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Anti-interleukin 5 Therapy for Eosinophilic Asthma: a Meta-analysis of Randomized Clinical Trials

Fa-Ping Wang[1] · Xiao-Feng Xiong[1] · Ting Liu[1] · Su-Yun Li[2] · De-Yun Cheng[1] · Hui Mao[1]

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Abstract Recently, more and more clinical trials have been performed to evaluate the effects of anti-interleukin (IL)-5 antibodies in eosinophilic asthma. However, a confirm conclusion has not been well established. We therefore sought to conduct a meta-analysis to assess the overall efficacy and safety of anti-interleukin 5 treatments in eosinophilic asthma. RCTs of anti-interleukin 5 treatments in eosinophilic asthma published up to June 2016 in PubMed, Embase, Cochrane library databases, and CBM, which reported pulmonary functions, quality-of-life scores, asthmatic exacerbations, and adverse events were included. Fixed-effect models were used to calculate mean difference, relative risks (RR), and 95 % CIs. Twelve studies involving 3340 patients were identified. Pooled analysis revealed significant improvements in FEV_1 (nine trials, 1935 subjects; MD = 0.12; 95 % CI, 0.08–0.16), and Asthma Quality-of-Life Questionnaire scores (five trials, 1334 subjects; MD = 0.23; 95 % CI, 0.13–0.34). Anti-interleukin 5 treatment was also associated with significantly decreased exacerbation risk than placebo (six trials, 875 subjects; RR = 0.52; 95 % CI, 0.46 to 0.59) and a lower incidence of adverse events (eight trials, 1754 subjects; RR = 0.93; 95 % CI, 0.89 to 0.97). Anti-interleukin 5 treatment is well tolerated and could significantly improve FEV_1, quality of life, and reduced exacerbations risk in patients with eosinophilic asthma. Further trials are necessary to assess the baseline blood eosinophil count to identify the optimal patients of eosinophilic asthma that could benefit from anti-interleukin 5 therapy.

Keywords Eosinophilic asthma · Anti-interleukin 5 · Meta-analysis

Introduction

Asthma is a heterogeneous disease that can be divided into different clinical phenotypes [1]. Eosinophilic asthma, which is the most predominant phenotype, accounts for approximately 50 to 60 % of the total asthma population [2]. The presence of eosinophils and helper T cell 2 (Th2) cytokines have been confirmed to participate in the eosinophilic asthmatic airways [3, 4]. Interleukin 5 (IL-5), the Th2 cell cytokine, plays an important role in eosinophil maturation, differentiation, recruitment, and survival [5]. Thus, the clinical application of antibodies that target IL-5 and its receptor has been considered for asthma treatment in recent years. The humanized anti-interleukin 5 monoclonal antibodies, mepolizumab (formerly termed SCH55700), reslizumab (formerly termed Res-5-0010), and benralizumab (formerly termed MEDI-563) have been developed for clinical application.

Earlier clinical trials showed mepolizumab was effective in mild-moderate asthmatics at reducing sputum and blood eosinophils but had no effect on clinical signs and symptoms [6]. Subsequent studies in a selected group of patients with severe asthma and persistent sputum or blood eosinophilia, mepolizumab decreased exacerbations, reduced use of oral corticosteroids, and improved symptoms and lung function compared with placebo [7–10]. Moreover, several trials

Fa-Ping Wang and Xiao-Feng Xiong contributed equally to this work.

✉ De-Yun Cheng
chengdeyunscu@163.com

✉ Hui Mao
merrymh@126.com

[1] Department of Respiratory Medicine, West China Hospital, Sichuan University, Chengdu 610041, China

[2] Department of Respiratory Medicine, First Affiliated Hospital of Henan College of Traditional Chinese Medicine, Zhengzhou 450000, China

evaluated the role of other alternative IL-5 blockers such as reslizumab and benralizumab. However, results from single studies have been less consistent and some analyses may have been underpowered to detect statistically significant differences. Therefore, we conducted a meta-analysis of randomized controlled trials (RCTs) to assess the overall efficacy and safety of anti-interleukin 5 treatments on eosinophilic asthma.

Methods

Data Sources and Searches

We searched PubMed, Embase, the Cochrane Library, and the Chinese Biological Medicine (CBM) database for articles published up to June 2016 to identify all trials assessing anti-interleukin 5 therapy for patients with eosinophilic asthma, using the following search strategies: (mepolizumab or benralizumab or reslizumab or monoclonal antibody or anti-interleukin 5 or anti-IL-5) and ("pulmonary eosinophilia" [Mesh] or eosinophilia, pulmonary or simple pulmonary eosinophilia or pneumonia, eosinophilic or eosinophilic pneumonias or pneumonias, eosinophilic or eosinophilic pneumonia). Publication species of humans was limited. No language restrictions were applied. In addition, the relevant review articles and their references were checked as well.

Study Selection

Specific inclusion criteria were as follows: (1) adults/adolescents (12 years or older) with a diagnosis of eosinophilic asthma, eosinophilic inflammation was shown by one or more criteria at study entry or in the previous year: a sputum eosinophil count ≥2.5 % or the eosinophil/lymphocyte and eosinophil/neutrophil (ELEN; a surrogate blood-based marker of sputum eosinophilia) index was positive, an exhaled nitric oxide concentration (FENO) ≥50 ppb, and an asthma-related peripheral blood eosinophil count ≥300 μL [11, 12]; (2) participants with anti-interleukin 5 therapy at any dose; (3) randomized (parallel group) placebo-controlled trials; and (4) RCTs reporting the following outcomes: lung function, asthma exacerbations, asthma control and quality-of-life scores, and adverse events. An exacerbation was defined as a worsening of asthma symptoms requiring treatment with systemic corticosteroids or increased doses of rescue medication, and/or the need for asthma-related hospitalization or an emergency room visit, or an unscheduled physician visit. Two authors (FPW) and (XFX) independently screened all references according to the selection criteria. Any disagreements were resolved through discussion or adjudicated by a third author (HM) when necessary.

Data Extraction and Quality Assessment

The Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) statement was followed [13]. Using a standardized data extraction form, FPW and XFX independently extracted data in blinded fashion from eligible studies based on authors, publication year, study design, patient demographic characteristics (age, gender, etc.), type of anti-interleukin 5, dose, and therapy duration and outcome definitions. Disagreements were resolved through consultation with a third author (HM). In addition, we assessed risk of bias using the Cochrane Collaboration's domains which included adequate sequence generation, allocation concealment, blinding of participants and personnel, incomplete outcome data, selective reporting, and other bias [14].

