



Comparative Efficacy of Anti IL-4, IL-5 and IL-13 Drugs for Treatment of Eosinophilic Asthma: A Network Meta-analysis

Imran H. Iftikhar¹ · Mathew Schimmel¹ · William Bender¹ · Colin Swenson¹ · David Amrol²

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Abstract

Background Several new biologics have been studied in patients with eosinophilic asthma with varying degrees of response on clinical outcomes. No head-to-head trial has directly compared the efficacy of these drugs.

Objective To synthesize data on the relative efficacy of benralizumab, dupilumab, lebrikizumab, mepolizumab, reslizumab, and tralokinumab using network meta-analysis.

Data sources We searched PubMed from inception to December 15th, 2017.

Data extraction and synthesis We used the ‘frequentist’ methodology with random effect models using primarily ‘netmeta’ function in R to generate network meta-analysis results. Outcomes assessed included changes in forced expiratory volume in 1 s (FEV₁), asthma control questionnaire (ACQ), and asthma quality of life questionnaire (AQLQ). We also separately analyzed the annualized rate ratios for asthma exacerbations for each drug and compared to placebo. For all outcomes assessed, all drugs were superior to placebo except tralokinumab. In terms of magnitude of effect, dupilumab, followed by reslizumab and benralizumab showed the greatest increase in FEV₁, 0.16L (95% CIs: 0.08–0.24), 0.13L (0.10–0.17), and 0.12L (0.08–0.17), compared to placebo. While mepolizumab, followed by dupilumab, benralizumab, and reslizumab showed reductions in ACQ scores, in order of magnitude of effect, dupilumab, followed by mepolizumab, benralizumab, and reslizumab showed the greatest increase in AQLQ scores. All drugs decreased asthma exacerbations but the results were only significant for reslizumab and dupilumab.

Conclusions All drugs except for tralokinumab showed improvements in FEV₁, ACQ, and AQLQ. Only reslizumab and dupilumab were associated with statistically significant reductions in asthma exacerbation rates.

Keywords Eosinophilic asthma · Benralizumab · Dupilumab · Mepolizumab · Reslizumab

Introduction

Based on the sputum and peripheral blood cellular profiles, asthma can be classified into eosinophilic or non-eosinophilic [1, 2]. Since eosinophilia can be seen across multiple clusters of asthma and disease severity, focus is shifting

toward identifying different mechanisms that cause eosinophilia [2]. Among these are elevated interleukin (IL)-4 and IL-13 expression in early-onset atopic asthma and predominant IL-5 expression in later-onset, or less-atopic asthma [2, 3]. Although a significant number of suboptimal outcomes in asthma are related to poor adherence or unavoidable environmental exposures, quite a few also have underlying refractory asthma, in whom standard therapies are ineffective [4]. Several new ‘biologics’ have emerged as promising personalized medicines specifically in the treatment of severe eosinophilic asthma. ‘Biologics’ are drugs produced by living cells through biological processes, and mimic natural biological substances such as antibodies targeting specific inflammatory pathways [5]. Anti-IL-5 monoclonal antibodies (mepolizumab and reslizumab) are approved in the United States for patients with severe asthma and peripheral eosinophilia [6]. Benralizumab, an antibody that

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✉ Imran H. Iftikhar
imran.hasan.iftikhar@emory.edu

¹ Division of Pulmonary, Allergy, Critical Care & Sleep Medicine, Emory University School of Medicine, 613 Michael St, NE, Atlanta, GA, USA

² Division of Allergy and Immunology, University of South Carolina School of Medicine, Columbia, SC, USA

binds to the alpha subunit of IL-5 receptor (IL-5R α), was recently approved [7]. Dupilumab is an antibody directed against the α subunit of the IL-4 receptor (IL-4R α) and by doing so behaves as a dual antagonist of both IL-4 and IL-13 [8]. Lebrikizumab and tralokinumab are monoclonal antibodies against IL-13 [9], and because the former showed variable results in two phase 3 randomized controlled trials (RCT) [10] for the primary endpoint (significant reduction in the rate of asthma exacerbations over 52 weeks), further research of this drug was eventually terminated.

A network meta-analysis allows for comparisons of interventions that may not have been directly compared in head-to-head trials by simultaneously analyzing both direct comparisons of interventions within RCT and indirect comparisons across multiple trials based on a common comparator [11, 12]. In this network meta-analysis we sought to compare the efficacies of the above-mentioned biologics used to treat eosinophilic asthma.

Methods

We searched PubMed from inception to December 15th, 2017 (Fig. 1). The search was not restricted per publication status or date. We also hand-searched reference lists for all retrieved studies. We did not search conference proceedings.

Study Selection

For inclusion in our meta-analysis, we considered only English language RCTs of patients with asthma treated with benralizumab, dupilumab, lebrikizumab, mepolizumab, reslizumab, and tralokinumab. For inclusion in the network meta-analysis, studies had to report data on change in forced expiratory volume-in 1 s (FEV₁), asthma control questionnaire (ACQ), and asthma quality of life questionnaire (AQLQ). Additional details are included in data supplement.

Data Extraction, Synthesis and Analysis

Data extracted from studies included first author's name, publication year, study design, population characteristics, treatments, length of follow-up, and change in FEV₁, ACQ scores, AQLQ scores, and number of asthma exacerbations on treatment. The studies were assessed for 'study quality' based on modified Cochrane methods [13] (additional details are provided in Online Resource).

Data were directly extracted on the working sheets of Comprehensive Meta-Analysis (CMA version 2.2.064; Biostat, Englewood, N.J. U.S.A) software. For studies in which data were reported for different doses of treatments or reported separately for eosinophilic and non-eosinophilic asthma population, we used the data for the highest dose, for

longest follow up period available, and preferably for eosinophilic asthma patients (if combined data for eosinophilic and non-eosinophilic asthma patients were not available).

Data Synthesis and Analysis

The Comprehensive Meta-Analysis software was used to generate effect size data in a common format, in specific as treatment effect with standard error. Network meta-analysis using 'frequentist' methods was then performed in R program version 3.2.2 (R Development Core Team, 2010), using package 'netmeta' [14]. This methodology has been previously described [11, 12]. Additional details for this methodology are provided in online resource.

We also calculated event rates for asthma exacerbations reported in each study. By calculating 'person-years' for each study (separately for treatment and placebo arms), we computed rate ratios and the overall pooled rate ratios for each drug separately.

Finally, for publication bias assessment, as no single analysis was representative of the total number of studies included in this network meta-analysis, funnel plot was constructed for studies reporting FEV₁.

We also analyzed sub-groups based on biomarkers ('biomarker-high' vs. 'biomarker-low'), an approach similar to that used by Hanania et al. [10]. Data stratified based on biomarkers was available only in a few studies. The cut-off for biomarkers used in these studies (to differentiate eosinophilic from non-eosinophilic) was either blood eosinophil count $\geq$ or $<$ 300 cells/ μ L [15–17] or $\geq$ or $<$ 400 cells/ μ L [18], or serum periostin $\geq$ or $<$ 50 ng/mL [10, 19] or the eosinophil/lymphocyte, and eosinophil/neutrophil index (positive or negative) [20].

Throughout the process, we adhered to the PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines [21] (checklist and study quality assessment reported in online resource tables E1 and E2, respectively).

Results

Search from the database yielded seven studies [15–17, 20, 22–24] for benralizumab, two [25, 26] for dupilumab, four [10, 19, 27, 28] for lebrikizumab, seven [29–35] for mepolizumab, four [18, 36–38] for reslizumab, and two [39, 40] for tralokinumab (Fig. 1). Across all studies included in this network meta-analysis, a total of 8444 (4406 in treatment arm and 4038 in control arm) were analyzed. Studies ranged from 12 to 56 weeks in duration. Most studies defined eosinophilic asthma *a priori*. Table 1 lists the baseline characteristics of study participants. Network evidence plots for studies analyzed for FEV₁, ACQ, and AQLQ analyses are presented in figures E1–E3 (in online resource).

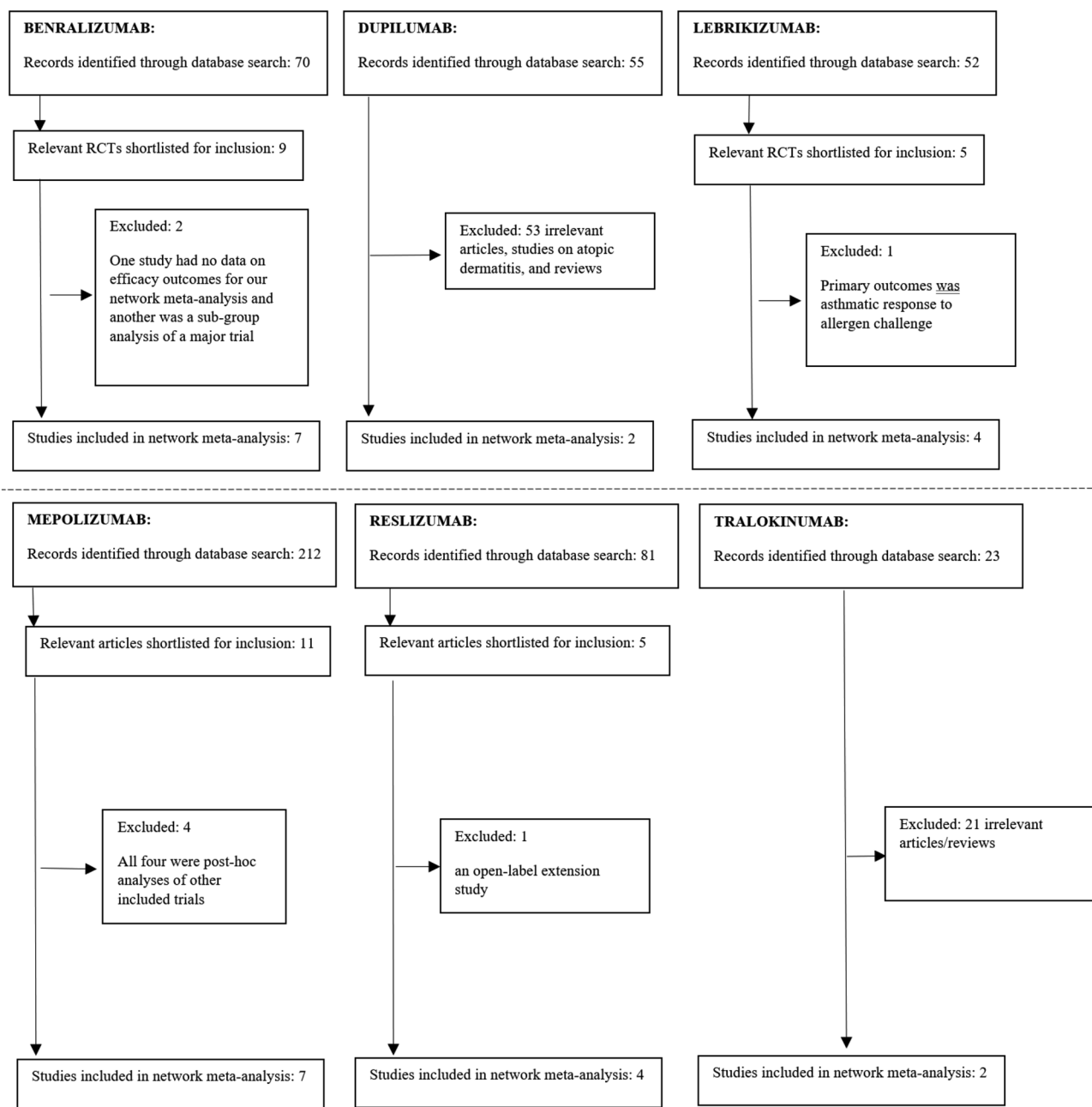


Fig. 1 Selection of studies. Details on studies excluded as shown in figure, are provided in data supplement

Effect on FEV₁

A total of 22 studies [10, 15–20, 22, 23, 25, 26, 28, 30–40] with 7957 participants (4167 participants with active treatments and 3790 participants with placebo) were analyzed for change in FEV₁. All drugs were superior to placebo (Table 2) except tralokinumab. Dupilumab, followed by reslizumab and benralizumab showed the greatest increase in FEV₁, 0.16L (95% CIs: 0.08–0.24), 0.13L (0.10–0.17), and 0.12L (0.08–0.17), compared to placebo, respectively (as

shown in forest plot Fig. 2). Lebrikizumab and mepolizumab had similar effects. There were no significant inter-treatment differences.

