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Review Article

Different IL-5 monoclonal antibody agents in treating severe asthma patients: a systemic review and network meta-analysis of randomized controlled trials (RCTs)

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Abstract: Background: Asthma affects more than 315 million people worldwide, with approximately 10% having severe or uncontrolled asthma. This study is based on the dose regimens derived from the phase III randomized controlled trials (RCTs) to find out the most beneficial regimen of IL-5 monoclonal antibody to decrease annual rate of exacerbations in patients with severe asthma. Methods: PubMed and the Web of Science were used to find out the including studies. RevMan 5.1 and Stata 15.1 were performed to this systemic review and network meta-analysis. Results: After searching and screening articles, 9 articles about 10 studies with 5408 patients, and 6 arms with 3 major antibodies (mepolizumab, benralizumab, reslizumab) were included. Compared with placebo, the IL-5 monoclonal antibody group has lower annual rate of exacerbations. Ranking the regimens in the order of estimated probabilities of each treatment by using the network meta-analysis, the results show that reslizumab 3 mg/ kg was the best one (57.3%), followed by mepolizumab 100 mg SC (14.9%), mepolizumab 75 mg IV (14.3%), benralizumab 30 mg q8w (10.8%), benralizumab 30 mg q4w (2.7%), and placebo (0.0%). Reslizumab 3 mg/ kg was more efficacious than other therapeutic regimens. Conclusion: IL-5 monoclonal antibody can decrease the annual rate of exacerbations in asthma patients. Therefore, the regimen of reslizumab 3 mg/kg is probably the best choice to treat patients with severe asthma.

Keywords: Severe asthma, IL-5 monoclonal antibody, annual rate of exacerbation

Introduction

Asthma affects more than 315 million people all around the world, with about 10% of them having severe asthma [1, 2]. Patients with severe asthma need high-dosage inhaled corticosteroids in combination with long-acting β_2-agonists (LABA) to control their disease and they have considerable morbidity, characterized by frequent symptoms and exacerbations that often require coming to the Emergency Department and Hospital, but sometimes asthma remains "uncontrolled" despite this treatment [3].

Currently, some IL-5 monoclonal antibody agents (benralizumab, reslizumab, mepolizumab) have been approved by the Food and Drug Administration (FDA) to be used for treating severe asthma and these studies showed that they can help control the symptoms of severe asthma, as well as decrease the annual rate of clinically significant exacerbations, defined as worsening of asthma requiring systemic corticosteroids administered intravenously or orally for ≥3 days or as a single intra-muscular dose, or an emergency room visit or admission to hospital [4].

There have been two studies for conducting the meta-analysis to compare the advantages of these people. One of them compared the dose regimens of these agents containing phase I and II RCTs, and the other just compared resli-