Statistical Analyses

Intervention effects were expressed with risk ratios (RR) and 95 % confidence intervals (CIs) for dichotomous data and mean differences (MD) and 95 % CIs for continuous data. If a study presents more than two interventions, we combined two or three intervention groups into a single-intervention group in accordance with the Cochrane handbook [14]. Dichotomous variables (asthma exacerbations, adverse events) were reported as frequency and proportion, while continuous (FEV_1, Asthma Quality-of-Life Questionnaire (AQLQ) were shown as mean change from baseline and standard derivation (SD). Heterogeneity was quantified by I^2 statistic and the chi-squared test. I^2 value of 50 % indicates significant heterogeneity [15]. Fixed-effect models were used except where we identified statistical heterogeneity when we used a random effect model. Publication bias was tested using funnel plot with the Begg's and Egger's tests [16]. All analyses were performed with according to the intention-to-treat principle. All statistical analysis was performed using Review Manager (version 5.3, The Cochrane Collaboration) and Stata (version 12.0, Stata Corporation, USA), and a P value <0.05 was considered statistically significant.

Meta-analyses may result in type I errors due to sparse data and repetitive testing of accumulating data [17]. To assess the risk of type I errors, we applied trial sequential analysis, a method which can determine whether the evidence in a meta-analysis is reliable and conclusive. If the cumulative z curve crosses the trial the boundaries and the required information size, evidence to reach a conclusion is sufficient and no further trials are needed. We estimated the required information size for FEV_1 using $\alpha = 0.05$ (two-sided), $\beta = 0.20$ (power of 80 %). TSA version 0.9 beta (http://www.ctu.dk/tsa) were used for the analyses [18].

Results

Search Results

A total of 457 potentially relevant articles were identified. Among all the potential studies, 34 duplicate records were removed, leaving 423 articles for screening. After reviewing the titles and abstracts, we identified and retrieved 45 database references in full text for review. Of these articles, 33 articles were excluded owing to wrong population ($n = 16$), no placebo control ($n = 5$), and data unavailable ($n = 12$). Ultimately, 12 studies were included for our systematic review and meta-analysis (Fig. 1).

Characteristics of Studies

We included 12 studies [7–12, 19–24] with 3340 participants (Table 1). The sample sizes ranged from 20 to 621 subjects. Of these, five studies used mepolizumab [7–11], four reslizumab [19–22], and three benralizumab [12, 23, 24]. Treatment duration ranged from 1 day to 52 weeks and follow-up ranged from 12 to 52 weeks. The mean age of patients was 46.8 years old. The anti-interleukin 5 was administered exclusively through intravenous infusion (IV) in seven studies [7, 8, 11, 19–22], and five studies [9, 10, 12, 23, 24] had a subcutaneous (SC) arm. Outcome reporting was varied among studies. FEV_1 was reported in liters in nine trials [7, 8, 10–12, 19–22], as percent of predicted in another two [9, 24], and as both in three trials [8, 10, 19]. Airway hyper-reactivity was reported as the dose of histamine required to produce a 20 % drop in FEV_1 (PC_{20}) in one trial [7]. Five studies included severe eosinophilic asthmatics [8–11, 19], three studies included refractory or uncontrolled eosinophilic asthmatics [7, 20, 22], and the remaining studies did not specify asthma severity [12, 21, 23, 24].

Lung Function

FEV_1 Nine trials reported the data on FEV_1. Mepolizumab was used in four studies showed significant effect on FEV_1 (MD = 0.09; 95 % CI, 0.03 to 0.14; $P = 0.002$). Reslizumab was reported in four studies, also could significantly improve FEV_1 (MD = 0.15, 95 % CI, 0.09 to 0.22; $P < 0.001$). Benralizumab was used in only one study (MD = 0.14, 95 % CI, 0.02 to 0.26; $P = 0.02$). Overall, anti-interleukin 5 treatment were associated with significant improvements in FEV_1 (MD = 0.12; 95 % CI, 0.08 to 0.16; $P < 0.001$) (Fig. 2), with minimal heterogeneity ($I^2 = 15$ %, $P = 0.3$), with no evidence of publication bias (Egger's $P = 0.61$; Begg's $P = 0.86$) (Fig. 3a). Trial sequential analysis found that the optimal

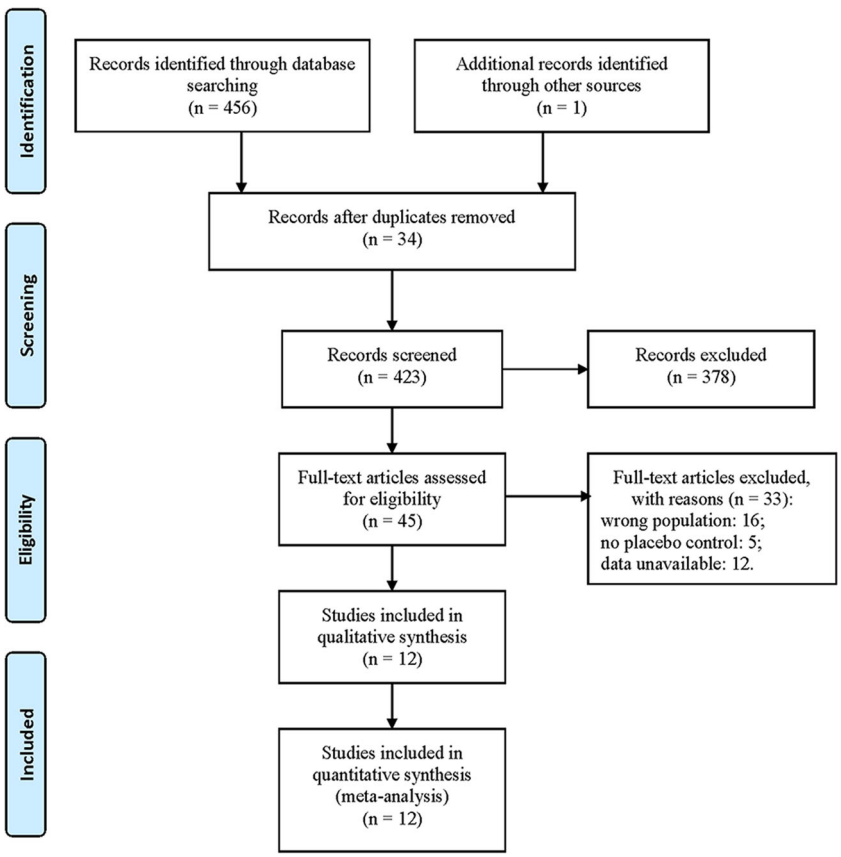

Fig. 1 Flow chart of study identification, inclusion, and exclusion

sample size needed to reliably detect a plausible effect of anti-interleukin 5 treatment on FEV_1 of eosinophilic asthma was 1789 patients, and the patients including in our analysis is far more than it. TSA showed that the cumulative z curve crossed both the conventional boundary and the sequential monitoring boundary, which suggested that the cumulative evidence is reliable and conclusive. Thus, further trials were not required and were unlikely to alter the conclusions (Fig. 4).

