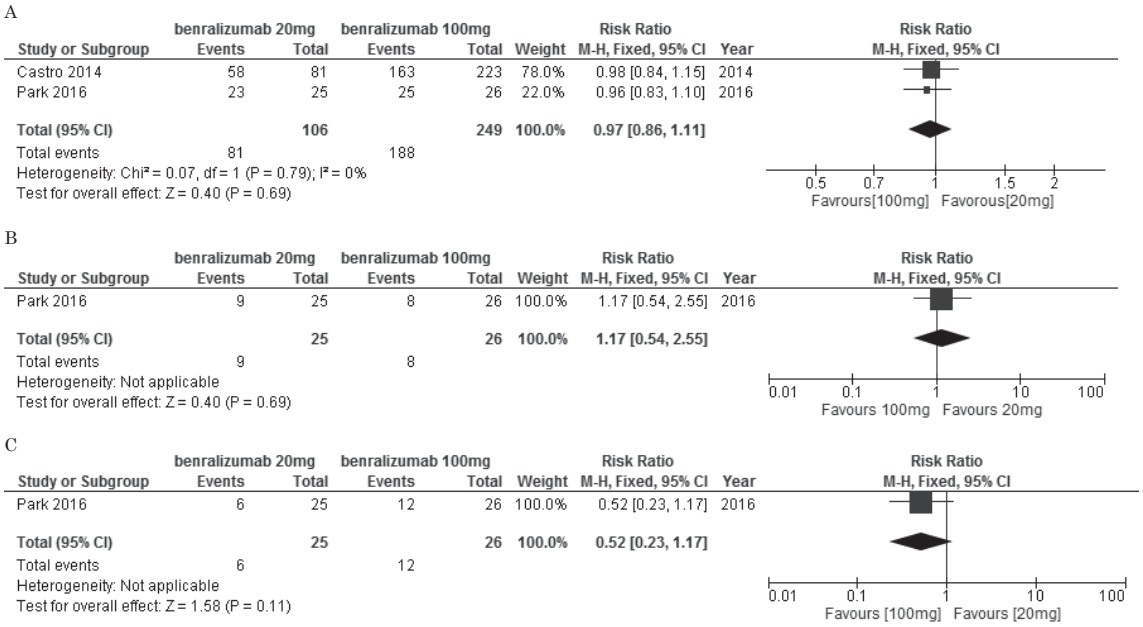

Fig. 4. Forest plots for the incidence of (A) adverse events, (B) injection site reactions, and (C) pyrexia or influenza-like illness in the studies of Park *et al*[10] and Castro *et al*[12] RR, relative risk; CI, confidence interval.

the margin of non-inferiority of −30.0; therefore, non-inferiority of low- versus high-dose benralizumab was not shown for this outcome (Fig. 3B).

Adverse events, injection site reactions, and pyrexia or influenza-like illness

Both trials investigated the effects of low-dose (20 mg) benralizumab on adverse events. The degree of heterogeneity measured by the I^2 statistic was not significant, so an analysis using a fixed-effect model was conducted. Because only one trial investigated the effects of benralizumab (20 and 100 mg) on injection site reactions and pyrexia or influenza-like illness[10], meta-analyses for these outcomes could not be performed. Only non-inferiority tests and comparisons between low- and high-dose groups were conducted. Non-inferiority of low- versus high-dose benralizumab was shown for the incidence of adverse events (RR = 0.97, 95% CI 0.86, 1.11), injection site reactions (RR = 1.17, 95% CI 0.54, 2.55), and pyrexia or influenza-like illness (RR = 0.52, 95% CI 0.23, 1.17; Fig. 4A-C). In addition, although not significant, the incidence of pyrexia or influenza-like illness tended to be lower in patients treated with low-dose benralizumab ($P = 0.11$; Fig. 4C). Results of non-inferiority tests and comparisons between the groups based on a meta-analysis of the studies included in the analysis are given in Table 3.

Bias assessment

A funnel plot (Fig. 5) showed that the two samples were distributed symmetrically. A Begg's test performed to evaluate the asymmetry of the funnel plot showed that there was no significant asymmetry ($P = 0.317$). This suggests that there was no significant publication bias or, at

Table 3. Results of non-inferiority tests and comparisons between groups in the meta-analysis

Outcome	No. patients		RR or WMD (95% CI)	Non-inferiority	*P*-value*
	20 mg benralizumab	100 mg benralizumab			
ACQ-6 score	89	118	0.22 (−0.15, 0.59)	Accepted	0.24
Exacerbation rate	70	97	−0.08 (−0.26, 0.10)	Accepted	0.38
% Change in $FEV_{1.0}$	48	68	0.01 (−0.17, 0.19)	Accepted	0.91
% Change in $FEV_{1.0}$ / predicted $FEV_{1.0}$	19	21	−19.0 (−37.97, −0.03)	NS	0.05
% Change in mean PEF	19	21	5.90 (−10.49, 22.29)	Accepted	0.48
% Change in FeNO	19	21	−0.30 (−21.61, 21.02)	Accepted	0.98
Adverse event	106	249	0.97 (0.86, 1.11)	Accepted	0.69
Injection site reaction	25	26	1.17 (0.54, 2.25)	Accepted	0.69
Pyrexia or influenza-like illness	25	26	0.52 (0.23, 1.17)	Accepted	0.11

**P*-values are shown for differences between groups.

ACQ-6, Asthma Control Questionnaire-6; $FEV_{1.0}$, forced expiratory volume in 1 second; PEF, peak expiratory flow; FeNO, fractional exhaled nitric oxide; RR, relative risk (used for comparisons of the incidence of adverse events, injection site reactions, and pyrexia or influenza-like illness); WMD, weighted mean difference (used for comparisons of changes in ACQ-6 scores, exacerbation rate, and percentage changes in $FEV_{1.0}$, $FEV_{1.0}$ / predicted $FEV_{1.0}$, PEF, and FeNO); CI, confidence interval.