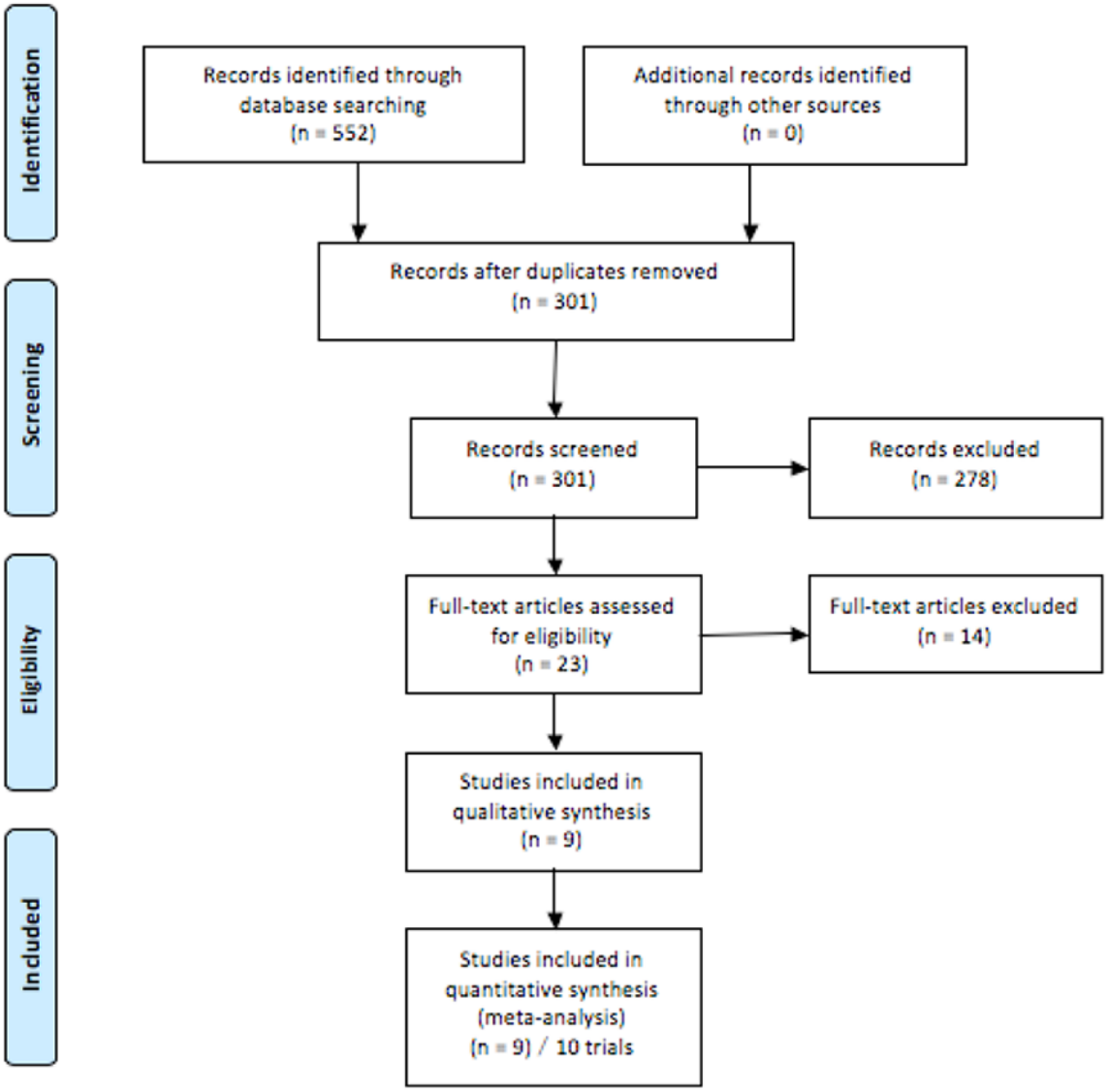

Figure 1. Flow Diagram of choosing the appropriated articles.

zumab and benralizumab [5, 6]. The result of these studies showed that reslizumab was superior. However, the results in these studies above were not ideal because more phase III RCTs showed up recently. Therefore, network meta-analysis was performed here to determine whether IL-5 monoclonal antibody would be more appropriate for treating severe asthma in clinical practice.

Methods

Search strategy

Two investigators independently reviewed the identified abstracts and selected articles for full reviewing and the discrepancies were resolved by a third reviewer. The reference lists of eligible studies and relevant papers were also manually searched and reviewed. The search terms were "mepolizumab", "benralizumab", "reslizumab", and "asthma" et al. The search date was until 2018/10/22. Finally 552 articles, excluding 251 duplications were found, which included 23 articles through reading the title and abstract, and 9 studies about 10 RCTs [4, 7-14] by reading the whole article (**Figure 1**).

Inclusion and exclusion

Inclusions contain: (1) research study focused on IL-5 antibody for treating severe asthma, (2)