Peak Expiratory Flow and Airway Hyper-reactivity

Only one trial depicted the change of peak expiratory flow (PEF) [24] and histamine PC_{20} [7] after treatment with anti-interleukin 5. However, both demonstrated that there was no difference between anti-interleukin 5 treatment and placebo in terms of PEF and histamine PC_{20} values.

Asthma Quality-of-Life Questionnaire

Five trials provided data about AQLQ scores. The pooled analysis showed anti-interleukin 5 treatment was associated with a significant increase in AQLQ scores (MD = 0.23; 95 % CI, 0.13–0.34; $P < 0.001$), with no significant heterogeneity ($I^2 = 0$ %; $P = 0.81$) (Fig. 5). When it comes to subgroups, AQLQ scores improved both in mepolizumab treatment (MD = 0.18; 95 % CI, 0.01–0.36; $P = 0.04$) and reslizumab (MD = 0.27; 95 % CI, 0.13–0.42; $P < 0.001$). Benralizumab only used in one study (MD = 0.21; 95 % CI, −0.12–0.54; $P = 0.22$). Egger and Begg test showed no evidence of publication bias ($P = 0.34$; $P = 0.45$) (Fig. 3b).

Asthma Exacerbations

Six studies were included. Overall, compared with placebo, asthma exacerbations risk was significantly decreased with anti-interleukin 5 treatment (RR = 0.52; 95 % CI, 0.46 to 0.59; $P < 0.001$) (Fig. 6), and there was no heterogeneity among studies ($I^2 = 0$ %, $P = 0.5$). When looking at subgroups, mepolizumab (RR = 0.55; 95 % CI, 0.47 to 0.64; $P < 0.001$) and reslizumab (RR = 0.46; 95 % CI, 0.37 to 0.58; $P < 0.001$) were also linked to markedly lower asthma exacerbations. There was no evidence of publication bias (Egger's $P = 0.41$; Begg's $P = 0.37$) (Fig. 3c).

Adverse Events

Eight studies mentioned adverse events. Anti-interleukin 5 treatment was associated with a trend of lower adverse events incidence (RR = 0.93; 95 % CI, 0.89 to 0.97; $P = 0.001$) (Fig. 7), with no heterogeneity ($I^2 = 0$ %, $P = 0.55$). In subgroup analysis, however, we found no significant differences in both mepolizumab (RR = 0.96; 95 % CI, 0.9–1.03; $P = 0.3$) and benralizumab treatment groups (RR = 0.91; 95 % CI, 0.81–1.02; $P = 0.09$). Only treatment with reslizumab was associated with a trend of lower adverse events incidence (RR = 0.92; 95 % CI, 0.87–0.97; $P = 0.003$). Publication bias was not found (Egger's $P = 0.16$; Begg's $P = 0.21$) (Fig. 3d). The incidence of serious adverse events was low in the anti-interleukin 5 treatment group (1–16 %). Common adverse events were nasopharyngitis, headache, asthma worsening, injection-site reactions and upper respiratory tract infection (Table 2).

Risk of Bias

All the studies had low risk of bias based on the six domains (Fig. 8). The allocation sequence was adequately generated and concealed in most trials except two studies [21, 22]. All the 12 studies were described as being double blinded and reported complete outcome data.

Discussion

Our meta-analysis indicated that anti-interleukin 5 treatment was well tolerated and could significantly improve FEV_1, and quality of life, and reduced the incidence of asthma exacerbations in patients with eosinophilic asthma.

Asthma is a heterogeneous condition that affects more than 300 million people worldwide [25]. Eosinophilic asthma phenotype is characterized by persistent eosinophilic airway inflammation. IL-5 is central to this asthma phenotype because it is responsible for eosinophil production, survival, maturation, recruitment, and activation at sites of allergic inflammation [26]. Given the relationship of IL-5 to eosinophilia and asthma severity, humanized monoclonal antibodies targeting IL-5 have shown great promise in eosinophilic asthma, especially for refractory/severe eosinophilic asthma. Several clinical trials have been performed evaluating the role of anti-interleukin 5 therapy in eosinophilic asthma. However, the evidence is inadequate for drawing robust conclusions, as the sample sizes of these studies are varied and their conclusions inconsistent. Therefore, it seems reasonable to explore this issue further.

Based on the pooled analyses, we found that anti-interleukin 5 could significantly improve FEV_1. The clinical relevance of this finding to patients may be clinically important. However, previous two systematic reviews [27, 28] failed to show a significant effect in lung function, because they were based only on studies with mepolizumab, and Liu et al. [27] only selected one pair of interventions and excluded the others when studies with multiple intervention groups, which is not generally recommended by Cochrane Collaboration [14]. Additionally, both the two systematic reviews included an unselected population of patients with asthma. In contrast to previous systematic reviews [27, 28], we identified a