Effect on ACQ Scores

A total of 20 studies [10, 15–20, 22–26, 29, 30, 34, 36–40] with 6987 participants (3657 participants with active treatments and 3330 participants with placebo) were analyzed for change in ACQ scores. All drugs were

Table 1 Baseline characteristics of study participants

Study ID (first author-year published)	Duration of treatment (weeks)	N (randomized to in each arm)	Age (mean $\pm$ SD) or mean (range)	Gender (% males)	Baseline FEV ₁ (in L or % predicted and mean $\pm$ SD)	Use of oral corticosteroids at baseline (%)	Use of inhaled steroids at baseline (%)	Criteria to assess 'eosinophilic' (in brackets reported in conventional units)
Benralizumab								
Castro 2014 [20]	52	Drug: 82 (for 100 mg eosinophilic group) Plc: 80	Drug: 47.8 (12.9) Plc: 45.6 (11.7)	Drug: 27% Plc: 44%	Drug: 66.1% pred (15.9%) Plc: 65% pred (15.3%)	Drug: 4% Plc: 5%	Drug: 50% Plc: 50%	ELEN index positive or FeNO of at least 50 ppb
Bleecker 2016 [15]	48	Drug: 267 (for 30 mg q8w group with eosinophilia) Plc: 267	Drug: 47.6 (14.6) Plc: 48.6 (14.7)	Drug: 35% Plc: 33%	Drug: 1.66 (0.57) Plc: 1.65 (0.58)	N/A	N/A	Blood eosinophil count $\geq$ 300 cells per μ L
Fitzgerald 2016 [17]	56	Drug: 441 (for 30 mg q8w group with eosinophilia) Plc: 440	Drug: 49.6 (13) Plc: 48.5 (14.1)	Drug: 42% Plc: 42%	Drug: 1.75 (0.62) Plc: 1.81 (0.64)	N/A	N/A	Blood eosinophil count $\geq$ 300 cells per μ L
Nair 2017 [22]	28	Drug: 73 (for q8w group) Plc: 75	Drug: 52.9 (10.1) Plc: 49.9 (11.7)	Drug: 36% Plc: 36%	Drug: 1.75 (0.63) Plc: 1.93 (0.66)	N/A	N/A	Blood eosinophil count $\geq$ 150 cells per ml ³ (150 cells per μ L)
Park 2016 [24]	52	Drug: 26 (for 100 mg dose) Plc: 26	Drug: 51.4 (13.8) Plc: 50.8 (11.8)	Drug: 38.5% Plc: 34.6%	Drug: 67.5% (15.8%) Plc: 68.8 (16.3%)	N/A	N/A	ELEN index positive or $\geq$ 2% sputum eosinophils or FeNO $\geq$ 50 ppb
Ferguson 2017 [16]	12	Drug: 28 (for the eosinophilic group) Plc: 33	Drug: 46.4 (16) Plc: 49.6 (13.3)	Drug: 50% Plc: 36%	Drug: 2.40 (0.71) Plc: 2.24 (0.69)	N/A	N/A	Blood eosinophil count $\geq$ 300 cells per μ L
Nowak 2015 [23]	12	Drug: 36 Plc: 38	Drug: 34.8 (19–54) Plc: 35.9 (22–55)	Drug: 36% Plc: 21%	Drug: 2.07 Plc: 1.68	N/A	Drug: 53% Plc: 61%	Blood eosinophil count $\geq$ 450 cells per μ L
Dupilumab								
Wenzel 2013 [26]	12	Drug: 52 Plc: 52	Drug: 37.8 (13.2) Plc: 41.6 (13.1)	Drug: 50% Plc: 50%	Drug: 2.47 (0.65) Plc: 2.54 (0.66)	N/A	Drug: 81% Plc: 79%	$\geq$ 3% sputum eosinophils or blood eosinophil count $\geq$ 300 cells per μ L
Wenzel 2016 [25]	24	Drug: 66 (for 300 mg q4w) Plc: 68	48.6 (13) (overall population)	37% (overall population)	1.84 (0.54) (overall population)	N/A	51%	Blood eosinophil count $\geq$ 300 cells per μ L

Table 1 (continued)

Study ID (first author-year published)	Duration of treatment (weeks)	N (randomized to in each arm)	Age (mean±SD) or mean (range)	Gender (% males)	Baseline FEV ₁ (in L or % predicted and mean±SD)	Use of oral corticosteroids at baseline (%)	Use of inhaled steroids at baseline (%)	Criteria to assess 'eosinophilic' (in brackets reported in conventional units)
Lebrikizumab								
Corren 2011 [19]	32	Drug: 107 Plc: 112	Drug: 45 (12) Plc: 44 (13)	Drug: 35% Plc: 34%	Drug: 64% (12%) Plc: 65% (11%)	N/A	N/A	Blood eosinophil count ≥ 0.14 × 10 ⁹ cells per L (140 cells per µL)
Noonan 2013 [28]	12	Drug: 52 (for 500 mg dose) Plc: 52	Drug: 40.6 (11.4) Plc: 40.8 (13.1)	Drug: 32.7% Plc: 36.5%	Drug: 2.4 (0.6) Plc: 2.4 (0.6)	N/A	N/A	Blood eosinophil count ≥ 0.14 × 10 ⁹ cells/L (140 cells per µL)
Hanania 2015 [27]	24	Drug: 118 Plc: 116	Drug: 47.9 (11.9) Plc: 50 (11.3)	Drug: 41.5% Plc: 36.2%	Drug: 60.9% (10.2%) Plc: 62.7% (10.2%)	N/A	N/A	Not defined <i>a priori</i> in protocol
Hanania 2016 [10]	52	LAVOLTA I: Drug: 359 (for 125 mg dose) Plc: 362 LAVOLTA II: Drug: 357 (for 125 mg dose) Plc: 354	LAVOLTA I: Drug: 51 (12.6) (for 125 mg dose) Plc: 51.3 (12.3) LAVOLTA II: Drug: 50.2 (12.6) (for 125 mg dose) Plc: 49.5 (13.3)	LAVOLTA I: Drug: 31% (for 125 mg dose) Plc: 36% LAVOLTA II: Drug: 34% (for 125 mg dose) Plc: 38%	LAVOLTA I: Drug: 1.82 (0.57) (for 125 mg dose) Plc: 1.85 (0.59) LAVOLTA II: Drug: 1.84 (0.58) (for 125 mg dose) Plc: 1.88 (0.57)	LAVOLTA I: Drug: 45% (for 125 mg dose) Plc: 44% LAVOLTA II: Drug: 51% (for 125 mg dose) Plc: 51%	Blood eosinophil count ≥ 300 cells per µL another inclusion criteria was per-ostin ≥ 50 ng/mL	
Mepolizumab								
Flood-Page 2007 [31]	20	Drug: 116 Plc: 126	Drug: 36.3 (10.4) Plc: 36.8 (10)	Drug: 52% Plc: 38%	Drug: 2.51 (0.58) Plc: 2.39 (0.59)	N/A	N/A	Not defined <i>a priori</i> in protocol
Haldar 2009 [32]	50	Drug: 29 Plc: 32	Drug: 48 (21–63) Plc: 50 (24–72)	Drug: 48% Plc: 56%	Drug: 78.1% (20.9%) Plc: 77.6% (24.1%)	N/A	N/A	Not defined <i>a priori</i> in protocol
Nair 2009 [33]	26	Drug: 9 Plc: 11	Drug: 54.6 (10.9) Plc: 58.2 (7.1)	Drug: 44% Plc: 72%	Drug: 1.40 (0.6) Plc: 1.60 (0.5)	N/A	N/A	≥ 3% sputum eosinophils
Pavord 2012 [35]	52	Drug: 156 (for the 750 mg dose) Plc: 155	Drug: 48.6 (11.1) Plc: 46.4 (11.3)	Drug: 40% Plc: 37%	Drug: 1.95 (0.67) Plc: 1.90 (0.65)	Drug: 30% Plc: 29%	N/A	≥ 3% sputum eosinophils or FeNO ≥ 50 ppb or Blood eosinophil count ≥ 0.3 × 10 ⁹ per L (300 cells per µL)

Table 1 (continued)

Study ID (first author-year published)	Duration of treatment (weeks)	N (randomized to in each arm)	Age (mean $\pm$ SD) or mean (range)	Gender (% males)	Baseline FEV ₁ (in L or % predicted and mean $\pm$ SD)	Use of oral corticosteroids at baseline (%)	Use of inhaled steroids at baseline (%)	Criteria to assess 'eosinophilic' (in brackets reported in conventional units)
Ortega 2014 [34]	32	Drug: 194 (for the 100 mg dose) Plc: 191	Drug: 51 (12–81) Plc: 49 (12–76)	Drug: 60% Plc: 56%	Drug: 1.73 (0.66) Plc: 1.86 (0.63)	Drug: 27% Plc: 23%	N/A	Blood eosinophils > 150 cells per μ L at screening or $\geq$ 300 cells per μ L at some time during the previous year
Chupp 2017 [30]	24	Drug: 276 Plc: 280	Drug: 49.8 (14.0) Plc: 52.1 (12.9)	Drug: 46% Plc: 36%	Drug: 1.80 (0.6) Plc: 1.7 (0.6)	Drug: 23% Plc: 24%	Drug: 99% Plc: 100%	Blood eosinophils > 150 cells per μ L at screening or $\geq$ 300 cells per μ L at some time during the previous year
Reslizumab								
Bjermer 2016 [36]	16	Drug: 106 Plc: 105	Drug: 43 Plc: 44.2	Drug: 42% Plc: 41%	Drug: 2.19 Plc: 2.22	N/A	N/A	Blood eosinophils $\geq$ 400 cells per μ L
Castro 2011 [37]	12	Drug: 53 Plc: 53	Drug: 44.9 (13.9) Plc: 45.8 (11.7)	Drug: 46% Plc: 45%	Drug: 2.1 (0.6) Plc: 2.3 (0.75)	N/A	N/A	Blood eosinophils $\geq$ 3% sputum eosinophils
Castro 2015 [38]	48	Study 1 Drug: 245 Plc: 244 Study 2 Drug: 232 Plc: 232	Study 1 Drug: 48 (38–57) Plc: 49 (38–57) Study 2 Drug: 48 (37–56.2) Plc: 48 (39.5–57)	Study 1 Drug: 42% Plc: 34% Study 2 Drug: 38% Plc: 35%	Study 1 Drug: 1.89 (0.73) Plc: 1.93 (0.80) Study 2 Drug: 2.13 (0.78) Plc: 2.00 (0.67)	Study 1 Drug: 19% Plc: 19% Study 2 Drug: 12% Plc: 12%	N/A	Blood eosinophils $\geq$ 400 cells per μ L
Corren 2016 [18]	16	Drug: 398 Plc: 98	Drug: 44.9 Plc: 45.1	Drug: 34% Plc: 45%	Drug: 2.10 Plc: 2.18	N/A	N/A	Not defined <i>a priori</i> in protocol
Tralokinumab								
Piper 2013 [40]	13	Drug: 48 (for the 600 mg dose) Plc: 48	Drug: 49.8 (10.4) Plc: 47.2 (9.8)	Drug: 41.7% Plc: 31.3%	Drug: 1.96 (0.66) Plc: 1.94 (0.48)	Drug: 6.3% Plc: 0%	N/A	Not defined <i>a priori</i> in protocol
Brightling 2015 [39]	52	Drug: 151 (for the q4w group) Plc: 151	Drug: 50.5 (11.8) Plc: 50.3 (12.9)	Drug: 34% Plc: 36%	Drug: 1.94 (0.71) Plc: 1.92 (0.60)	N/A	N/A	Not defined <i>a priori</i> in protocol

