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Effect of Anti-IL5, Anti-IL5R, Anti-IL13 Therapy on Asthma Exacerbations: A Network Meta-analysis

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Abstract

Background—Several new treatments for severe asthma have become available in the last decade; yet, little data exist to guide their use in specific patient populations.

Objective—A network meta-analysis was conducted comparing the efficacy of FDA-approved monoclonal antibody therapies in preventing exacerbations in patients with severe eosinophilic asthma.

Methods—PubMed and Ovid were searched from inception until July 2019 for randomized controlled trials that studied the efficacy of benralizumab, dupilumab, mepolizumab, and reslizumab, in preventing acute exacerbations of asthma. Studies were included if they reported data for patients with severe eosinophilic asthma (defined in this meta-analysis as absolute eosinophil count ≥ 250 cells/μL). Annualized rate ratios for asthma exacerbations (during treatment) were calculated and converted to log rate ratios. Direct and indirect treatment estimates (for inter-drug differences) were analyzed using frequentist network meta-analysis methodology in R and treatments were ranked based on *P*-scores.

Results—In total, nine studies were included in the final analysis. Network meta-analysis revealed that all drugs were superior to placebo in preventing rates of asthma exacerbation in the study population and no inter-drug differences existed. Dupilumab was found to have the greatest magnitudes of effect on decreasing log rate ratio of asthma exacerbation based on *P*-score (0.83).

Conclusion—Benralizumab, dupilumab, mepolizumab, and reslizumab are all associated with decreased asthma exacerbations in patients with eosinophilic asthma, with no significant inter-drug differences.

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Author Contributions IHI had full access to all of the extracted data in the network meta-analysis and takes responsibility for the integrity of the data and the accuracy of the data analysis. IHI conceptualized and designed the study protocol, conducted the analyses and wrote the first draft manuscript. IHI and RPR contributed to assessment of study quality. Both authors contributed substantially to the interpretation of analyses and in revisions of manuscript.

Compliance with Ethical Standards

Conflicts of interest None.

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Keywords

Eosinophilic asthma; Benralizumab; Dupilumab; Mepolizumab; Reslizumab

Introduction

Anti-interleukin (IL)5, anti-IL5 receptor (IL-5R), and anti-IL4R have now been officially incorporated into GINA 2019 guidelines [1] as add-on controller medications for difficult-to-treat and severe asthma with type-2 inflammatory phenotypes. Type-2 inflammation, found in ~ 50% of severe asthma phenotypes, is primarily driven by the production of IL-4, IL-5, and IL-13, by type 2 helper T cells. (Th2), type 2 innate lymphoid cells and by the production of epithelial cell-derived alarmins such as thymic stromal lymphopoietin (TSLP). Increased sputum (≥ 2%) or blood eosinophils (≥ 150 cells/μL), as well as fractional exhaled nitric oxide (FeNO) ≥ 20 ppb, characterizes type-2 inflammation and even though these are criteria that have been primarily used to exclude non-eosinophilic asthma (rather than confirm eosinophilic asthma), these markers have been useful to guide treatment for eosinophilic asthma [1, 2]. Mepolizumab, reslizumab, benralizumab, and dupilumab are currently approved for treatment of severe eosinophilic asthma.

Although these drugs have not been compared in a direct head-to-head randomized controlled trial (RCT), network meta-analyses have attempted to compare the relative efficacy these drugs, but with inconsistent results, especially with regard to their effects on decreasing asthma exacerbations [3–6]. Two of these network meta-analyses [4, 6])ranked reslizumab and mepolizumab as superior, another [5] only ranked mepolizumab, while another [3] ranked both reslizumab and dupilumab as superior (as compared to others for asthma exacerbations). The discordant results could be from the differences in the inclusion criteria for RCTs in these meta-analyses or the differences could have resulted from not accounting for follow-up duration or analyzing incidence density ratios for exacerbations. Since RCTs varied in their definitions for ‘eosinophilic asthma’—i.e., some [7] used blood eosinophil count cut-off of 300 cells/μL, some others [8] used 150 cells/μL, or 450 cells/μL [9], as well as varied in their study durations, lumping all RCTs in a meta-analysis with heterogeneous study populations could have led to inconsistent conclusions. This meta-analysis aimed to study the effects of most FDA-approved biologics (benralizumab, dupilumab, mepolizumab, and reslizumab) in decreasing asthma exacerbations in a well-defined population, with similar or almost similar baseline characteristics using person-time incidence rates, to allow for a fair comparison amongst the new biologic drugs.