Table 1 Characteristic of randomized controlled trials included

Reference	Study design	No. of subjects	Age	Selection criteria[a]	Drug	Routine	Treatment duration	Outcomes	Follow-up	Exacerbation definition
Haldar [7]	Single-center double-blind, parallel	61	18–72	(1)	Mepolizumab 750 mg	IV	50 weeks	Blood and sputum eosinophils; FEV_1; AQLQ; JACQ; histamine PC_{20}; asthma exacerbations	50 weeks	Periods of deterioration in asthma control in subjects who had been treated with high-dose oral prednisolone for at least 5 days
Nair [8]	Single-center, double-blind, parallel	20	NM	(1)	Mepolizumab 750 mg	IV	16 weeks	Blood and sputum eosinophils; FEV_1; JACQ; asthma exacerbations; reduction in the dose of prednisone	26 weeks	A patient initiated increase in the daily dose of albuterol of 4 or more puffs to control symptoms of chest tightness or as any 1 of the following: nocturnal or waking respiratory symptoms on 2 consecutive days, a decrease of more than 15 % in the FEV_1 from the level at randomization after the use of albuterol, or a 2-point worsening in the Likert score for cough by the investigators at their discretion on the basis of general clinical worsening.
Pavord [11]	Multi-center, double-blind	621	12-74	(1) or (2) or (3)	Mepolizumab 75, 250, or 750 mg	IV	52 weeks	Blood and sputum eosinophils; FEV_1; AQLQ; ACQ-6; asthma exacerbations	52 weeks	Worsening of asthma requiring use of oral corticosteroids for 3 or more days, admission, or a visit to the emergency department, 50 % increase in rescue medication on at least 2 of 3 successive days, increased frequency of nocturnal awakening due to asthma for at least 2 of 3 successive nights, or overall asthma symptom score of 5 (scale 1 to 5) for at least 2 of 3 successive days
Bel [9]	Multi-center double-blind, parallel	135	16–74	(3)	Mepolizumab 100 mg	SC	20 weeks	Asthma exacerbations; ACQ-5;SGRQ; reduction in the oral glucocorticoid dose	32 weeks	A worsening of asthma leading to the doubling (or more) of the existing maintenance dose of oral glucocorticoids for 3 or more days or hospital admission or an emergency department visit for asthma treatment
Ortega [10]	Multi-center double-blind,	576	12–84	(3)	Mepolizumab 75 or 100 mg	IV and SC	32 weeks	Asthma exacerbations; ACQ-5; FEV1; blood eosinophil	40 weeks	Worsening of asthma such that the treating physician elected to administer systemic glucocorticoids for at least 3 days or the patient visited an emergency department or was hospitalized
Castro [19]	Multi-center, double-blind	106	18–75	(1)	Reslizumab 3 mg/kg	IV	12 weeks	Blood and sputum eosinophils; ACQ-7; FEV_1; asthma exacerbations	15 weeks	A 20 % or more decrease from baseline in FEV_1; or worsening of asthma requiring emergency treatment, hospital admission, or 3 or more days of oral corticosteroid treatment.
Castro [20]	2 duplicate multi-center, double-blind parallel	Study 1:489; study 2:464	12–75	(3)	Reslizumab 3 mg/kg	IV	52 weeks	Blood eosinophils; asthma exacerbations; FEV_1; AQLQ; ACQ-7; rescue SABAs	52 weeks	Worsening of asthma that resulted in use of systemic corticosteroids in patients not already receiving treatment, or a 2 times increase in the dose of either inhaled corticosteroids or systemic corticosteroids

Table 1 (continued)

Reference	Study design	No. of subjects	Age	Selection criteria[a]	Drug	Routine	Treatment duration	Outcomes	Follow-up	Exacerbation definition
										for 3 or more days, or the need for asthma-related emergency treatment
Corren [21][b]	Multi-center, double-blind	96	18–65	(3)	Reslizumab 3 mg/kg	IV	16 weeks	Blood eosinophils; ACQ-7; FEV_1; rescue SABAs	28 weeks	NM
Bjermer [22]	Multi-center, double-blind parallel	315	12–75	(3)	Reslizumab 0.3 mg/kg, 3 mg/kg	IV	16 weeks	Blood eosinophils; FEV_1; FVC; ACQ-6; AQLQ	20 weeks	a reduction in FEV_1 of ≥20 %, hospitalization due to asthma, emergency treatment of asthma, or use of systemic corticosteroids for ≥3 days
Laviolette [23]	Multi-center, double-blind	Cohort 1:13 cohort 2:14	18–65	(1)	Benralizumab cohort 1:1 mg/kg cohort 2:100 or 200 mg	Cohort 1:IV cohort 2:SC	1 day or 56 days	Blood, sputum eosinophils; adverse events	84 days or 140 days	NM
Castro [12][b]	Multi-center, double-blind	324	18–75	(1) or (2)	Benralizumab 2, 20 or 100 mg	SC	1 year	Blood eosinophils; asthma exacerbations; FEV_1; AQLQ	1 year	An increase in asthma symptoms that did not resolve after rescue medication and needed treatment with systemic steroids for at least 3 days
Park [24]	Multi-center, double-blind	106	20–75	(1) or (2)	Benralizumab 2, 20 or 100 mg	SC	40 weeks	Blood eosinophils; asthma exacerbations; FEV1; PEF; ACQ-6	52 weeks	An increase in asthma symptoms that required treatment with systemic steroids for at least 3 days.

FEV1 forced expiratory volume in 1 s, *PEF* peak expiratory flow, *histamine PC20* provocative concentration of histamine required to cause a 20 % fall in *FEV1* asthma exacerbation rates, *JACQ* Juniper Asthma Control Questionnaire, *ACQ* Asthma Control Questionnaire, *AQLQ* the Asthma Quality-of-Life Questionnaire, *SABAs* short-acting beta-agonists (SABAs), *IV* intravenous infusion, *SC* subcutaneous injections, *NM* not mentioned

[a] Eosinophilic asthma was selected by at least one of the following criteria during the screening period: (1) a sputum eosinophil count ≥2.5 % or the eosinophil/lymphocyte and eosinophil/neutrophil ((ELEN) index, a surrogate blood-based marker of sputum eosinophilia) was positive; (2) an exhaled nitric oxide concentration (FENO) ≥50 ppb; (3) an asthma-related peripheral blood eosinophil count ≥300 μL