Table 1. Characteristics of studies included in the network meta-analysis

Study	Intervention	Total number of patients	Number of annual exacerbation	Trial	RCT	One Center	Phase	Country	Age	Follow up	Precondition
Basu 2017	Mep 75 IV/Mep 100 SC/Placebo	191/194/191	178/161/332	Mensa	Yes	Multi	/	USA	Total: 12-82 years 50±14/51±14.5/49±14.3	40 w	≥2 asthma exacerbations; require high-dose ICS in the previous years
Bleecker 2017	Ben 30 Q4 w/Ben 30 Q8 w/Placebo	399/398/407	306/305/524	SIROCCO	Yes	Multi	3	USA	Total: 12-75 years 50.1± 13.4/47.6±14.5/48.7±14.9	48 w	Medium or high-dose ICS plus LABA treatment in the previous years
Chupp 2017	Mep 100 SC/ Placebo	274/277	140/335	NCT 02281318	Yes	Multi	3 b	USA	Total: ≥12 years 49.8±14/52.1±12.9	24 w.l,	≥2 asthma exacerbations; require high-dose ICS or others in the previous years
FitzGerald 2016	Ben 30 Q4 w/Ben 30 Q8 w/Placebo	357/364/370	235/249/379	CALIMA	Yes	Multi	3	USA	Total: 12-75years 50±13.6/ 49±14.3/48.8±15.1	56 w	≥2 asthma exacerbations; require high-dose ICS in the previous years
Halder 2009	Mep 750 IV/ Placebo	29/32	58/109	ISRCTN 75169762	Yes	One	/	UK	Total: ≥18 years 48 (21-63)/50 (24-72)	50 w	≥2 asthma exacerbations; require high-dose ICS in the previous years
Nair 2017	Ben 30 Q4 w/Ben 30 Q8 w/Placebo	72/73/75	60/39/137	ZONDA; NCT 02075255	Yes	Multi	/	Germany	Total: ≥18 years 50.2±12 /52.9±10.1/49.9±11.7	28 w	Require oral glucocorticoids for 6 months or more
Castro 2015; study 1	Res/Placebo	245/245	221/441	NCT 01287039	Yes	Multi	3	USA	Total: 12-75 years 48 (38-57)/49 (38-57)	52 w	≥1 asthma exacerbations; Require high-dose ICS in the previous years
Bel 2014	Mep 100 SC/ Placebo	69/66	99/140	NCT 01691508	Yes	Multi	3	Australia	Total: ≥16 years 50 (16-74)/50 (28-70)	32 w	≥2 asthma exacerbations; require high-dose ICS in the previous years
Castro 2015; study 2	Res/Placebo	232/232	200/490	NCT 01285323	Yes	Multi	3	USA	12-75 years 48 (39.5-57)/ 48 (37-56.5)	52 w	≥1 asthma exacerbations; Require high-dose ICS in the previous years
Pavord 2012	Mep 75/Mep 250/Mep 750/ Placebo	153/152/156/155	190/222/179/372	DREAM	Yes	Multi	/	UK	Total: 12-74 years 50.2±10.8/49. 4±11.6/48.6±11.1/46.4±11.3	52 w	≥2 asthma exacerbations

IV: intravenously; SC: subcutaneous injection; ICS: inhaled corticosteroids; LABA: long acting B agonist therapy; Ben 30 Q4w: Benralizumab 30 mg Q4w; Ben 30 Q8w: Benralizumab 30 mg Q8w; Mep 100 SC: Mepolizumab 100 SC; Mep 75 IV: Mepolizumab 75 IV; Res 3 mg / kg: Reslizumab 3 mg/kg.

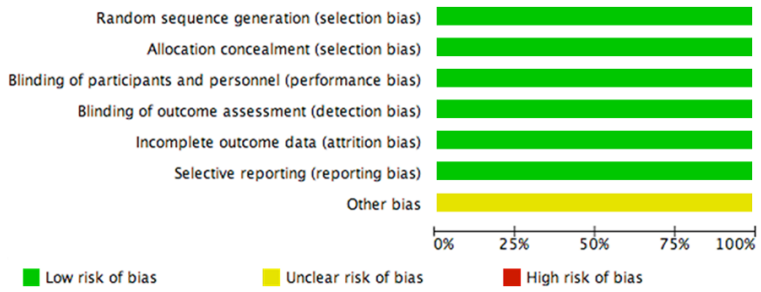

Figure 2. Risk of bias graph.