Methods

The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Search Strategy and Study Eligibility Criteria

PubMed and Ovid were searched from inception to July 2019 (Fig. 1). Inclusion criteria for our meta-analysis included (a) studies had to be RCTs, (b) published in only English

language, (c) RCTs studying eosinophilic asthma patient population (eosinophilic asthma population defined in our meta-analysis as those with mean baseline blood eosinophil count ≥ 250 cells/μL), aged 12 years or older, and in study participants who had been on medium-to-high dose inhaled corticosteroids prior to intervention and who had shown ≥ 1 asthma exacerbation in the 6 to 12 months prior to enrollment in the RCT, (d) RCTs studying benralizumab, dupilumab, mepolizumab, and reslizumab, as the drugs of intervention, and (e) RCTs had to report data on asthma exacerbation for patients on drug and placebo during the intervention period. It was decided a priori to exclude the studies on omalizumab as they did not report data based on blood eosinophil count. For our meta-analysis, clinical asthma exacerbations were defined as a worsening of asthma that resulted in corticosteroid treatment, emergency department or urgent care, or hospitalization and expressed as events per patient-year of exposure, to adjust for differences in observation time between studies (reported in Appendix Table E1). Studies were excluded from meta-analysis if the drug was studied at experimental doses that are now not used in clinical practice (reasons for exclusion of excluded studies reported in Table E2). We strictly adhered to the inclusion criteria as defined above to ensure that the study population for this meta-analysis was similar enough in baseline characteristics across all studies (included in this meta-analysis). Two reviewers (IHI and RR) independently screened the titles and abstracts of all publications and resolved any issues of disagreement through consensus.

Data Extraction and Synthesis

Data extracted from studies included first author's name, publication year, study design, population characteristics, treatments, length of follow-up, person-years, number of asthma exacerbations on treatment or on placebo. The studies were assessed for 'study quality' based on modified Cochrane methods. Data were first extracted on Microsoft Excel sheets and then on the working sheets of Comprehensive Meta-Analysis (CMA version 2.2.064; Biostat, Englewood, NJ, USA) software. Where rate ratios with 95% confidence intervals (CIs) were provided, data were used as such from those studies, and in studies where these data were not reported as such, rate ratios were calculated using reported event rate and person-years in CMA software. Relative risks reported for 52 weeks were converted into annualized rate ratios. For benralizumab, data were extracted for the 30 mg every 8 weeks regimen for both studies [7], whereas for dupilumab data were extracted for 30 mg subcutaneously every 2 weeks for 3 studies [10–12] and 30 mg subcutaneously every week for 1e study [13]. Reslizumab dosing regimen in the study [14] included in this meta-analysis was 3 mg/kg intravenously every 4 weeks. Mepolizumab dosing regimen in the 2 studies [15, 16] included in this meta-analysis was 100 mg subcutaneously every 4 weeks. Rate ratios and calculated standard errors were pooled in CMA using random effects methods and data were converted into log of rate ratios for plotting on a graphical scale. Log data were then imported into R and network meta-analysis was conducted using package 'netmeta' [17] (details in Appendix). Heterogeneity was assessed with I^2 index in direct pairwise analyses.

Results

From the initial search of 26 studies, a total of 9 studies [7, 10–16, 18] were included in our meta-analysis for quantitate data synthesis (Fig. 1). Appendix Table E2 lists the reasons for excluding other studies. The total study population consisted of 3089 study participants (1566 receiving drug and 1523 receiving placebo) and their baseline demographics are reported in Table 1. Study duration ranged from 12 to 56 weeks.

Direct Pairwise Meta-analysis

Figure 2 shows the direct pairwise meta-analysis estimates of log rate ratios for all drug classes (computed in CMA). Compared to placebo the log rate ratios (and their 95% CIs) for benralizumab, dupilumab, mepolizumab, and reslizumab were − 0.52 [(− 0.90 to − 0.14), I^2 72%], − 1.02 [(− 1.65 to − 0.39) I^2 73%], − 0.80 [(− 0.98 to − 0.61) I^2 0%], and − 0.77 [(− 1.00 to − 0.55), I^2 0%], respectively. Sensitivity analysis by selectively excluding one study [13] (which studied a dosing regimen different from the rest of the studies in the drug class) from the overall analysis did not alter the significance of the pooled analysis (e-Fig. 1).