[b] We only choose the data of eosinophilic asthma

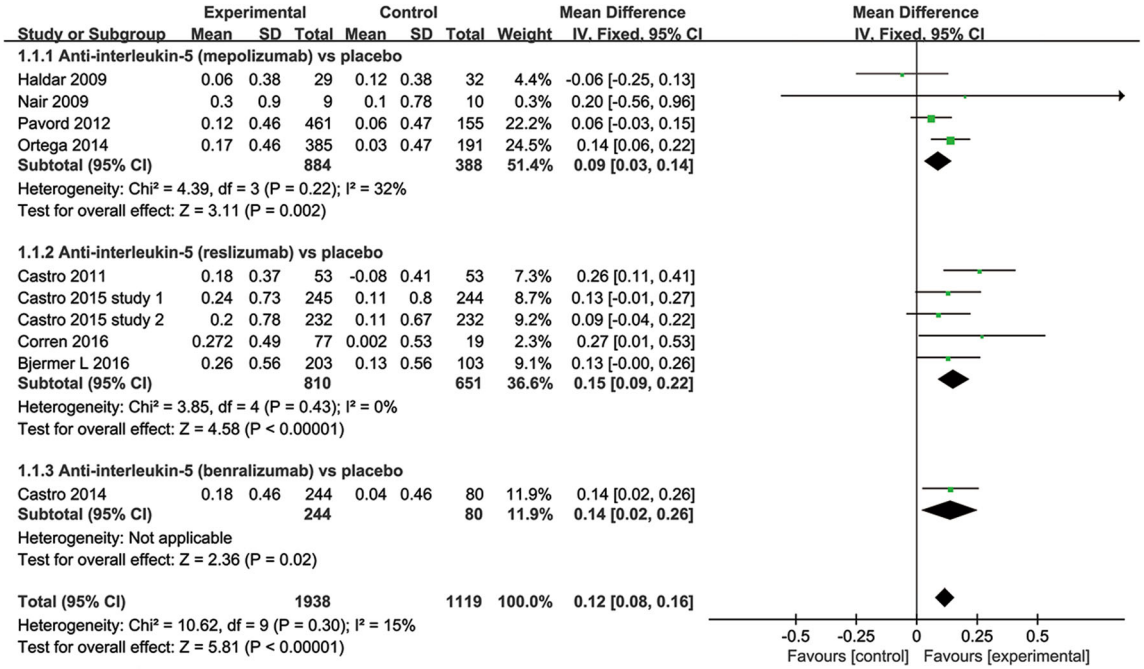

Fig. 2 The effect of anti-interleukin 5 versus placebo on FEV_1. Fixed-effects model. *SD* standard derivation, *IV* inverse variance, *CI* confidence interval, *FEV_1* forced expiratory volume in 1 s

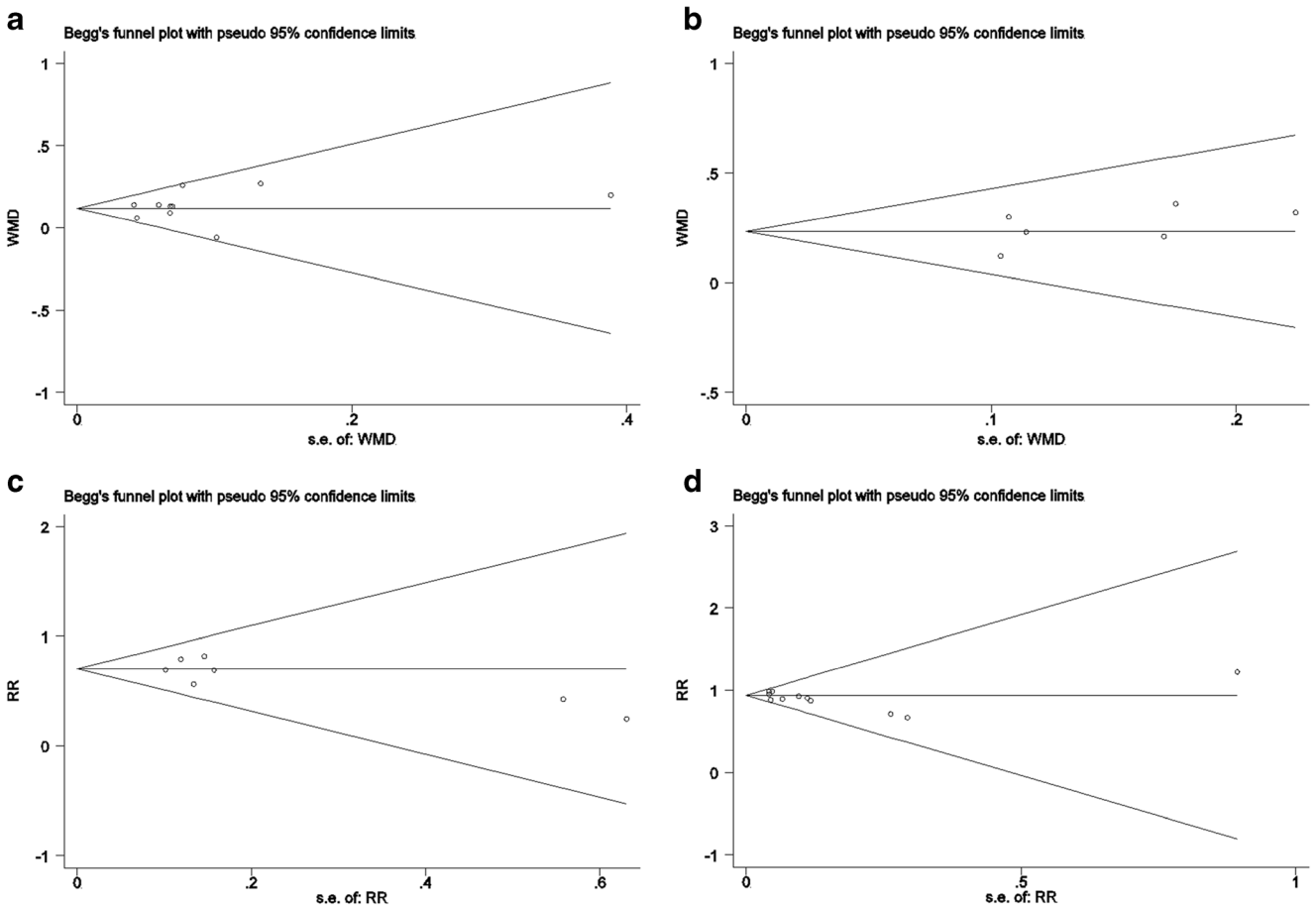

Fig. 3 Begg's test of all outcomes: **a** Begg's test of FEV_1 in the meta-analysis. **b** Begg's test of AQLQ in the meta-analysis. c Begg's test of asthma exacerbationsin the meta-analysis. **d** Begg's test of adverse events in the meta-analysis