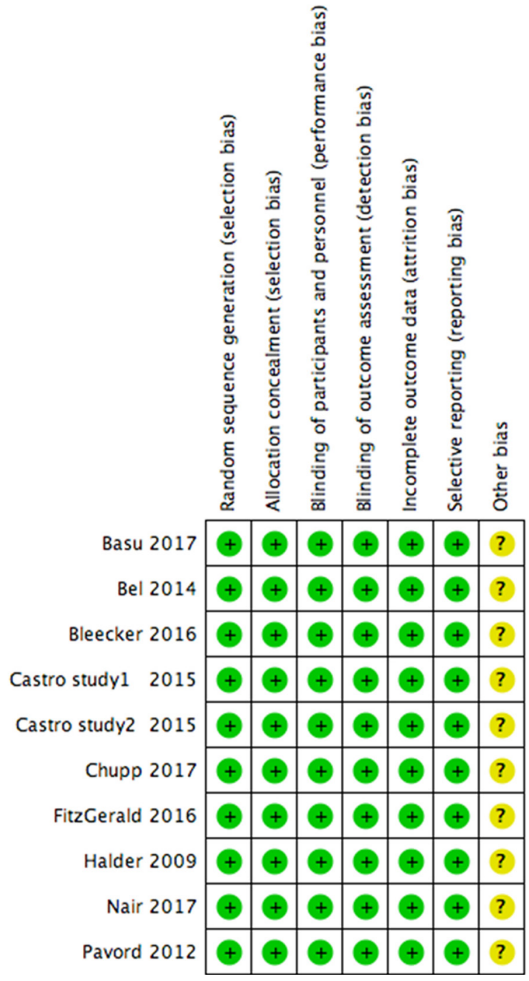

Figure 3. Risk of bias summary.

outcome: annual exacerbation rate, (3) the dose of agents based on phase III randomized control trial, (4) only be published by English.

Exclusions contain: (1) review, retrospective research, case report, (2) insufficient data in the articles, (3) the dose of agents based on phase II or I.

Data elected

Two authors independently reviewed the identified abstracts and selected articles to full review. The third reviewer addressed the discrepancies. For each selected publication, the following baselines and study characteristics were extraced: first author, publiction year, country, participant characteristics, experiment and control group, experimental step, predication for enrolling in the study, and the baseline characteristics of these studies were concluded below (**Table 1**).

Statistical analysis

Data was pooled and odd ratios (OR) were used for the dichotomy outcome: the incidence of annual exacerbation of asthma. The total numbers of patients were multiplied by 10 to produce new total numbers, which were bigger than the annual rate of exacerbations multiplied by the number of asthma patients in each group of every study. Because in network metaanalysis of dichotomy, the total number must be bigger than every event. To make the new total number, every patient had 10 times the chance to have exacerbation in a year. All statistical analyses were carried out with Review Manager 5.2 (The Cochrane Collaboration) and Stata 15.1.

Results

This study included 10 RCTs with 5408 patients to determine what kind of regimen in IL-5 monoclonal antibodies based on the phase III RCTs could decrease the rate of annual exacerbations in patients with severe asthma. The quality of the article evaluations are as follows, and the studies included were well-prepared (**Figures 2** and **3**).

Network evidence of the comparisons for the different IL-5 monoclonal antibody agents are shown in **Figure 4**. Compared with placebo, all therapeutic regimens (benralizumab 30 mg q4w, benralizumab 30 mg q8w, mepolizumab 100 mg SC, mepolizumab 75 mg IV, and reslizumab 3 mg/kg) decreased the annual exacerbations with the OR (95% CI) value of 1.89 (95%