Network Meta-analysis Estimates

Figure 3 shows the network evidence graph, which is a network laid out in two-dimensional plane, in which the nodes in the graph layout corresponded to the drug class and connecting lines displaying the treatment comparisons (thickness of lines indicating number of studies in each comparison). Table 2 (league table) presents the network meta-analysis estimates for inter-drug differences in log rate ratios for asthma exacerbations (calculated using R). The results are arranged in hierarchical and ranking order. While all drugs were superior to placebo, no inter-drug differences existed. Table 3, which is a comparison of direct and indirect treatment estimates (log rate ratios) to check for consistency of network meta-analysis, shows that no inconsistency existed in analyses. Corresponding forest plot for network meta-analysis is presented in Appendix (e-Fig. 2). Even though no inter-drug differences existed, based on the magnitude of effect (decreased log rate ratio for asthma exacerbation), ranking of treatments based on *P*-scores showed the following order: dupilumab, mepolizumab, reslizumab, and benralizumab (Table 4). A comparison-adjusted funnel plot did not show any statistical evidence of plot asymmetry, based on Egger's test, Begg and Mazumdar rank correlation test, and the Thompson–Sharp tests (Fig. 4).

Discussion

With regards to their comparative effectiveness in reducing asthma exacerbations, this network meta-analysis shows no significant inter-drug differences between benralizumab, dupilumab, mepolizumab, and reslizumab. Although the conclusion is based only on 9 studies in total, the results suggest that dupilumab may have a role in the treatment of eosinophilic asthma and should be compared to mepolizumab, reslizumab, and benralizumab in a direct, RCT.

This network meta-analysis differs from the previously published network meta-analyses. In the network meta-analysis by Casale et al. [19], only benralizumab and reslizumab studies were analyzed, and in the matching-adjusted indirect comparison meta-analysis by Bourdin

et al. [20], only benralizumab, reslizumab, and mepolizumab were analyzed. In the network meta-analyses by Cabon et al. [6] and He et al. [4], only benralizumab, reslizumab, and mepolizumab were compared. While the former [6] attempted to analyze data separately for those with eosinophilic asthma, not all included studies had a uniform criteria for defining eosinophilic asthma [21], as such 'clinical asthma exacerbation' was not an 'a priori' defined outcome in the meta-analysis, and the analysis incorporated data from studies with drug dosing that is not clinically used (e.g., studying mepolizumab at 75 mg, 250 mg, and 750 mg doses). In the network meta-analysis by He et al. [4], not only was 'eosinophilic asthma' or 'clinical asthma exacerbation' defined a priori, incidence density rates (using person-time) were not reported, and drugs with irrelevant clinical dosing were used (e.g., studying mepolizumab at 75 mg, 250 mg and 750 mg doses, and combining benralizumab 0.3 mg/kg with other doses). The indirect treatment comparison by Busse et al. [5] did compare the licensed doses of benralizumab, mepolizumab, and reslizumab and adequately defined 'clinical asthma exacerbation,' as well as parsed out the data based on different blood eosinophil counts. This network meta-analysis resembles the meta-analysis by Busse et al. in having stringent inclusion criteria for studies but differs in some other respects: (1) this meta-analysis included dupilumab studies, as well as (2) used log of rate ratios in analyses. The argument for using logarithmic scale as opposed to an arithmetic scale is taken from the policy of American Journal of Epidemiology (instructions to authors), which states, "when plotting relative measures of effect (e.g., relative risks, relative odds), a logarithmic scale must be used unless there is a compelling reason to use an arithmetic scale" (https://aje.oxfordjournals.org/). This is because the null effect of 1.0 divides the scale into two regions that are equivalent in strength of association. For every point above 1.0, there is a corresponding inverse point below 1.0. However, visually, on an arithmetic scale, points below the null (the preventive effects below the null) are squeezed into a small region from 0 to 1 (finite scale), and the causative effects are stretched across the infinite region above 1.0. This apparent visual imbalance can be corrected if the effects are plotted on a log scale allowing for symmetry between preventive and causative effects [22, 23].