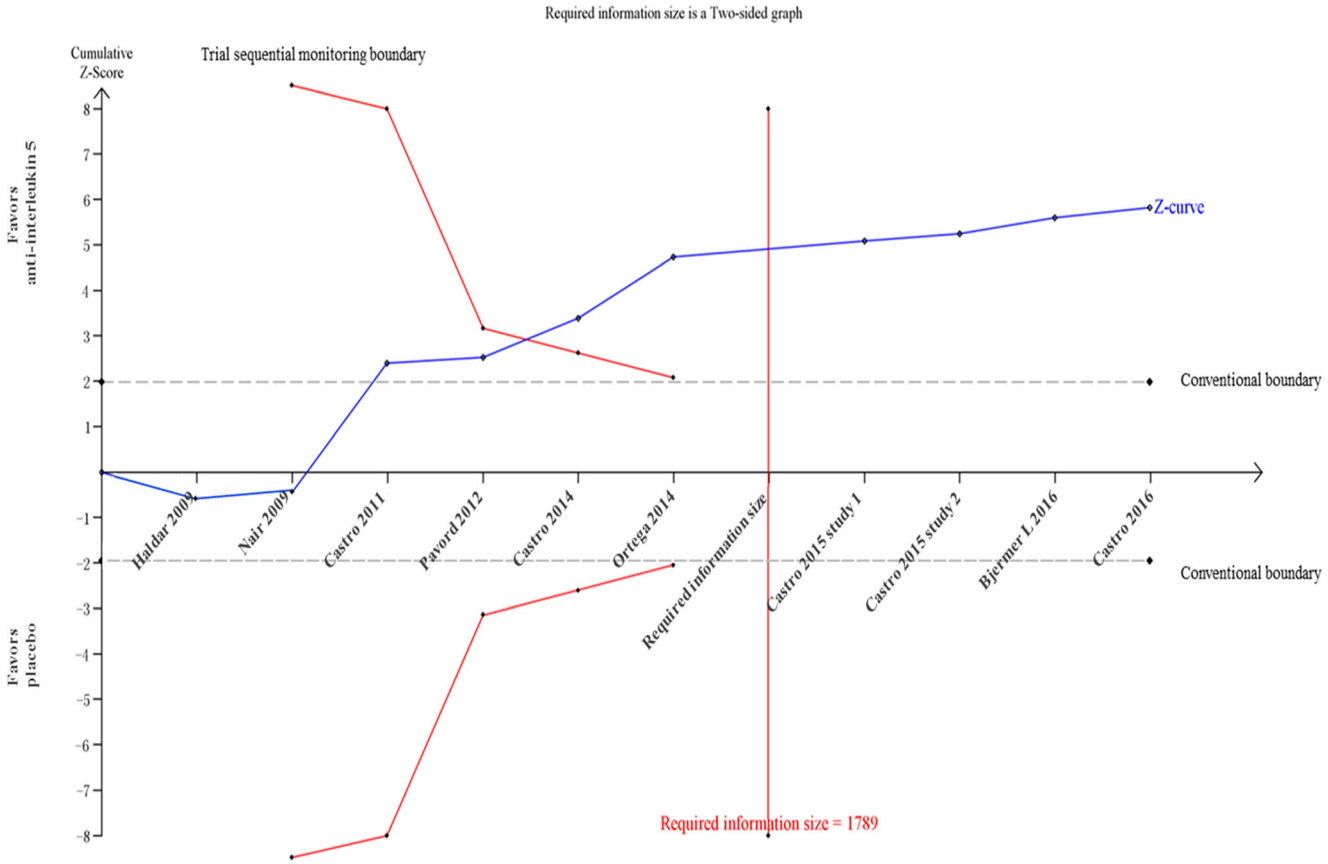

Fig. 4 Trial sequential analysis of 12 trials comparing anti-interleukin 5 with placebo for FEV_1. Trial sequential analysis of ten groups (one trial contains two groups) illustrating that the cumulative *z* curve crossed both the conventional boundary and the trial sequential monitoring boundary, establishing sufficient and conclusive evidence and suggesting that further trials are not required. Using $\alpha = 0.05$ (two-sided) and $\beta = 0.20$ (power of 80 %) calculate that the optimal sample size was 1789 patients

selected population of patients with eosinophilic asthma and included all trials involving anti-interleukin 5 treatment (mepolizumab, reslizumab, benralizumab), not only just mepolizumab. In addition, we used TSA to calculate a

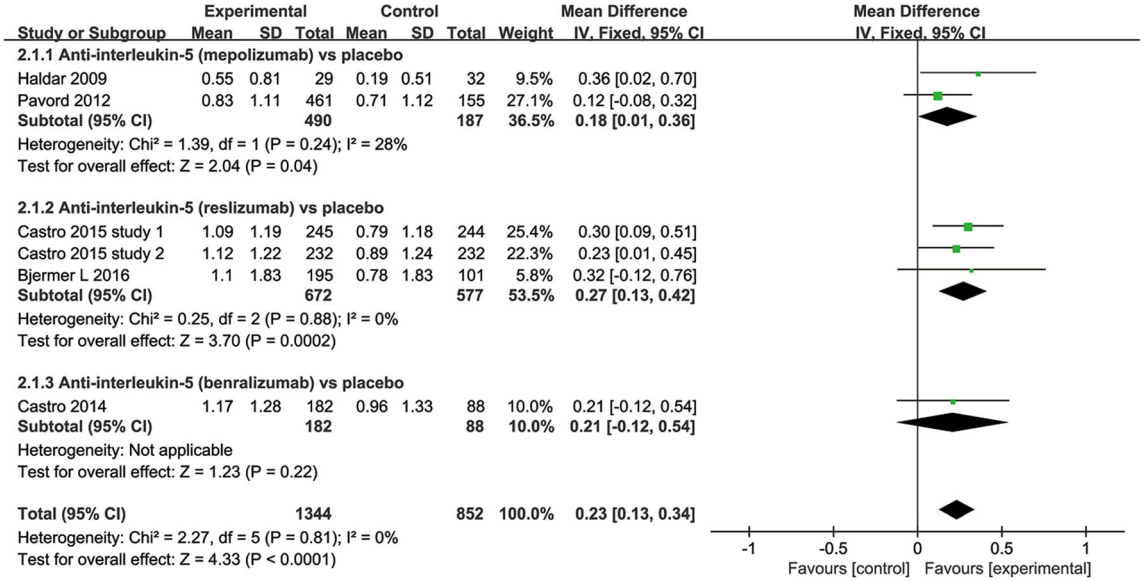

Fig. 5 The effect of anti-interleukin 5 versus placebo on Asthma Quality-of Life-Questionnaire (AQLQ). Fixed-effects model. *SD* standard derivation, *CI* confidence interval