N Number of study participants, SD Standard deviation, FEV₁ Forced expiratory volume-in 1 s, Plc Placebo group, ELEN index Eosinophil/lymphocyte and eosinophil/neutrophil index—a mathematical algorithm to predict elevated sputum eosinophils, ppb Parts per billion, FeNO Fraction of exhaled nitric oxide, N/A Not available, q4w Every 4 weeks, q8w Every 8 weeks, q4w Every 4 weeks

Table 2 Mean difference in FEV₁ across comparisons

	Benralizumab	Dupilumab	Lebrikizumab	Mepolizumab	Placebo	Reslizumab	Tralokinumab
Benralizumab	–	–0.03 (–0.12 to 0.05)	0.02 (–0.04 to 0.10)	0.03 (–0.04 to 0.10)	0.12 (0.08 to 0.17)*	–0.009 (–0.06 to 0.04)	0.06 (–0.03 to 0.15)
Dupilumab	0.03 (–0.05 to 0.12)	–	0.06 (–0.03 to 0.15)	0.06 (–0.03 to 0.16)	0.16 (0.08 to 0.24)*	0.02 (–0.06 to 0.11)	0.09 (–0.01 to 0.20)
Lebrikizumab	–0.02 (–0.10 to 0.04)	–0.06 (–0.15 to 0.03)	–	0.001 (–0.07 to 0.08)	0.09 (0.04 to 0.15)*	–0.03 (–0.10 to 0.02)	0.03 (–0.06 to 0.12)
Mepolizumab	–0.03 (–0.10 to 0.04)	–0.06 (–0.16 to 0.03)	–0.001 (–0.07 to 0.08)	–	0.09 (0.03 to 0.15)*	–0.03 (–0.10 to 0.02)	0.03 (–0.07 to 0.13)
Placebo	–0.12 (–0.17 to –0.08)*	–0.16 (–0.24 to –0.08)*	–0.09 (–0.15 to –0.04)*	–0.09 (–0.15 to –0.03)*	–	–0.13 (–0.17 to –0.10)*	–0.06 (–0.14 to 0.01)
Reslizumab	0.009 (–0.04 to 0.06)	–0.02 (–0.11 to 0.06)	0.03 (–0.02 to 0.10)	0.03 (–0.02 to 0.10)	0.13 (0.10 to 0.17)*	–	0.07 (–0.01 to 0.15)
Tralokinumab	–0.06 (–0.15 to 0.03)	–0.09 (–0.20 to 0.01)	–0.03 (–0.12 to 0.06)	–0.03 (–0.13 to 0.07)	0.06 (–0.01 to 0.14)	–0.07 (–0.15 to 0.01)	–

Tau²: 0I²: 15.4%

Tests of heterogeneity:

Within designs heterogeneity: $p=0.26$

Results are reported in liters

Tau² and I² show low level of heterogeneity across studies

Example how to analyze table: difference between benralizumab and dupilumab is reported in the cell in 3rd column 2nd row. When dupilumab is compared to benralizumab, the effect direction is changed and results are reported in 2nd column 3rd row. Similarly, the difference between dupilumab and lebrikizumab is reported in 4th column 3rd row and that between lebrikizumab and dupilumab is in 3rd column and 4th row, so on and so forth. Total number of studies analyzed for benralizumab: 6; for dupilumab: 2; for lebrikizumab: 3; for mepolizumab: 5; for reslizumab: 4; for tralokinumab: 2

*represents statistically significant

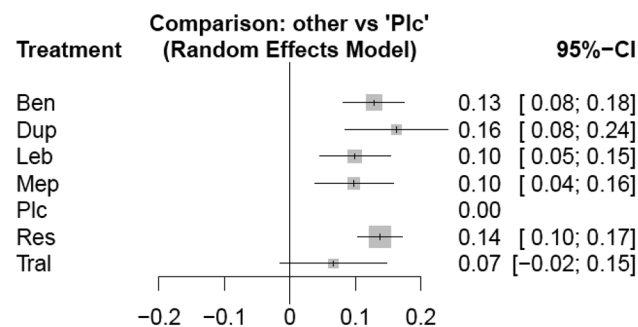


Fig. 2 Forest plot for the analysis of change in FEV₁. The size of the square indicates the weight of the effect size as determined by the number of studies and participants. CI confidence interval, Ben benralizumab, Dup dupilumab, Leb lebrikizumab, Mep mepolizumab, Plc placebo, Res reslizumab, Tral tralokinumab. Total number of studies analyzed for benralizumab: 6; for dupilumab: 2; for lebrikizumab: 3; for mepolizumab: 5; for reslizumab: 4; for tralokinumab: 2

superior to placebo (Fig. 3; Table 3), except tralokinumab. Mepolizumab, followed by dupilumab, benralizumab, and reslizumab showed reductions in ACQ scores [–0.42 (–0.55 to –0.29), –0.31 (–0.50 to –0.12), –0.28 (–0.38 to –0.18), –0.26 (–0.39 to –0.13)], and tralokinumab [0.15 (–0.36 to 0.04)] and lebrikizumab

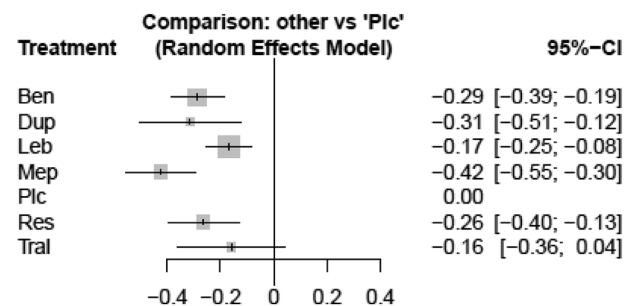


Fig. 3 Forest plot for the analysis of change in ACQ. The size of the square indicates the weight of the effect size as determined by the number of studies and participants. CI confidence interval, Ben benralizumab, Dup dupilumab, Leb lebrikizumab, Mep mepolizumab, Plc placebo, Res reslizumab, Tral tralokinumab. Total number of studies analyzed for benralizumab: 7; for dupilumab: 2; for lebrikizumab: 2; for mepolizumab: 3; for reslizumab: 4; for tralokinumab: 2

[–0.16 (–0.25 to –0.08)] lagged behind. Mepolizumab was also superior to lebrikizumab [inter-treatment difference: –0.25 (–0.41 to –0.10)], and tralokinumab [inter-treatment difference: –0.26 (–0.50 to –0.02)]. There were no other significant inter-treatment differences.

Table 3 Mean difference in ACQ scores across comparisons

	Benralizumab	Dupilumab	Lebrikizumab	Mepolizumab	Placebo	Reslizumab	Tralokinumab
Benralizumab		0.02 (−0.18 to 0.24)	−0.11 (−0.24 to 0.01)	0.13 (−0.02 to 0.29)	−0.28 (−0.38 to −0.18)*	−0.02 (−0.18 to 0.14)	−0.12 (−0.35 to 0.09)
Dupilumab	−0.02 (−0.24 to 0.18)		−0.14 (−0.35 to 0.06)	0.11 (−0.11 to 0.34)	−0.31 (−0.50 to −0.12)*	−0.04 (−0.28 to 0.18)	−0.15 (−0.43 to 0.12)
Lebrikizumab	0.11 (−0.01 to 0.24)	0.14 (−0.06 to 0.35)		0.25 (0.10 to 0.41)*	−0.16 (−0.25 to −0.08)*	0.09 (−0.06 to 0.25)	−0.008 (−0.22 to 0.21)
Mepolizumab	−0.13 (−0.29 to 0.02)	−0.11 (−0.34 to 0.11)	−0.25 (−0.41 to −0.10)*		−0.42 (−0.55 to −0.29)*	−0.16 (−0.34 to 0.02)	−0.26 (−0.50 to −0.02)*
Placebo	0.28 (0.18 to 0.38)*	0.31 (0.12 to 0.50)*	0.16 (0.08 to 0.25)*	0.42 (0.29 to 0.55)*		0.26 (0.13 to 0.39)*	0.15 (−0.04 to 0.36)
Reslizumab	0.02 (−0.14 to 0.18)	0.04 (−0.18 to 0.28)	−0.09 (−0.25 to 0.06)	0.16 (−0.02 to 0.34)	−0.26 (−0.39 to −0.13)*		−0.10 (−0.34 to 0.13)
Tralokinumab	0.12 (−0.09 to 0.35)	0.15 (−0.12 to 0.43)	0.008 (−0.21 to 0.22)	0.26 (0.02 to 0.50)*	−0.15 (−0.36 to 0.04)	0.10 (−0.13 to 0.34)	

Tau²: 0
I²: 0%
Tests of heterogeneity:
Within designs heterogeneity: *p* 0.53

Tau² and I² show low level of heterogeneity across studies

Follow legend of Table 2 to analyze this table

Total number of studies analyzed for benralizumab: 7; for dupilumab: 2; for lebrikizumab: 2; for mepolizumab: 3; for reslizumab: 4; for tralokinumab: 2

*Statistically significant

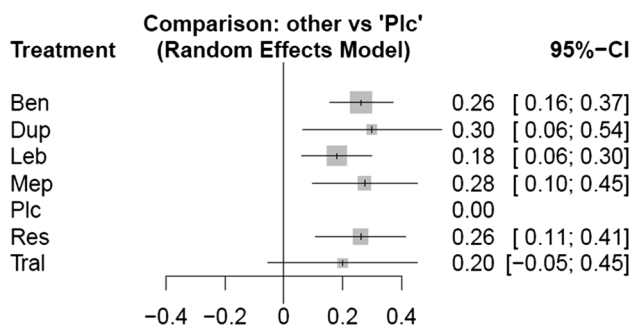


Fig. 4 Forest plot for the analysis of change in AQLQ. The size of the square indicates the weight of the effect size as determined by the number of studies and participants. *CI* confidence interval, *Ben* benralizumab, *Dup* dupilumab, *Leb* lebrikizumab, *Mep* mepolizumab, *Plc* placebo, *Res* reslizumab, *Tral* tralokinumab. Total number of studies analyzed for benralizumab: 6; for dupilumab: 1; for lebrikizumab: 2; for mepolizumab: 2; for reslizumab: 2; for tralokinumab: 1

Effect on AQLQ scores

A total of 14 studies [10, 15–17, 20, 22, 23, 25, 27, 32, 35, 36, 38, 39] with 5317 participants (2679 participants with active treatments and 2638 participants with placebo) were analyzed for change in AQLQ scores. All drugs were superior to placebo except tralokinumab (Fig. 4; Table 4). Dupilumab, mepolizumab, benralizumab, and reslizumab showed the greatest increase in AQLQ scores [0.27

(0.09–0.45), 0.26 (0.15–0.37), 0.26 (0.10–0.41)], whereas, tralokinumab [0.20 (−0.05–0.45)] and lebrikizumab [0.18 (0.06 to 0.30)] lagged behind. There were no significant inter-treatment differences.