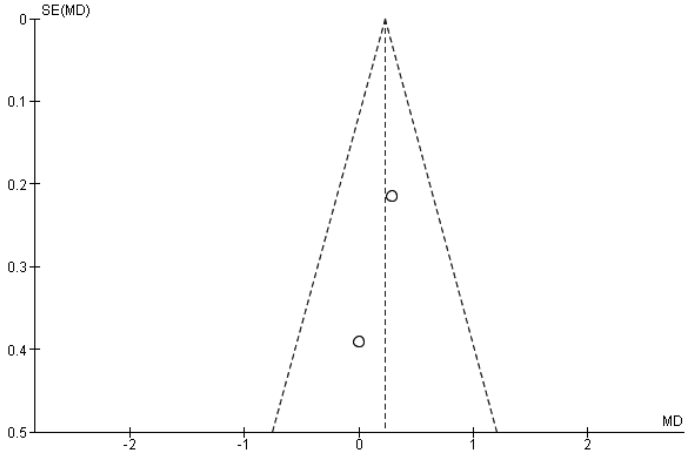

Fig. 5. Bias assessment plot. SE, standard error; MD, mean difference.

least, no bias that had a substantial effect on the conclusions. Therefore, the meta-analysis was considered to be valid.

Discussion

The non-inferiority of low-dose (20 mg) versus high-dose (100 mg) benralizumab for the treatment of uncontrolled eosinophilic asthma was evaluated in a meta-analysis of RCTs. Non-inferiority was shown for change in ACQ-6 score, exacerbation rate, percentage changes in $FEV_{1.0}$,

mean PEF, FeNO, and in the incidence of adverse events, injection site reactions, and pyrexia or influenza-like illness, but not for percentage change in $FEV_{1.0}$ / predicted $FEV_{1.0}$. The incidence of pyrexia or influenza-like illness tended to be lower in the low-dose benralizumab group, although the difference did not reach statistical significance.

Previous studies have shown mixed results for the efficacy of low-dose compared with high-dose benralizumab for preventing exacerbation, due, in part, to differences in asthma severity among patients and in the definition of complications[10, 12]. The results of the present study indicate that both high- and low-dose benralizumab is effective for preventing exacerbations and for symptom control in patients with uncontrolled eosinophilic asthma. These results may be biologically plausible because the maximal stimulatory effect of benralizumab on eosinophil elimination is approximately 170-fold higher than the baseline elimination rate, and the maximal inhibitory effect of benralizumab on eosinophil production is approximately 90% of the baseline production rate[24]. Peripheral blood eosinophils were substantially depleted in subjects who received injections of benralizumab 100 or 25 mg within a few days of administration, and remained at this level for at least 160 days[24]. These results support the hypothesis that the low dose of benralizumab (20 mg) has an inhibitory effect on eosinophil production, and this may have contributed to the non-inferiority of the low dose relative to the high dose for clinical outcomes such as exacerbation rate or ACQ-6 score. Therefore, the present meta-analysis suggests that treatment with an inhibitory dose of benralizumab may be effective in preventing exacerbations, controlling symptoms, and lowering costs for patients with uncontrolled eosinophilic asthma for whom the dose of benralizumab is limited because of adverse events, such as pyrexia or influenza-like illness.

Two recent Phase 3 studies have shown that benralizumab (30 mg) administered subcutaneously every 8 weeks resulted in a significant reduction in the exacerbation rate and ACQ score compared with placebo, and that benralizumab (30 mg) was effective and well tolerated in patients with uncontrolled eosinophilic asthma[25, 26].

The present study has several limitations that should be acknowledged. First, only published studies were included in the analysis, and thus some publication bias may be present, even though this was not apparent in the funnel plot. Second, a meta-analysis is a form of retrospective research that is subject to the metrological deficiencies of the studies included in the analysis. Finally, only one or two articles were used in each analysis.

Within these limitations, the meta-analysis showed the non-inferiority of low-dose (20 mg) relative to high-dose (100 mg) benralizumab in terms of exacerbation rate and asthma symptoms in uncontrolled eosinophilic asthma, in association with lower cost. These results suggest that a low dose of benralizumab can be effective in preventing exacerbations and for the management of asthma at a relatively low cost. Given the limitations of the present meta-analysis, there is a need for further research to confirm the efficacy of treatment using low-dose benralizumab.

Conflict of interest disclosure

None of the authors has a conflict of interest with regard to the results of the study.

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