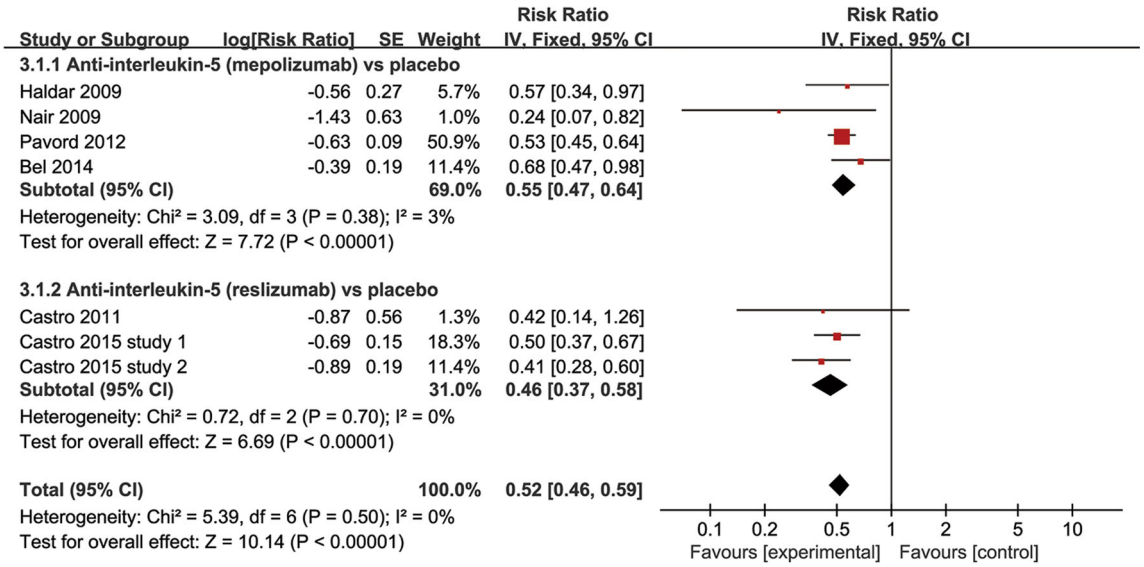

Fig. 6 Forest plot of the effect of anti-interleukin 5 treatment on asthma exacerbations verse placebo. Fixed-effects model. *SE* standard error, *IV* inverse variance, *CI* confidence interval

required information size for meta-analysis, which can correct for the increased risk of random errors. Therefore, our results may be more believable. On the other hand, the different outcomes between our meta-analysis and the previous two systematic reviews suggested that anti-interleukin 5 therapy might be effective only in a targeted subgroup with an eosinophilic phenotype. For example, early trials of mepolizumab were disappointing because the recruitment of asthmatics did not include specifying the presence of eosinophilic airway inflammation [6, 29]. In subsequent studies, when anti-interleukin 5 therapies have been used in a patient population selected for eosinophils, results have been more

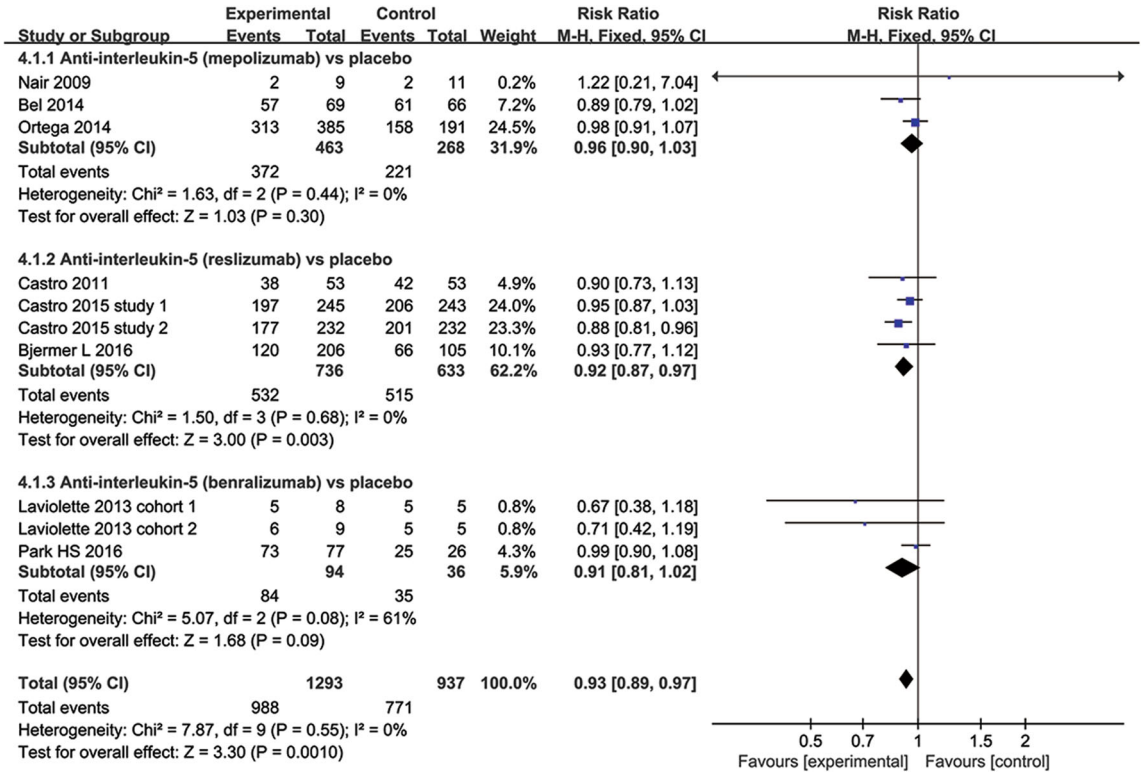

Fig. 7 Forest plot of the effect of anti-interleukin 5 treatment on adverse events verse placebo. Fixed-effects model. *M-H* Mantel-Haenszel, *CI* confidence interval

Table 2 Summary of adverse events in the anti-interleukin 5 treatment arm

Reference	Adverse events	Serious adverse events	Common adverse events				
			Nasopharyngitis	Headache	Asthma worsening	Injection-site reactions	Upper respiratory tract infection
Mepolizumab							
Haldar [7]	NM	3 (10)	NM	NM	NM	0 (0)	1 (3)
Nair [8]	2 (22)	0 (0)	NM	NM	NM	NM	NM
Pavord [11]	NM	63 (14)	96 (21)	91 (20)	NM	39 (8)	NM
Bel [9]	57 (83)	1 (1)	NM	NM	2 (3)	4 (8)	NM
Ortega [10]	313 (81)	31 (8)	78 (20)	85 (22)	31 (8)	22 (6)	46 (12)
Reslizumab							
Castro [19]	38 (72)	2 (4)	11 (21)	2 (4)	1 (2)	NM	2 (4)
Castro [20] study 1	197 (80)	24 (10)	28 (11)	19 (8)	97 (40)	NM	39 (16)
Castro [20] study 2	177 (76)	18 (8)	45 (19)	33 (14)	67 (29)	2 (1)	8 (3)
Bjermer [22]	120 (58)	4 (2)	12 (6)	19 (9)	22 (11)	NM	8 (4)
Benralizumab							
Laviolette [23] cohort 1	5 (63)	NM	2 (25)	0 (0)	2 (25)	NM	NM
Laviolette [23] cohort 2	6 (67)	NM	2 (22)	1 (11)	1 (11)	NM	NM
Park HS [24]	25 (95)	12 (16)	23 (30)	8 (10)	9 (12)	21 (27)	21 (27)

Data are *n* (%)

NM not mentioned

promising [7–11]. In addition, an FDA advisory committee has recently approved the use of mepolizumab for patients with eosinophilic severe asthma. Therefore, the clinical effects of anti-interleukin 5 treatment are much more influenced by patient selection.