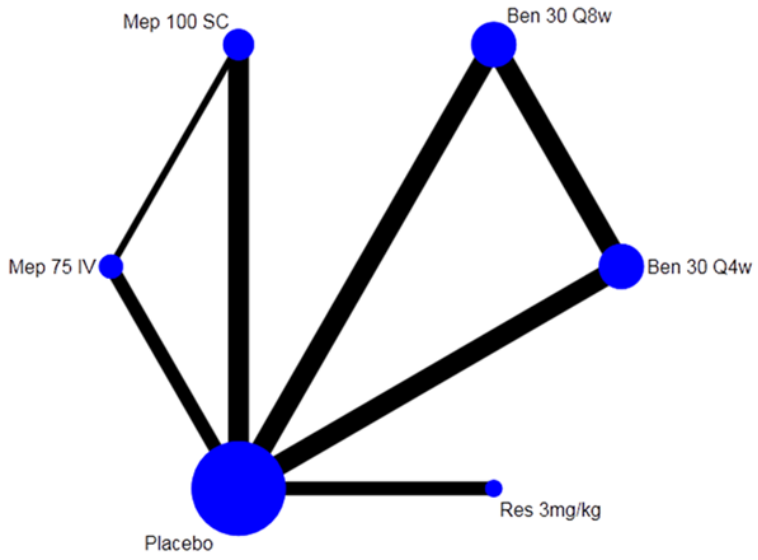

Figure 4. Network evidence of the comparisons for the IL-5 monoclonal antibody therapy.

CI 1.43, 2.51), 2.06 (95% CI 1.54-2.77), 2.17 (95% CI 1.64, 2.88), 2.09 (95% CI 1.51-2.89), 0.40 (95% CI 0.29-0.56), respectively. However, there was no significant difference between these therapeutic regimens (**Figures 5**, **6**).

In network meta-analysis, heterogeneity was not compared in the study, but an inconsistency test was applied to find out whether the data of these studies could be mixed and calculated. The inconsistency test showed that the comparison could be performed by consistency (P>0.05) (**Table 2**). In the rank of network meta-analysis, it was found that reslizumab 3 mg/kg (57.3%) was the most effective therapeutic regimen to down the incidence of annual exacerbation in these patients with severe asthma, followed by mepolizumab 100 mg SC (14.9%), mepolizumab 75 mg IV (14.3%), benralizumab 30 mg q8w (10.8%), benralizumab 30 mg q4w (2.7%), and placebo (0.0%). The biggest probability means this therapeutic regimen has the biggest chance to be the best treatment (**Table 3**).

Discussion

Eosinophilic inflammation is evident in approximately half of patients with asthma and associated with increased disease severity, exacerbation frequency, symptom burden, as well as decreased lung function [15, 16]. IL-5, a critical cytokine for eosinophil development, activation, and survival, is present in increased concentrations in patients with asthma [17, 18]. Current asthma treatment guidelines reommend add-on IL-5 monoclonal antibody agents (mepolizumab, benralizumab, reslizumab) for patients with severe, untrolled, eosinophilic asthma [19]. A bronchoscopy study showed that treatment with IL-5 monoclonal antibody reduced airway mucosal eosinophil numbers by 55% in contrast to the 85% or more reduction in blood and sputum eosinophils [20]. IL-5 monoclonal antibody treatment had no effect on asthma symptoms, FE_{NO}, or lung function, which suggests that symptoms, FE_{NO}, and lung function have no connection with eosinophilic inflammation and will be improved by corticosteroid treatment through another mechanism [14].

Furthermore, compared with placebo, the IL-5 monoclonal antibody group had a lower annual rate of exacerbations. Ranking the regimens in the order of estimated probabilities of each treatment by using the network meta-analysis, showed that reslizumab 3 mg/kg was the best, followed by mepolizumab 100 mg SC, mepolizumab 75 mg IV, benralizumab 30 mg q8w, benralizumab 30 mg q4w, and placebo.

Mepolizumab is an IL-5 monoclonal antibody approved in Europe, Canada, USA, and other countries as an add-on therapy to patients aged 12 years or older with severe asthma and an eosinophilic phenotype [4]. Benralizumab is a humanized, afucosylated, monoclonal antibody against the alpha subunit of the IL-5 receptor, which can induce depletion of eosinophils through enhancing antibody-dependent cell-mediated cytotoxicity involving natural killer cells [8, 21, 22]. Reslizumab is a IgG4/k humanized monoclonal antibody composed of the complementarity-determining regions of a murine antibody to human IL-5 that has been grafted onto human frameworks. Reslizumab neutralizes circulating IL-5 by preventing it from