Annualized Asthma Exacerbation Rate on Treatment

The annualized rate ratios for asthma exacerbations were analyzable for six benralizumab [15–17, 22–24], four reslizumab [18, 36–38], six mepolizumab [29–32, 34, 35], two dupilumab [25, 26], four lebrikizumab [10, 19, 27, 28], and two tralokinumab studies [39, 40]. While all drugs (during their respective study phases) showed less asthma exacerbations, the calculated annualized rate ratios for asthma exacerbations (compared to placebo) were only significant for dupilumab and reslizumab [rate ratios: 0.37 (0.17–0.80), and 0.64 (0.53–0.78), respectively], as shown in Fig. 5.

Sub-Group Analyses

Sub-group analyses based on biomarkers are reported in Table 5 and their respective forest plots are shown in figures E4–6 (online resource). Eight studies [10, 15–20, 25] met the inclusion criteria for the FEV₁ analyses, seven [10, 15, 17, 18, 20, 25, 27] for the ACQ analyses, and four [10, 20, 25, 27] for the AQLQ analyses. Neither of the included mepolizumab (except Ortega et al. [34]) and tralokinumab

Table 4 Mean difference in AQLQ scores across comparisons

AQLQ	Benralizumab	Dupilumab	Lebrikizumab	Mepolizumab	Placebo	Reslizumab	Tralokinumab
Benralizumab		−0.03 (−0.29 to 0.22)	0.08 (−0.07 to 0.24)	−0.01 (−0.21 to 0.19)	0.26 (0.15 to 0.37)*	0.002 (−0.18 to 0.19)	0.06 (−0.21 to 0.34)
Dupilumab	0.03 (−0.22 to 0.29)		0.11 (−0.14 to 0.38)	0.02 (−0.27 to 0.32)	0.30 (0.06 to 0.53)*	0.03 (−0.24 to 0.31)	0.10 (−0.24 to 0.44)
Lebrikizumab	−0.08 (−0.24 to 0.07)	−0.11 (−0.38 to 0.14)		−0.09 (−0.30 to 0.12)	0.18 (0.06 to 0.30)*	−0.07 (−0.27 to 0.11)	−0.01 (−0.29 to 0.26)
Mepolizumab	0.01 (−0.19 to 0.21)	−0.02 (−0.32 to 0.27)	0.09 (−0.12 to 0.30)		0.27 (0.09 to 0.45)*	0.01 (−0.22 to 0.24)	0.07 (−0.23 to 0.38)
Placebo	−0.26 (−0.37 to −0.15)*	−0.30 (−0.53 to −0.06)*	−0.18 (−0.30 to −0.06)*	−0.27 (−0.45 to −0.09)*		−0.26 (−0.41 to −0.10)*	−0.20 (−0.45 to 0.05)
Reslizumab	0.002 (−0.19 to 0.18)	−0.03 (−0.31 to 0.24)	0.07 (−0.11 to 0.27)	−0.01 (−0.24 to 0.22)	0.26 (0.10 to 0.41)*		0.06 (−0.23 to 0.35)
Tralokinumab	−0.06 (−0.34 to 0.21)	−0.10 (−0.44 to 0.24)	0.01 (−0.26 to 0.29)	−0.07 (−0.38 to 0.23)	0.20 (−0.05 to 0.45)	−0.06 (−0.35 to 0.23)	

Tau²: 0
I²: 0%
Tests of heterogeneity:
Within designs heterogeneity: *p* 0.76

Tau² and I² show low level of heterogeneity across studies

Follow legend of Table 2 to analyze this table

Total number of studies analyzed for benralizumab: 6; for dupilumab: 1; for lebrikizumab: 2; for mepolizumab: 2; for reslizumab: 2; for tralokinumab: 1

*represents statistically significant

studies provided data based on biomarkers. Additionally, the data provided by Ortega et al. was only for pre- and post-intervention.

The results show that for FEV₁, benralizumab, dupilumab, lebrikizumab, and reslizumab, all showed comparatively greater response in the sub-group with elevated biomarkers (biomarker-high) than in those with low biomarkers. While there was no significant inter-treatment difference, in terms of magnitude of response, in the biomarker-high sub-group, dupilumab showed the greatest response, followed by benralizumab, lebrikizumab, and reslizumab. In the biomarker-low sub-group, the order was dupilumab, followed by benralizumab, lebrikizumab, and reslizumab. Similarly, in the ACQ analyses for the sub-groups, the magnitude of response was comparatively greater in the biomarker-high versus the biomarker-low sub-group. There was no significant inter-treatment difference. In the biomarker-high sub-group, benralizumab's magnitude of effect was greater than dupilumab followed by lebrikizumab and in the biomarker-low sub-group, dupilumab's effect was greater than benralizumab followed by lebrikizumab. For the AQLQ analyses, only, dupilumab and lebrikizumab showed greater response in the biomarker-high sub-group compared to the biomarker-low sub-group. Additionally, in both sub-groups, dupilumab had the greatest effect in terms of magnitude of effect compared to benralizumab and lebrikizumab.

Data on asthma exacerbation rates based on this stratification were not analyzable as not many studies reported asthma exacerbation rates using this approach.

Assessment of Publication Bias

The funnel plot for studies evaluating FEV₁ is shown in Fig. E7 (in online resource). Visual inspection of the plot does not show evidence of bias.

Discussion

The results of our overall network meta-analysis suggest that in terms of efficacy, all drugs except tralokinumab significantly improved FEV₁, ACQ, and AQLQ (compared to placebo), with no significant inter-treatment differences, except that mepolizumab was superior to lebrikizumab and tralokinumab in its effects on ACQ scores. All treatments were comparable in terms of magnitude of improvement in FEV₁ (except for tralokinumab) and AQLQ (except for tralokinumab and lebrikizumab). However, in the analysis of ACQ scores, mepolizumab had the greatest effect in terms of magnitude of improvement. Additionally, only dupilumab and reslizumab were associated with significantly less asthma exacerbations on treatment compared to others.

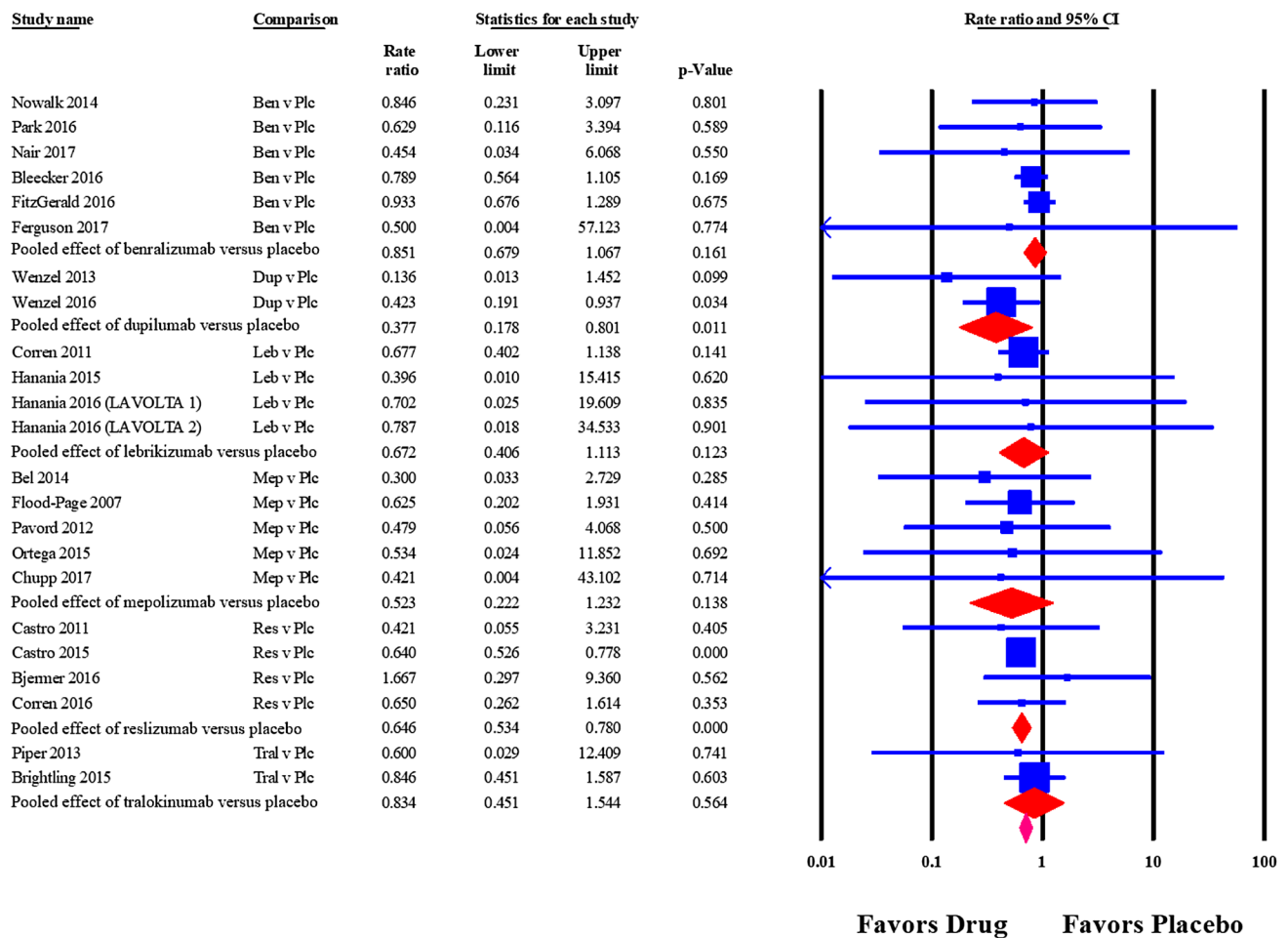


Fig. 5 Forest plot of rate ratio of asthma exacerbations (during treatment) compared to placebo. The size of the square indicates the weight of the effect size as determined by the number of studies and participants. The diamond indicates the pooled overall effect size. *CI*

When analyzed based on the biomarkers, important observations were noted. Based on these sub-group analyses, our network meta-analysis suggests that apparent superiority of drugs over one another is linked to the selection criteria used in individual trials and how eosinophilic asthma was defined. Neither of the mepolizumab or tralokinumab studies were included in the sub-group analyses. Therefore, the results of the sub-group analyses need to be interpreted with caution. As such, results of the sub-group analyses should be considered hypothesis-generating. Table 5 results contrast the effect of the same drugs when analyzed with different levels of biomarkers. In general, the magnitude of response seems comparatively greater in the biomarker-high versus the biomarker-low sub-group. While mepolizumab and tralokinumab were not included (an important selection bias) in the sub-group analyses, dupilumab and benralizumab

confidence interval, *Ben* benralizumab, *Plc* placebo, *Dup* dupilumab, *Leb* lebrikizumab, *Mep* mepolizumab, *Res* reslizumab, *Tral* tralokinumab

seem to be the two drugs exerting the most effect in terms of magnitude of effects on FEV₁, ACQ, and AQLQ.