This meta-analysis has important limitations. Most notably, the inclusion criteria were made stringent a priori to ensure that the study population was as homogenous as possible. As a result, the total number of trials included was limited but the data presented are more precise because the definitions of asthma exacerbation and eosinophilic asthma were relatively consistent across the included studies. The definition of eosinophilic asthma for this study was lowered to include patients with peripheral eosinophilia ≥ 250 cells/μL to allow inclusion of a relatively bigger study population, although more consensus definitions seem to be adopting an eosinophil blood count of ≥ 300 cells/μL. Although this did not affect the outcome of the analysis, future meta-analyses and RCTs will need to utilize a stricter definition of eosinophilic asthma once that is established. Another limitation of this meta-analysis is that it does not capture all of the currently available biologics, most notably, omalizumab, which is a monoclonal antibody targeting the high-affinity IgE receptor (FceRI) binding site of immunoglobulin E. Although this biologic therapy is FDA approved and has shown clinical benefits across several trials, none of the published RCTs specified 'eosinophilic asthma' in their inclusion criteria (which could have theoretically allowed inclusion in this network meta-analysis) [24–30]. As such, omalizumab data would have

been applicable in our analysis because IgE does play a role in eosinophil biology through its interaction with mast cells. When IgE on the surface of mast cells encounters cognate antigen, it causes mast cell degranulation producing prostaglandin D2, which is a known eosinophil chemokine via the chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2) [31]. Retrospective data about the efficacy of omalizumab that stratified patients into “high” and “low” eosinophil subgroups based on a blood eosinophil count ≥ 300 cells/μL found that omalizumab has similar efficacy in patients with eosinophilic asthma as in non-eosinophilic asthma [32]. Another limitation of this meta-analysis is that we excluded all studies that evaluated drug dosing not approved by the FDA. The only exception to this rule was the inclusion of a study which administered dupilumab at a dose of 30 mg weekly instead of every 2 weeks [13]. As such, sensitivity analysis (e-Fig. 1) by selectively excluding this study did not change the overall outcome or conclusions. We believe that the strength of the data presented outweighs the exclusion of the excluded studies (Table E2 lists the reasons for exclusion of excluded studies), but it is important to note that our analysis is not comprehensive and needs to be updated with further studies as more trials become available.

In conclusion, this meta-analysis confirms that anti-IL-5/anti-IL-5R monoclonal antibody therapies are associated with a decrease in asthma exacerbations in patients with eosinophilic asthma, almost to a similar degree. While these clinical findings are biologically plausible, our analysis highlights the need not only for a large, direct, randomized trial comparing all biologic therapies in asthma phenotypes but also reinforces the need for further study of non-anti-IL-5/anti-IL-5R biologics in eosinophilic asthma.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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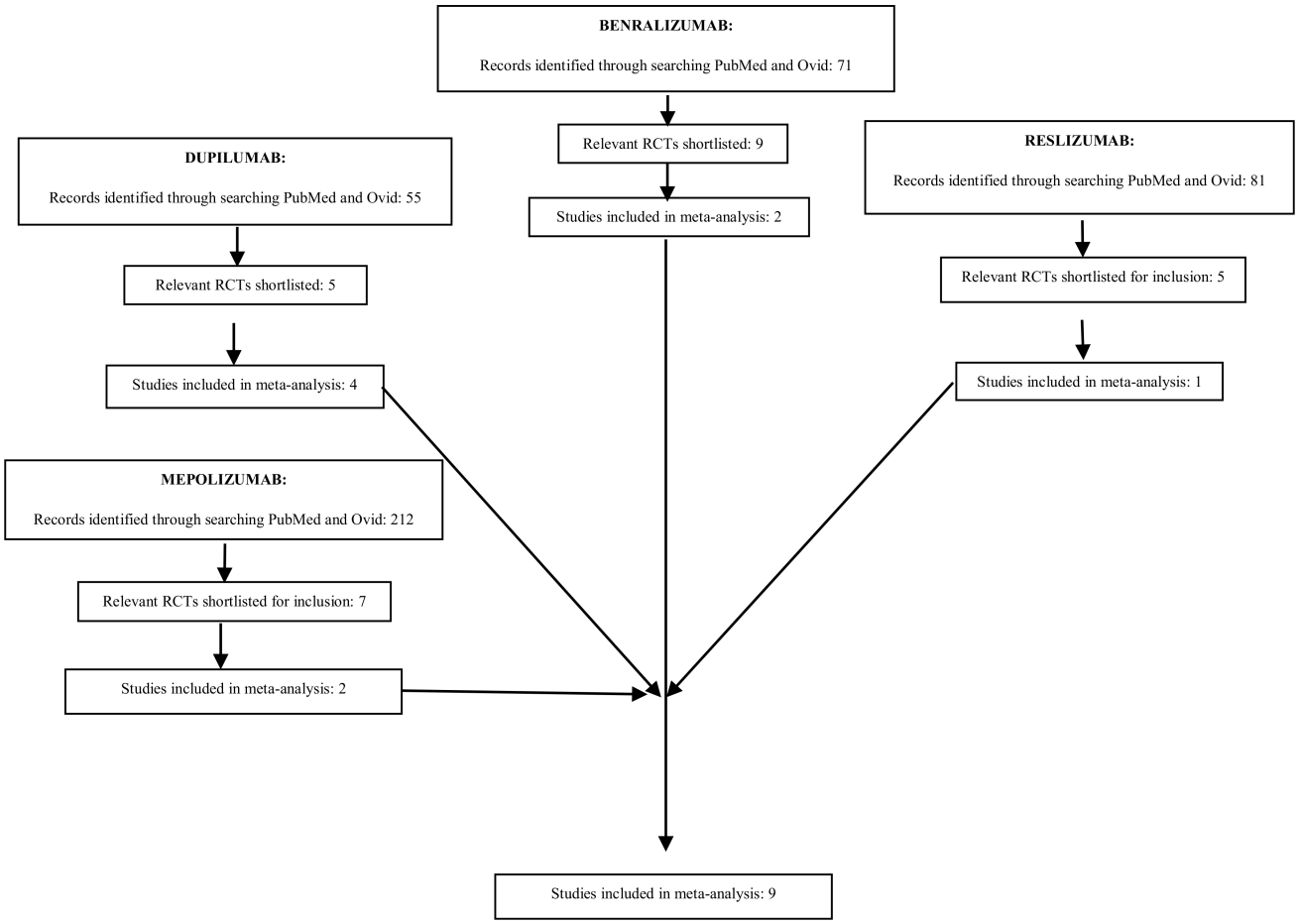