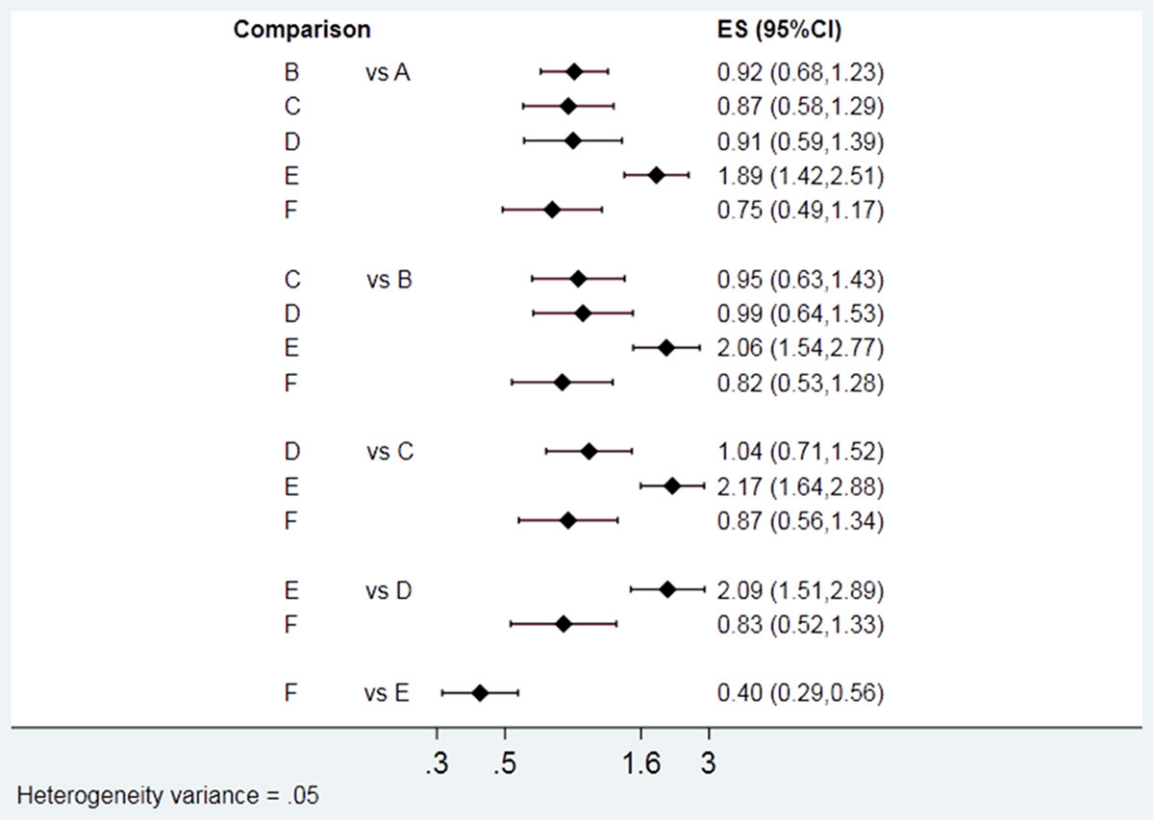

Figure 5. Odd ratios of the comparisons for the IL-5 monoclonal antibody therapy.