AQLQ is a disease-specific health-related quality-of-life instrument which contains 32 items, and it has proved responsive in before-after studies and in clinical trials [30]. Asthma Control Questionnaire (ACQ) applied in studies are used variously, some used ACQ-6, while others used ACQ-5 or ACQ-7, which makes this parameter was unsuitable for analysis. Therefore, our meta-analysis used AQLQ score to evaluate the life quality of patients. In our study, there was a significant improvement in AQLQ. This result was consistent with previous systematic reviews [27, 28]. However, the mean change in AQLQ is less the clinical minimally important difference of 0.5 units [31]. So, the clinical relevance of this finding to patients may not be clinically important.

Asthma exacerbations are associated with substantial morbidity and mortality [32]. Decreasing the asthma exacerbations rate is a key goal of asthma management. Previous studies revealed that increased blood and sputum eosinophil counts have emerged as independent risk factors for future asthma exacerbations [33, 34]. Studies using specific inhibitors of have also shown a link between eosinophils and the pathogenesis of asthma exacerbations [35, 36]. These foundings strongly suggested that the presence of airway eosinophilia is a clinically relevant finding, and anti-interleukin 5 treatments might be a promising strategy to treat asthma. Further support of this idea, our meta-analysis showed a significant reduction in exacerbation rates. The improvements in asthma-related quality of life with anti-IL-5 treatment may probably be attributed to preventing asthma exacerbations.

Not all studies reported adverse events. The safety profile of mepolizumab has been up to par with the placebo in the RCTs we included, and the most frequently reported adverse events were nasopharyngitis and headache. Consistent with mepolizumab, the overall safety profile of reslizumab was similar to that of placebo based on studies we included, and the most widely reported adverse events were asthma worsening, nasopharyngitis, upper respiratory tract infection, and sinusitis. As for benralizumab, nasopharyngitis and injection-site reactions were most common adverse events. One RCT which assessed the efficacy and safety of benralizumab both in patients with eosinophilic asthma and non-eosinophilic asthma revealed the overall incidence of adverse events irrespective of causality was slightly higher in the benralizumab treatment groups than in the placebo groups [12]. However, adverse events were summarized for eosinophilic and non-eosinophilic participants combined in this study, which makes us unable to get detailed data, and we only included two studies on benralizumab to analysis.

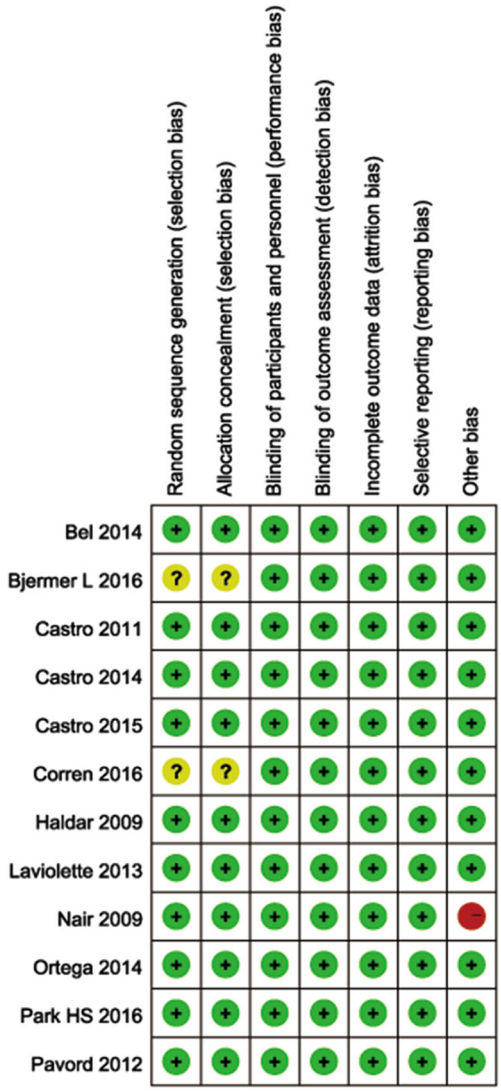

Fig. 8 Risk of bias summary of included studies

Pooled analysis found treatment with reslizumab was associated with a trend of lower adverse event incidence, but the numbers of patients reporting adverse events was similar in both mepolizumab and benralizumab treatment groups when compared with the placebo. Therefore, benralizumab needs more data to support its safety profile.

There are several potential limitations that need to be considered. Firstly, the severity and baseline therapy of eosinophilic asthma varied among studies, so it is not possible to investigate the impact of those on the results. Secondly, several studies were of a small scale, which may affect the power to explore the real outcomes. Moreover, given the variety of the anti-interleukin 5 therapy, we were unable to assess factors that may impact the effects of anti-interleukin 5 therapy, such as dose, and treatment duration. Lastly, as commended by the Cochrane handbook, we combined two or three intervention groups into a single intervention group regardless of different intervention dosage and administration routine, which made it difficult to determine the optimal dose. Another important aspect that we should pay attention is that we used a blood eosinophil count more than 300 cells/μL at baseline to select patients with the eosinophilic phenotype. However, a recent study re-examined baseline blood eosinophil counts from previous two studies [10, 11] on mepolizumab found that the use of the baseline at a threshold of at least 150 cells/μL will select patients with the phenotype that is likely to achieve important reductions in the rate of exacerbations and resultant improvements in the quality of life and asthma control with mepolizumab [37]. However, given the lack of individual patient data among all studies, we failed to further analysis the relationship between blood eosinophil counts ≥150 cells/μL at baseline and outcomes of treatment.

Conclusions

In summary, the current meta-analysis indicated that anti-interleukin 5 treatment was well tolerated and could significantly improve FEV_1, quality of life, and reduced asthma exacerbation risk in patients with eosinophilic asthma. Therefore, the humanized anti-interleukin 5 monoclonal antibodies may be effective and safe for eosinophilic asthma. The results highlight the importance of selection asthma phenotypes could derive clinical benefit from anti-interleukin 5 therapy. Nasopharyngitis was the most frequently reported adverse event in either study involving anti-interleukin 5 treatments, and benralizumab needs more data to support its safety profile. Further trials are necessary to assess the baseline blood eosinophil count to identify the optimal patients of eosinophilic asthma that could benefit from anti-interleukin 5 treatment.

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Compliance with Ethical Standards

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Conflict of Interest The authors declare no conflict of interest.

Author Contributions Fa-Ping Wang and Xiao-Feng Xiong performed the literature searches, selected the studies, analyzed the data, and wrote the manuscript draft. Ting Liu and Su-Yun Li aided in the data analysis. Hui Mao and De-Yun Cheng designed the study and revised manuscript.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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