While we used the ‘biomarker-high versus biomarker-low’ approach to highlight the differences in the sub-group analyses, perhaps it may be possible to discern trends in the outcomes with different levels of each of the different biomarkers (for example, using blood eosinophil count > 150 or > 300 or > 400 cells/μL) using an ‘individual-patient-data’ meta-analysis technique. As to which biomarker should be used for future studies is an evolving discussion. Much debate already exists in the literature as to which biomarker should be used to define ‘eosinophilic asthma’. Sputum and blood eosinophils do not always correlate well. Hastie and colleagues reported an R-value of 0.19 with approximately 40% misclassification [41]. On the other hand, extremes of blood eosinophil counts may be more sensitive and specific for predicting sputum eosinophils [42, 43], however, the

Table 5 Sub-group analyses

	Benralizumab	Dupilumab	Lebrikizumab	Placebo	Reslizumab
FEV ₁ (biomarker high) ^a					
Benralizumab	–	–0.02 (–0.16 to 0.12)	0.01 (–0.04 to 0.08)	0.12 (0.08 to 0.17)*	0.05 (–0.05 to 0.16)
Dupilumab	–0.02 (–0.12 to 0.16)	–	0.04 (–0.10 to 0.18)	0.15 (0.01 to 0.28)*	0.08 (–0.08 to 0.24)
Lebrikizumab	–0.01 (–0.08 to 0.04)	–0.04 (–0.18 to 0.10)	–	0.10 (0.05 to 0.15)*	0.03 (–0.07 to 0.14)
Placebo	–0.12 (–0.17 to –0.08)*	–0.15 (–0.28 to –0.01)*	–0.10 (–0.15 to –0.05)*	–	–0.07 (–0.16 to 0.02)
Reslizumab	–0.05 (–0.16 to 0.05)	–0.08 (–0.24 to 0.08)	–0.03 (–0.14 to 0.07)	0.07 (–0.02 to 0.16)	–
FEV ₁ (biomarker low) ^b					
Benralizumab	–	–0.05 (–0.15 to 0.05)	–0.02 (–0.10 to 0.05)	0.04 (0.00 to 0.09)*	0.01 (–0.08 to 0.12)
Dupilumab	0.05 (–0.05 to 0.15)	–	0.02 (–0.09 to 0.14)	0.10 (0.00 to 0.19)*	0.07 (–0.06 to 0.20)
Lebrikizumab	0.02 (–0.05 to 0.10)	–0.02 (–0.14 to 0.09)	–	0.07 (0.00 to 0.13)*	0.04 (–0.07 to 0.16)
Placebo	–0.04 (–0.09 to –0.004)*	–0.10 (–0.19 to –0.002)*	–0.07 (–0.13 to –0.006)*	–	–0.03 (–0.12 to 0.06)
Reslizumab	–0.01 (–0.12 to 0.08)	–0.07 (–0.20 to 0.06)	–0.04 (–0.16 to 0.07)	0.03 (–0.06 to 0.12)	–
ACQ (biomarker high) ^c					
Benralizumab	–	–0.09 (–0.34 to 0.15)	–0.15 (–0.34 to 0.02)	–0.29 (–0.42 to –0.16)*	–0.17 (–0.42 to 0.07)
Dupilumab	0.09 (–0.15 to 0.34)	–	–0.06 (–0.31 to 0.18)	–0.20 (–0.41 to 0.01)	–0.08 (–0.38 to 0.22)
Lebrikizumab	0.15 (–0.02 to 0.34)	0.06 (–0.18 to 0.31)	–	–0.13 (–0.26 to –0.006)*	–0.01 (–0.26 to 0.23)
Placebo	0.29 (0.16 to 0.42)*	0.20 (–0.01 to 0.41)	0.13 (0.006 to 0.26)*	–	0.12 (–0.09 to 0.33)
Reslizumab	0.17 (–0.07 to 0.42)	0.08 (–0.22 to 0.38)	0.01 (–0.23 to 0.26)	–0.12 (–0.33 to 0.09)	–
ACQ (biomarker low) ^d					
Benralizumab	–	0.06 (–0.25 to 0.37)	–0.14 (–0.37 to 0.09)	–0.15 (–0.29 to –0.002)*	–0.03 (–0.29 to 0.23)
Dupilumab	–0.06 (–0.37 to 0.25)	–	–0.20 (–0.53 to 0.12)	–0.21 (–0.48 to 0.06)	–0.09 (–0.43 to 0.25)
Lebrikizumab	0.14 (–0.09 to 0.37)	0.20 (–0.12 to 0.53)	–	–0.008 (–0.19 to 0.17)	0.11 (–0.17 to 0.39)
Placebo	0.15 (0.00 to 0.29)*	0.21 (–0.06 to 0.48)	0.008 (–0.17 to 0.19)	–	0.12 (–0.09 to 0.33)
Reslizumab	0.03 (–0.23 to 0.29)	0.09 (–0.25 to 0.43)	–0.11 (–0.39 to 0.17)	–0.12 (–0.33 to 0.09)	–
AQLQ (biomarker high) ^e					
Benralizumab	–	–0.15 (–0.55 to 0.25)	–0.04 (–0.39 to 0.31)	0.15 (–0.18 to 0.48)	
Dupilumab	0.15 (–0.25 to 0.55)	–	0.11 (–0.15 to 0.37)	0.30 (0.06 to 0.53)*	
Lebrikizumab	0.04 (–0.31 to 0.39)	–0.11 (–0.37 to 0.15)	–	0.19 (0.06 to 0.31)*	
Placebo	–0.15 (–0.48 to 0.18)	–0.30 (–0.53 to –0.06)*	–0.19 (–0.31 to –0.06)*	–	
AQLQ (biomarker low) ^f					
Benralizumab	–	–0.01 (–0.43 to 0.41)	0.13 (–0.23 to 0.50)	0.18 (–0.13 to 0.49)	
Dupilumab	0.01 (–0.41 to 0.43)	–	0.14 (–0.20 to 0.49)	0.19 (–0.10 to 0.48)	
Lebrikizumab	–0.13 (–0.50 to 0.23)	–0.14 (–0.49 to 0.20)	–	0.04 (–0.14 to 0.23)	
Placebo	–0.18 (–0.49 to 0.13)	–0.19 (–0.48 to 0.10)	–0.04 (–0.23 to 0.14)	–	

I² show low level of heterogeneity across studies. Follow legend of Table 2 to analyze this table

^aI²: 0%. Within design heterogeneity: $p=0.43$. Total number of studies analyzed for benralizumab: 4; for dupilumab: 1; for lebrikizumab: 2; for reslizumab: 1

^bI²: 0%. Within design heterogeneity: $p=0.50$. Total number of studies analyzed for benralizumab: 4; for dupilumab: 1; for lebrikizumab: 2; for reslizumab: 1

^cI²: 0%. Within design heterogeneity: $p=0.73$. Total number of studies analyzed for benralizumab: 3; for dupilumab: 1; for lebrikizumab: 2; for reslizumab: 1

^dI²: 0%. Within design heterogeneity: $p=0.97$. Total number of studies analyzed for benralizumab: 3; for dupilumab: 1; for lebrikizumab: 2; for reslizumab: 1

^eI²: 0%. Within design heterogeneity: $p=0.34$. Total number of studies analyzed for benralizumab: 1; for dupilumab: 1; for lebrikizumab: 1

^fI²: 0%. Within design heterogeneity: $p=0.72$. Total number of studies analyzed for benralizumab: 1; for dupilumab: 1; for lebrikizumab: 1

*Statistically significant

former is not a true point-of-care test as the values may fluctuate from time to time [44, 45]. With several different studies using different biomarkers, this network meta-analysis highlights the difficulty in comparing drugs.

In this network meta-analysis, we only analyzed studies for FEV₁, ACQ, AQLQ, and exacerbations rates to compare their relative efficacies. However, several other efficacy endpoints have been analyzed in studies, including reduction in the need for long-term steroids, or reduction in blood eosinophil counts. Because the latter efficacy endpoints were not uniformly reported in all studies, we were limited in analyzing the ones reported in this network-meta-analysis. Based on the overall network meta-analysis results, while all drugs more or less improved FEV₁, ACQ, and AQLQ with variable effects when analyzed based on the sub-groups, it is note-worthy that with regards to exacerbation rates, only two drugs (reslizumab and dupilumab) showed superiority over other drugs. Since all drugs are expected to improve lung function, as shown in this network meta-analysis, should ranking of drugs be based on other clinically meaningful outcomes, such as reduction in asthma exacerbations and reduction in the need for long-term oral corticosteroids? This is a question that future trialists ought to consider when designing studies on newer drugs.

Based on the results of this network meta-analysis, besides other drugs (especially, benralizumab, mepolizumab, reslizumab and lebrikizumab), dupilumab remains a drug of interest, primarily in terms of the magnitude of its effect on FEV₁, ACQ, and AQLQ scores as well as on asthma exacerbations. Perhaps the reason why dupilumab stands out is because it is a dual receptor blocker for both IL-4 and IL-13 as opposed to other drugs that selectively block IL-4, IL-5, or IL-13 pathways. Besides the ones analyzed in this network meta-analysis, several other trials of dupilumab in asthma are currently ongoing—NCT02134028, NCT02573233, and NCT02948959. Results of NCT02414854 trial (Liberty Asthma Quest) and NCT02528214 (Venture trial) are not published yet but based the manufacturer's press releases the dupilumab showed significant reduction in asthma exacerbations. Results of this network-meta-analysis will have to be updated when results of these trials are published, as the apparent superiority of dupilumab from our analysis is based on only two dupilumab studies [25, 26] included.

In terms of comparison in this network meta-analysis, mepolizumab as a drug is at a disadvantage, primarily because the drug was not included in the sub-group analyses. Even otherwise, controversy exists over the apparent superiority of the newer drugs (such as benralizumab) over mepolizumab. This is in part because the earlier trials [31, 46, 47] of mepolizumab used an 'all-comers' approach irrespective of the underlying endotype, whereas trials on the newer drugs mostly did specify the endotype (as shown in

our sub-group analyses). However, as one can discern from the results of the overall network meta-analysis, the effects of mepolizumab are not so dissimilar (in terms of magnitude of effects on outcomes) when compared to either of the two sub-groups (biomarker-high and biomarker-low). Perhaps future trials on mepolizumab could compare the drug with other drugs by classifying based on biomarkers.