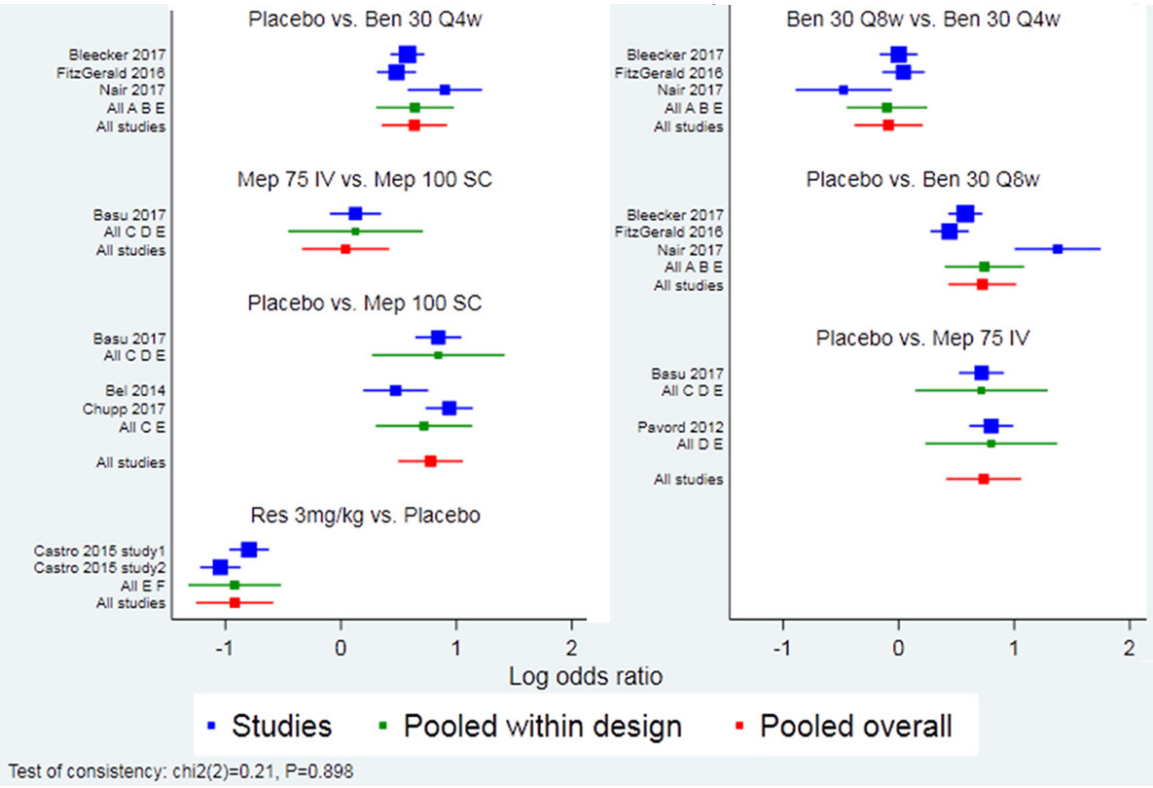

Figure 6. Forest plots of the comparisons for the IL-5 monoclonal antibody therapy.

Table 2. Inconsistency test

	Direct		Indirect		Differ		P
	Coef	Std. Err	Coef	Std. Err	Coef	Std. Err	
AB	-0.879	0.151	-0.625	788.005	0.537	788.005	0.999
AE	0.636	0.144	0.366	335.322	0.271	335.322	0.999
BE	0.724	0.150	0.187	688.592	0.538	688.592	0.999
CD	0.127	0.269	-0.829	0.322	0.210	0.420	0.617
CE	0.764	0.158	1.009	0.709	-0.245	0.725	0.736
DE	0.759	0.187	0.474	0.607	0.285	0.634	0.653
EF	-0.919	0.170	-1.411	1199.943	0.493	1199.943	1.000

A: Benralizumab 30 mg Q4w; B: Benralizumab 30 mg Q8w; C: Mepolizumab 100 SC; D: Mepolizumab 75 IV; E: Placebo; F: Reslizumab 3 mg/kg.

Table 3. Estimated probabilities (%) of each treatment being the best

Treatment					
Ben 30 Q4w	Ben 30 Q8w	Mep 100 SC	Mep 75 IV	Placebo	Res 3 mg/kg
2.7	10.8	14.9	14.3	0.0	57.3

binding to eosinophils [23]. Although placebos or sham treatments, which leave airway inflammation untreated sometimes can control asthma symptoms [24, 25], they did not decrease annual exacerbations of asthma in this study.

The previous two meta-analyses both showed that reslizumab may be more efficacious than other regimens [5, 6], which is similar to this study. However, the result presented here could be better applied in clinical practice.

In conclusion, IL-5 monoclonal antibody can decrease the annual rate of exacerbations in patients with severe asthma. Probably, the regimen of reslizumab 3 mg/kg is the optimal choice to treat these patients.

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