Fig. 1.

Selection of studies. Details on studies excluded as shown in figure are provided in Appendix/Data Supplement

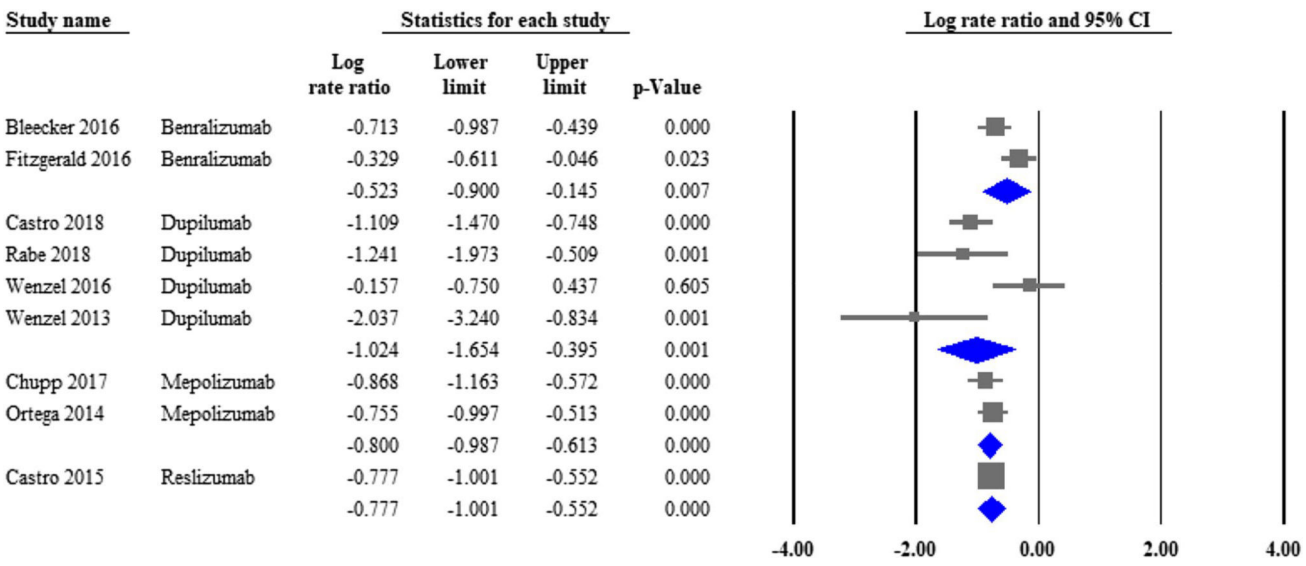

Fig. 2.