Although further studies on lebrikizumab have been terminated after variable results were seen from two phase 3 RCTs [10], the future of tralokinumab is also uncertain after the recent STRATOS-2 (NCT02194699) and TROPOS (NCT02281357) trials (unpublished) based on recent press releases did not reach the primary endpoint of statistically significant reduction in annual asthma exacerbation rates.

Aside from the above-mentioned limitations of our network meta-analysis, we were also limited with the drugs analyzed in this study and were not able to include certain other biologics that have been tested in asthma patients, such as pitakinra, tezepelumab, and drugs targeting IL-25 and IL-33. Additionally, several other secondary outcomes in studies, such as reduction in airway or blood eosinophil counts, periostin etc., were also not analyzed. Another limitation of this network meta-analysis is that we focused on eosinophilic asthma and the biologics targeting the Th-2 cytokines. Emerging evidence [48] suggests mixed cellular phenotypes and possible, although controversial role for combination therapies. Choy et al. [49] in an endobronchial tissue gene expression analysis revealed three major patient clusters- Th2-high, Th17-high, and Th2/17-low, along with compelling evidence of a reciprocal regulation between Th2 and Th17 pathways in asthma patients. More importantly, the study showed presence of tissue eosinophils in many of the patients classified as Th17-high and measures of neutrophilic inflammation were found not to be significantly different between the three groups.

In conclusion, in patients with steroids-refractory eosinophilic asthma, several novel monoclonal antibodies or small molecule therapies exist. All drugs except for tralokinumab showed improvements in FEV₁, ACQ, and AQLQ. Only reslizumab and dupilumab were associated with statistically significant reductions in asthma exacerbation rates.

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, MS, WB, and CS contributed to assessment of study quality. All authors contributed substantially to the interpretation of analyses and in revisions of manuscript.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflicts of interest.

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ONLINE RESOURCE (DATA SUPPLEMENT)

Title: Comparative Efficacy of Anti IL-4, IL-5 and IL-13 Drugs for Treatment of Eosinophilic Asthma: A Network Meta-analysis

Authors: Imran H. Iftikhar¹, Mathew Schimmel¹, William Bender¹, Colin Swenson¹, David Amrol²

Authors' affiliations:

¹Division of Pulmonary, Allergy, Critical Care & Sleep Medicine, Emory University School of Medicine; ²Division of Allergy and Immunology, University of South Carolina School of Medicine.

Corresponding author:

Imran Iftikhar, MD, FACP, FCCP

613 Michael St, NE, Division of Pulmonary, Allergy, Critical Care & Sleep Medicine, Emory University School of Medicine, Atlanta, GA

T: 803-873-3193; email: imran.hasan.iftikhar@emory.edu

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, MS, WB, and CS contributed to assessment of study quality. All authors contributed substantially to the interpretation of analyses and in revisions of manuscript.

Additional details of methods:

We searched PubMed from inception to December 15th, 2017 (figure 1). The search was not restricted per publication status or date. We also hand-searched reference lists for all retrieved studies. We did not search conference proceedings.

Study Selection

For inclusion in our meta-analysis, we considered only English language RCTs of patients with asthma treated with benralizumab, dupilumab, lebrikizumab, mepolizumab, reslizumab and tralokinumab. For inclusion in the network meta-analysis, studies had to report data on change in forced expiratory volume-in 1 second (FEV₁), asthma control questionnaire (ACQ), and asthma quality of life questionnaire (AQLQ). Additionally, studies had to report either pre- and post-intervention data for outcomes of interest, or data on the difference in outcomes between the intervention and control arms. Studies were excluded if they reported data in median and interquartile range. This was decided a priori, as the available methods for estimating means and standard deviations from median and interquartile range are based on the ‘normal distribution assumption’ that may not hold if data are skewed [E1]. One author (IHI) screened titles and abstracts identified by the searches. Full manuscripts were obtained for studies considered potentially relevant in the initial search. Disagreements were resolved by consensus. Such disagreement arose only for inclusion of one study [E2], which by mutual discussion was excluded.

Data Extraction and Quality Assessment

One author (IHI) extracted the data. Data extracted from studies included first author’s name, publication year, study design, population characteristics, treatments, length of follow up and change in FEV₁, ACQ scores, AQLQ scores and number of asthma exacerbations on

treatment. The studies were divided between 4 authors (IHI, MS, WB, and CS) for scoring study quality based on modified Cochrane methods [E3] reported in Table E2. One reviewer (IHI) independently evaluated the scoring for all studies to ensure consistency.

Data were directly extracted on the working sheets of Comprehensive Meta-Analysis (CMA version 2.2.064; Biostat, Englewood, N.J. U.S.A) software. For studies in which data were reported for different doses of treatments or reported separately for eosinophilic and non-eosinophilic asthma population, we used the data for the highest dose, for longest follow up period available and preferably for eosinophilic asthma patients (if combined data for eosinophilic and non-eosinophilic asthma patients were not available). For studies [E4-8] where different dosing frequency of drugs or routes was studied, we have specified in table 1 which specific dosing frequency/regimen was included in our analyses.

Data Synthesis and Analysis

The format for reporting results for IRLS scores differed in different studies. Three different formats were used: (1) data reported as pre- and post- intervention means and SDs, (2) mean difference (between pre- and post- intervention) with standard deviation (SD), separately for active intervention and control or active comparator, and (3) overall mean difference (between active intervention and control or active comparator) with 95% confidence intervals (CI).

We used the CMA software to generate effect size data in a common format, in specific as treatment effect (TE) with standard error (se). Network meta-analysis using '*frequentist*' methods was then performed in R program version 3.2.2 (R Development Core Team, 2010), using package 'netmeta' [E9] This methodology has been previously described [E10,11]. Data entry for this function requires entry in contrast-based format, that is, difference between two

treatments (TE) with standard error (seTE). All pairwise comparisons are provided for a given study with multiple arms (such as those studying 2 different drugs and a placebo). A random effects model is added to the observed sampling variance seTE^2 of each comparison in the network (after appropriate adjustment for multi-arm studies). The procedure is repeated with the resulting enlarged standard errors. The function 'netmeta' accounts for within-study correlation by reweighting all comparisons of each multi-arm study. After this step, we created a network graph using STATA-13 using package 'mvmeta'. Network graph is a geometrical graph of the evidence/treatment network. The network was laid out in the plane, where the nodes in the graph layout corresponded to the treatments and edges displaying the observed treatment comparisons. For the default setting, nodes were placed on a circle. Evidence from direct treatment comparisons was considered to determine the line width [E12,13]. The model used for this approach was the non-differential combined placebo network model, which assumed that all placebos or control had the same effect, hence combined into a single group/circle [E12]. Forest plots, also called confidence interval plots, were drawn out in the active graphics window in R [E13]. The between-design heterogeneity was calculated by 'method of moments' and provided as ' Tau^2 '. Net Heat plots to check for 'inconsistency' in the network meta-analysis were considered. However, the since the heterogeneity detected by Tau^2 between the studies was low, 'netmeta' function in R did not construct any Net Heat plots for any of the analyses.

We calculated event rates for asthma exacerbations reported in each study. By calculating 'person-years' for each study (separately for treatment and placebo arms), we computed rate ratios and the overall pooled rate ratios for each drug separately.

Finally, for publication bias assessment, as no single analysis was representative of the total number of studies included in this network meta-analysis, funnel plot was constructed for studies reporting FEV₁.

We also analyzed sub-groups based on biomarkers ('biomarker-high' versus 'biomarker-low'), an approach similar to that used by Hanania et al [E14]. Data stratified based on biomarkers was available only in a few studies. The cut-off for biomarkers used in these studies (to differentiate eosinophilic from non-eosinophilic) was either blood eosinophil count $\geq$ or $<$ 300 cells/ μ L [E4,5,15] or $\geq$ or $<$ 400 cells/ μ L [E16], or serum periostin $\geq$ or $<$ 50 ng/mL [E14,17] or the eosinophil/lymphocyte and eosinophil/neutrophil (ELEN) index (positive or negative) [E18].

Throughout the process, we adhered to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-analyses) guidelines [E19] for all stages of the design, implementation, and reporting of this meta-analysis. (checklist and study quality assessment reported in online resource e-tables 1 and 2, respectively).

Additional details on study selection process:

As shown in figure 1, several studies were excluded from this network meta-analysis. In the search for benralizumab studies in PubMed, one study [E20] was excluded as the primary outcome was change in eosinophil counts with no data on other outcomes of our interest and another [E2] was excluded as it was a sub-group analysis of an included major trial [E5]. One study [E21] on lebrikizumab was excluded as the primary outcome was change in lung functions after an allergen response. Several studies [E22-25] reporting post-hoc analyses of some mepolizumab studies included in the network meta-analysis were excluded. One reslizumab

study [E26] was also excluded as this was a non-randomized open-label extension study which did not meet the inclusion criteria of this network meta-analysis.

Table E1: PRISMA checklist

Section/topic	Checklist Item	Reported (Y/N)
TITLE		
Title	Identify the report as a systematic review <i>incorporating a network meta-analysis (or related form of meta-analysis)</i> .	Y
ABSTRACT Structured summary	Provide a structured summary including, as applicable: Background: main objectives Methods: data sources; study eligibility criteria, participants, and interventions; study appraisal; and <i>synthesis methods, such as network meta-analysis</i> . Results: number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; <i>treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.</i> Discussion/Conclusions: limitations; conclusions and implications of findings. Other: primary source of funding; systematic review registration number with registry name.	Y
INTRODUCTION		
Rationale	Describe the rationale for the review in the context of what is already known, <i>including mention of why a network meta-analysis has been conducted</i> .	Y
Objectives	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Y
METHODS		
Protocol and registration	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	Y http://joannabriggs.org/research/registered_titles.aspx
Eligibility criteria	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. <i>Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).</i>	Y
Information sources	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Y
Search	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Y (table E3)
Study selection	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Y
Data collection process	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Y
Data items	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Y
Geometry of the network	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	Y
Risk of bias within individual studies	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Y
Summary measures	State the principal summary measures (e.g., risk ratio, difference in means). <i>Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.</i>	Y
Planned methods of analysis	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: <i>Handling of multigroup trials; Selection of variance structure;</i>	Y

	<i>Selection of prior distributions in Bayesian analyses; and Assessment of model fit.</i>	
Assessment of inconsistency	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	N/A
Risk of bias across studies	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Y
Additional analyses	Describe methods of additional analyses if done, indicating which were prespecified. This may include, but not be limited to, the following: Sensitivity or subgroup analyses; Meta-regression analyses; <i>Alternative formulations of the treatment network; and Use of alternative prior distributions for Bayesian analyses (if applicable).</i>	Y
RESULTS		
Study selection	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Y
Presentation of network structure	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	Y
Summary of network geometry	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	Y
Study characteristics	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Y
Risk of bias within studies	Present data on risk of bias of each study and, if available, any outcome level assessment.	Y
Results of individual studies	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. <i>Modified approaches may be needed to deal with information from larger networks.</i>	Y
Synthesis of results	Present results of each meta-analysis done, including confidence/credible intervals. <i>In larger networks, authors may focus on comparisons versus a particular comparator (e.g., placebo or standard care), with full findings presented in an appendix. League tables and forest plots maybe considered to summarize pairwise comparisons.</i> If additional summary measures were explored (such as treatment rankings), these should also be presented.	Y
Exploration for inconsistency	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, <i>P</i> values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	Y
Risk of bias across studies	Present results of any assessment of risk of bias across studies for the evidence base being studied.	Y
Results of additional analyses	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, <i>alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses, and so forth).</i>	Y
DISCUSSION		
Summary of evidence	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, researchers, and policymakers).	Y
Limitations	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). <i>Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).</i>	Y
Conclusions	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Y
FUNDING		
Funding	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	Y

Y indicates 'yes', we reported; N indicates, 'no, we did not report; N/A indicates not applicable to this paper.