Meta-analysis of pooled log rate ratios for asthma exacerbations. The size of the square indicates the weight of the effect size as determined by the number of studies and participants. *CI* confidence interval

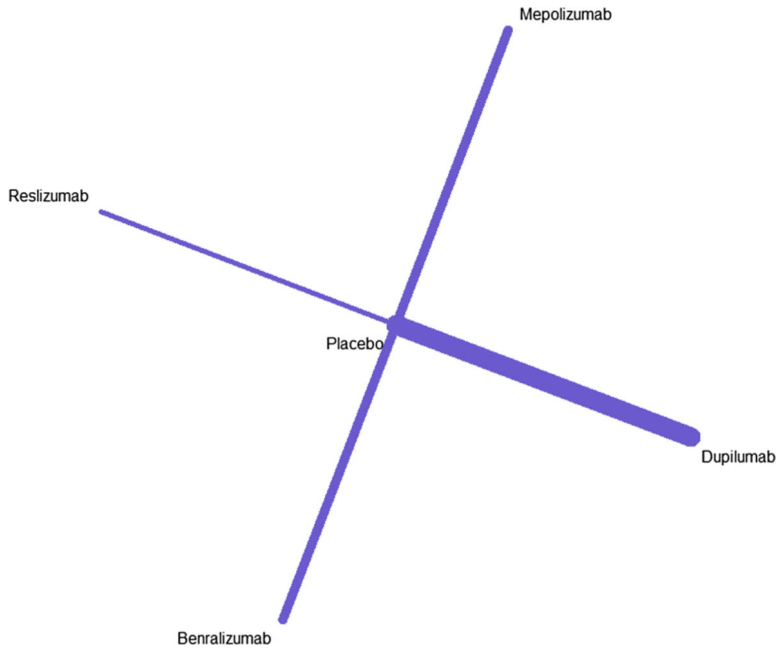

Fig. 3.

Network evidence graph. Graph plotted on a two-dimensional plane, in which the connecting lines between treatment names display the treatment comparisons (thickness of lines indicating number of studies in each comparison)

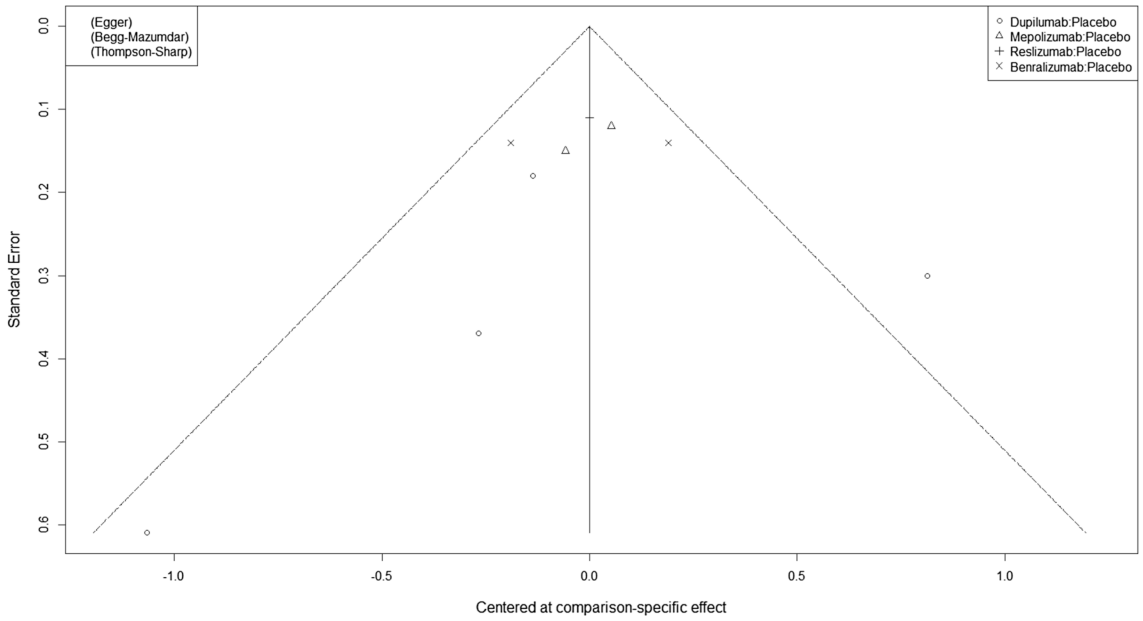

Fig. 4.