Table E2: Assessment of study quality

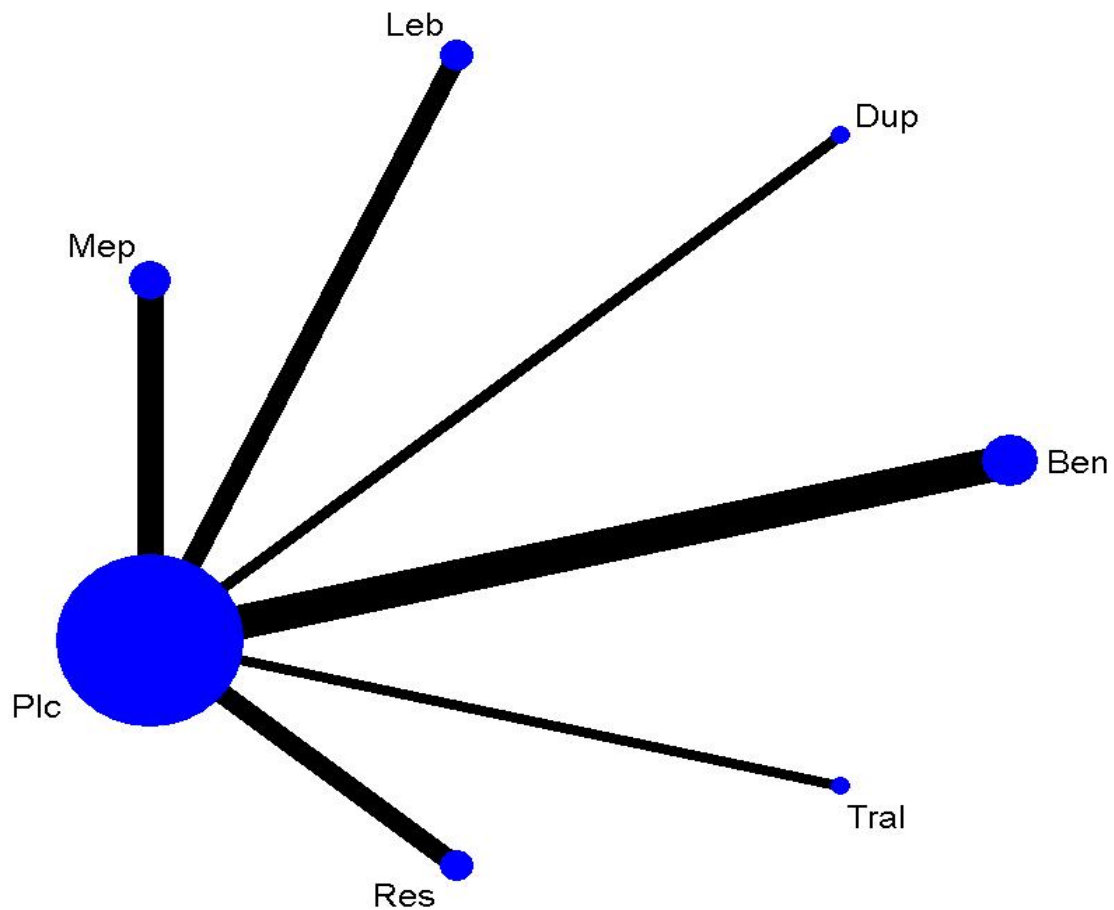
Study ID (First author – year published)	Random sequence generation	Allocation concealment	Blinding of outcomes assessment	Incomplete outcome data	Selective reporting
Benralizumab					
Castro 2014 [E18]	L	L	L	L	L
Bleecker 2016 [E4]	L	L	L	L	L
Fitzgerald 2016 [E5]	L	L	L	L	L
Nair 2017 [E27]	L	L	L	U	U
Park 2016 [E28]	L	L	L	U	U
Ferguson 2017 [E15]	L	L	L	U	U
Nowak 2015 [E29]	L	L	L	L	L
Dupilumab					
Wenzel 2013 [E30]	L	L	L	U	U
Wenzel 2016 [E6]	L	L	L	U	U
Lebrikizumab					
Corren 2011 [E17]	L	L	L	L	L
Noonan 2013 [E31]	L	L	L	U	U
Hanania 2015 [E32]	L	L	L	U	U
Hanania 2016 [E14]	L	L	L	U	U
Mepolizumab					
Flood-Page 2007 [E33]	L	L	L	L	L
Haldar 2009 [E34]	L	L	L	L	L
Nair 2009 [E35]	L	L	L	L	L
Pavord 2012 [E36]	L	L	L	L	L
Ortega 2014 [E7]	L	L	L	L	L
Chupp 2017 [E37]	L	L	L	L	L
Reslizumab					
Bjermer 2016 [E38]	L	L	L	L	L
Castro 2011 [E39]	L	L	L	L	L
Castro 2015 [E40]	L	L	L	L	L
Corren 2016 [E16]	L	L	L	L	L
Tralokinumab					
Piper 2013 [E41]	L	L	L	U	U
Brightling 2015 [E8]	L	L	L	U	U

Y indicates ‘yes’ reported; N indicates ‘not’ reported

Table E3: MeSH and key words used for search in PubMed

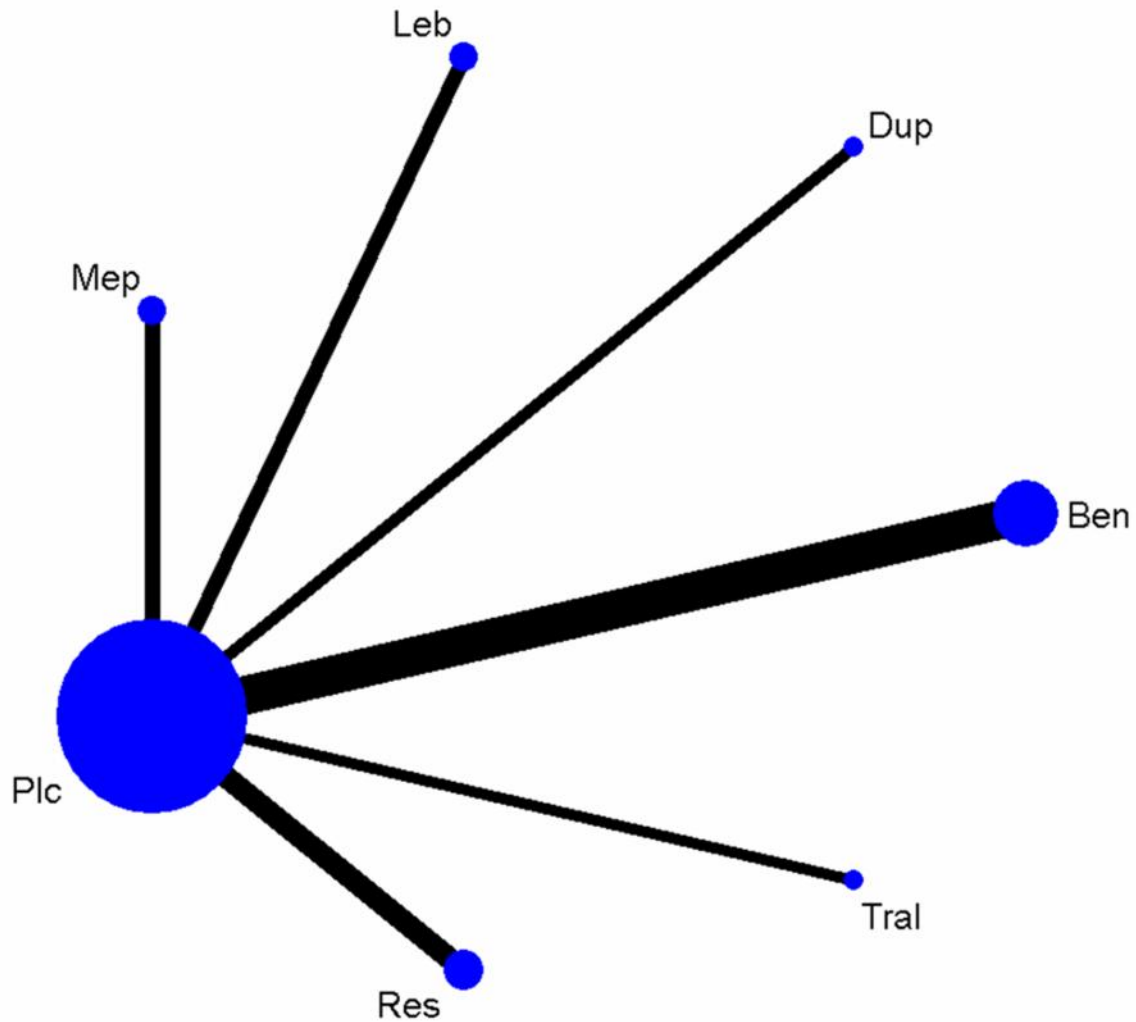
Benralizumab	‘benralizumab’ AND ‘Asthma’
Dupilumab	‘dupilumab’ AND ‘Asthma’
Lebrikizumab	lebrikizumab’ AND ‘Asthma’
Mepolizumab	‘mepolizumab’ AND ‘Asthma’
Reslizumab	‘reslizumab’ AND ‘Asthma’
Tralokinumab	‘tralokinumab’ AND ‘Asthma’

Figure E1: Network evidence plot/geometry of the treatment network of studies for the analysis of FEV₁.