Comparison-adjusted funnel plot. Comparison-adjusted funnel plot for publication bias assessment with statistical tests for plot asymmetry reported in top left corner

Table 1

Baseline characteristics of study participants

Study ID (first author year published)	Duration of treatment (weeks)	*N* (randomized to in eosinophilic asthma patients and placebo)	Age (mean ± SD) or mean (range)	Gender (% males)	Baseline FEV_1 (in L or % predicted and mean ± SD)	Drug dose	Blood eosinophil count threshold for inclusion criteria	Similarity in inclusion criteria (asthma exacerbation history and inhaler use)
Benralizumab								
Bleecker 2016 [7]	48	Drug: 267	Drug: 47.6 (14.6)	Drug: 35%	Drug: 1.66 (0.57)	30 mg intramuscularly q 8w	≥ 300 cells/μL	Ex: ≤ 2 in last year
		Plc: 267	Plc: 48.6 (14.7)	Plc: 33%	Plc: 1.65 (0.58)			Baseline treatment: medium–high dose ICS–LABA
Fitzgerald 2016 [6]	56	Drug: 239	Drug: 49.6 (13)	Drug: 42%	Drug: 1.75 (0.62)	30 mg intramuscularly q 8w	≥ 300 cells/μL	Ex: ≤ 2 in last year
		Plc: 248	Plc: 48.5 (14.1)	Plc: 42%	Plc: 1.81 (0.64)			Baseline treatment: medium–high dose ICS–LABA
Dupilumab								
Castro 2018 [10]	52	Drug: 277	Drug: 47.7 (15.6)	Drug: 38%	Drug: 1.78 (0.60)	300 mg subcutaneously q 2w	≥ 300 cells/μL	Ex: > 1 in the last year
		Plc: 142	Plc: 48.2 (14.7)	Plc: 32%	Plc: 1.75 (0.57)			Baseline treatment: medium–high dose ICS–LABA + 2 add-on controllers
Rabe 2018 [11]	24	Drug: 48	Drug: 51.9 (12.5)	Drug: 40%	Drug: 1.53 (0.53)	300 mg subcutaneously q 2w	≥ 300 cells/μL	Ex: not specified
		Plc: 41	Plc: 50.7 (12.8)	Plc: 39%	Plc: 1.63 (0.61)			Baseline treatment: high dose ICS + 2 controllers + maintenance steroids
Wenzel 2016 [12]	24	Drug: 64	48.6 (13) (Overall population)	37% (Overall population)	1.84 (0.54) (Overall population)	300 mg subcutaneously q 2w	≥ 300 cells/μL	Ex: > 1 in the last year
		Plc: 68						Baseline treatment: medium–high dose ICS–LABA
Wenzel 2013 [13]	12	Drug: 52	Drug: 37.8 (13.2)	Drug: 50%	Drug: 2.47 (0.65)	300 mg subcutaneously q 1w	≥ 300 cells/μL	Ex: > 1 in the last year

Study ID (first author year published)	Duration of treatment (weeks)	*N* (randomized to in eosinophilic asthma patients and placebo)	Age (mean ± SD) or mean (range)	Gender (% males)	Baseline FEV_1 (in L or % predicted and mean ± SD)	Drug dose	Blood eosinophil count threshold for inclusion criteria	Similarity in inclusion criteria (asthma exacerbation history and inhaler use)
		Plc: 52	Plc: 41.6 (13.1)	Plc: 50%	Plc: 2.54 (0.66)			Baseline treatment: medium–high dose ICS–LABA
Reslizumab								
Castro 2015 [14]	48	Drug: 151 (pooled)	Study 1	Study 1	Study 1	3 mg/kg intravenously q 4w	≥ 400 cells/μL	Ex: > 1 in the last year
		Plc: 237 (pooled)	Drug: 48 (38–57)	Drug: 42%	Drug: 1.89 (0.73)			Baseline treatment: medium dose ICS with or without another controller drug
			Plc: 49 (38–57)	Plc: 34%	Plc: 1.93 (0.80)			
			Study 2	Study 2	Study 2			
			Drug: 48 (37–56.2)	Drug: 38%	Drug: 2.13 (0.78)			
			Plc: 48 (39.5–57)	Plc: 35%	Plc: 2.00 (0.67)			
Mepolizumab								
Chupp 2017 [15]	24	Drug: 274	Drug: 49.8 (14.0)	Drug: 46%	Drug: 1.80 (0.6)	100 mg subcutaneously q 4w	≥ 300 cells/μL * (in the ITT placebo and drug groups, the baseline eosinophil counts were 350 cells/μL, respectively)	Ex: ≥2 in the last year
		Plc: 277	Plc: 52.1 (12.9)	Plc: 36%	Plc: 1.7 (0.6)			Baseline treatment: high dose ICS + additional controller drug
Ortega 2014 [16]	32	Drug: 194	Drug: 51 (12–81)	Drug: 60%	Drug: 1.73 (0.66)	100 mg subcutaneously q 4w	≥ 300 cells/μL * (at randomization actual mean baseline eosinophil counts were 320 cells/μL in placebo and 290 cells/μL in drug groups)	Ex: ≥ 2 in the last year
		Plc:191	Plc: 49 (12–76)	Plc: 56%	Plc: 1.86 (0.63)			Baseline treatment: high dose ICS + additional controller drug

N number of study participants randomized to in eosinophilic asthma patients analyzed in this meta-analysis and placebo, *SD* standard deviation, *FEV1* forced expiratory volume-in 1 s. *Plc* placebo group, *q* 'every', *w* weekly

* count in the last 12 months prior to inclusion.

Ex number of asthma exacerbations prior to participants enrolling in study, *ICS* inhaled corticosteroids, *LABA* long acting bronchodilator

Table 2

League table for differences in log rate ratio of asthma exacerbations

Dupilumab	–	–	–	−0.97 [−1.39; −0.56] *
−0.16 [−0.76; 0.44]	**Mepolizumab**	–	–	−0.81 [−1.24; −0.38] *
−0.19 [−0.91; 0.53]	−0.03 [−0.76; 0.69]	**Reslizumab**	–	−0.78 [−1.37; −0.19] *
−0.45 [−1.06; 0.15]	−0.29 [−0.90; 0.32]	−0.26 [−0.99; 0.47]	**Benralizumab**	−0.52 [−0.95; −0.09] *
−0.97 [−1.39; −0.56] *	−0.81 [−1.24; −0.38] *	−0.78 [−1.37; −0.19] *	−0.52 [−0.95; −0.09] *	**Placebo**

League table for random effects model with network estimates in lower triangle and direct estimates in upper triangle

* Statistically significant. Example to interpret this table: difference between dupilumab and mepolizumab is −0.16 [−0.76; 0.44]; between dupilumab and reslizumab is −0.19 [−0.91; 0.53]

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Table 3

Comparison of direct and indirect treatment estimates

Comparison	*k*	prop	nma	Direct	Indirect
Benralizumab:dupilumab	0	0	0.45	–	0.45
Benralizumab:mepolizumab	0	0	0.29	–	0.29
Benralizumab:placebo	2	1.00	−0.52	−0.52	–
Benralizumab:reslizumab	0	0	0.26	–	0.26
Dupilumab:mepolizumab	0	0	−0.16	–	−0.16
Dupilumab:placebo	4	1.00	−0.97	−0.97	–
Dupilumab:reslizumab	0	0	−0.19	–	−0.19
Mepolizumab:placebo	2	1.00	−0.81	−0.81	–
Mepolizumab:reslizumab	0	0	−0.03	–	−0.03
Placebo:reslizumab	1	1.00	0.78	0.78	–

A comparison of direct and indirect treatment estimates (log rate ratios) to check for consistency of network meta-analysis comparison

k Number of studies providing direct evidence, *prop* direct evidence proportion, *nma* estimated treatment effect in network meta-analysis, *direct* estimated treatment effect derived from direct evidence, *indirect* estimated treatment effect derived from indirect evidence

Table 4

Ranking of treatments

	***P*-score**
Dupilumab	0.83
Mepolizumab	0.66
Reslizumab	0.62
Benralizumab	0.36
Placebo	0.00

P-scores are based solely on the point estimates and standard errors of the network estimates