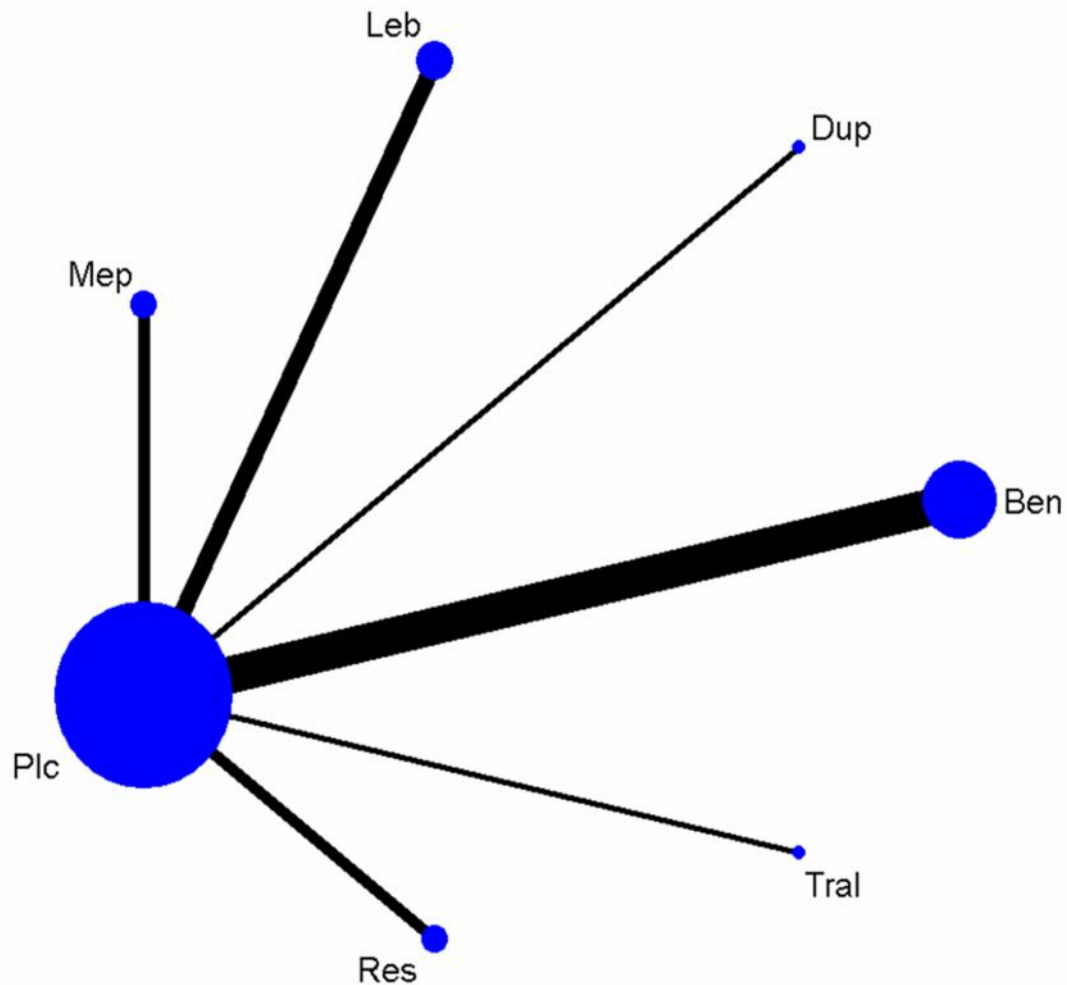
Circle size reflects number of participants and line width reflects number of direct comparisons, no connecting line between two circles indicates that there was no direct comparison between two treatments. 'Ben', benralizumab; 'Dup', dupilumab; 'Leb', lebrikizumab; 'Mep', mepolizumab; 'Plc', placebo; 'Res', reslizumab; 'Tral', tralokinumab.

Figure E2: Network evidence plot/geometry of the treatment network of studies for the analysis of ACQ.



Circle size reflects number of participants and line width reflects number of direct comparisons, no connecting line between two circles indicates that there was no direct comparison between two treatments. 'Ben', benralizumab; 'Dup', dupilumab; 'Leb', lebrikizumab; 'Mep', mepolizumab; 'Plc', placebo; 'Res', reslizumab; 'Tral', tralokinumab.

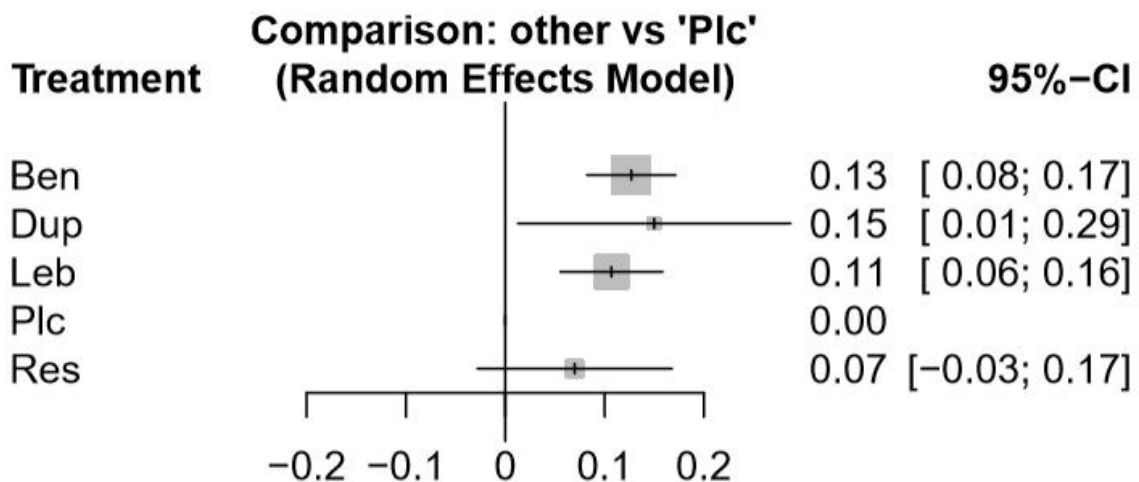
Figure E3: Network evidence plot/geometry of the treatment network of studies for the analysis of AQLQ.



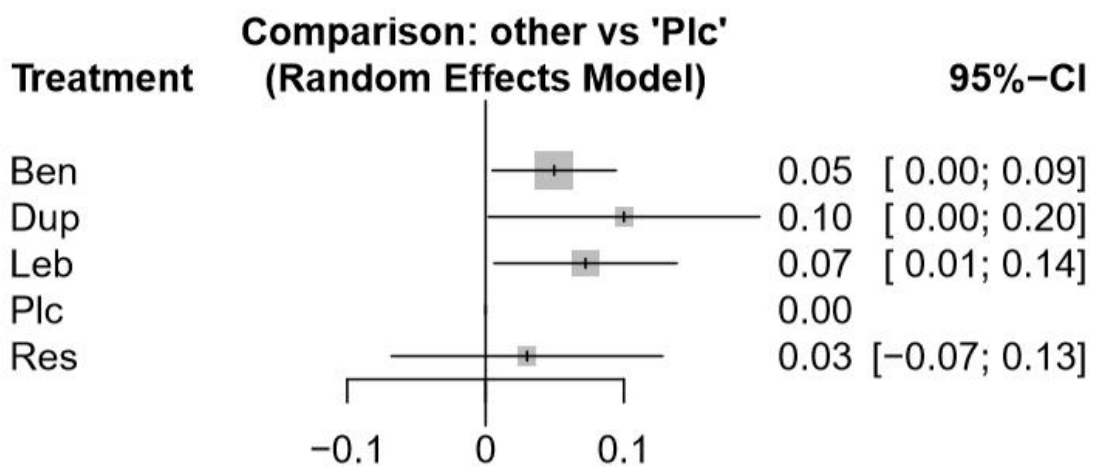
Circle size reflects number of participants and line width reflects number of direct comparisons, no connecting line between two circles indicates that there was no direct comparison between two treatments. 'Ben', benralizumab; 'Dup', dupilumab; 'Leb', lebrikizumab; 'Mep', mepolizumab; 'Plc', placebo; 'Res', reslizumab; 'Tral', tralokinumab.

Figure E4: FEV1 subgroup analyses

Biomarker-high sub-group:



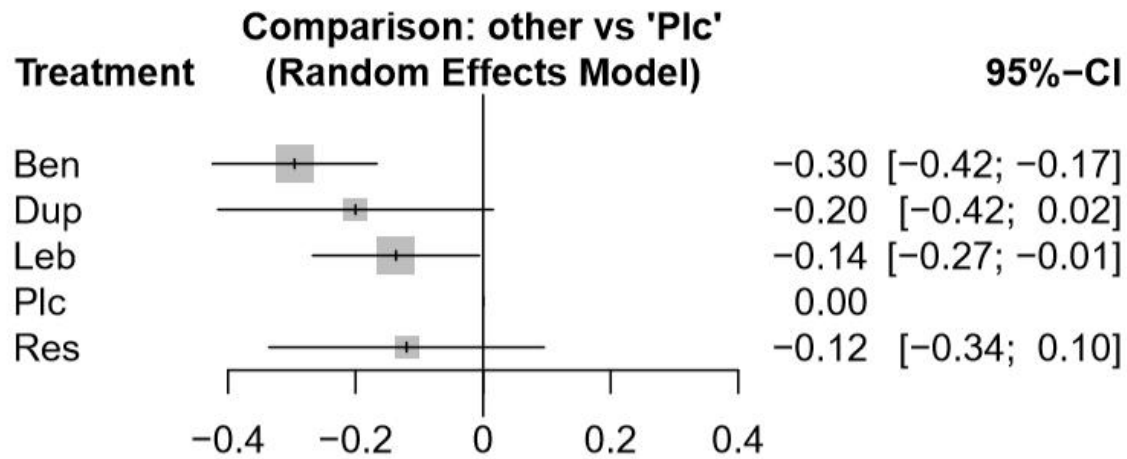
Biomarker-low sub-group:



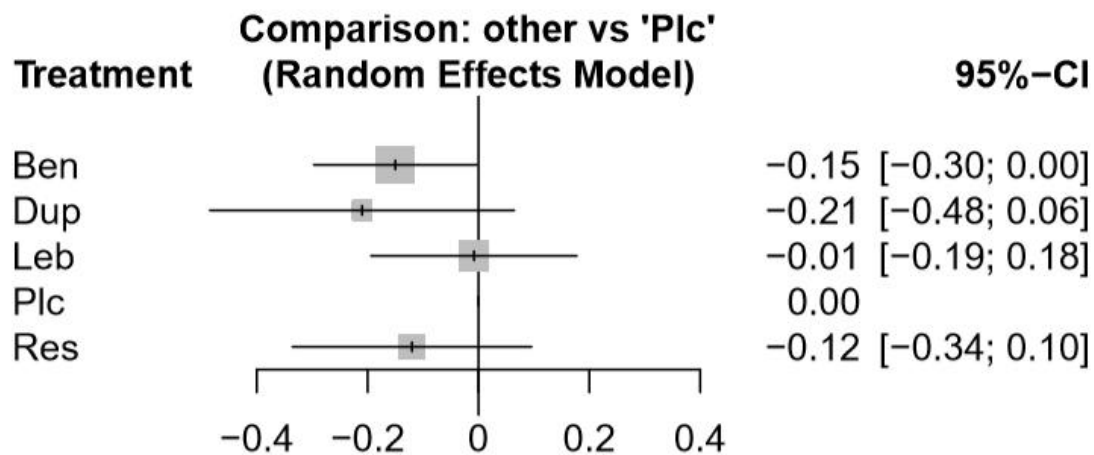
The size of the square indicates the weight of the effect size as determined by the number of studies and participants. CI, confidence interval; 'Ben', benralizumab; 'Dup', dupilumab; 'Leb', lebrikizumab; 'Plc', placebo; 'Res', reslizumab. Total number of studies analyzed for benralizumab: 4; for dupilumab: 1; for lebrikizumab: 2; for reslizumab: 1

Figure E5: ACQ subgroup analyses

Biomarker-high sub-group:



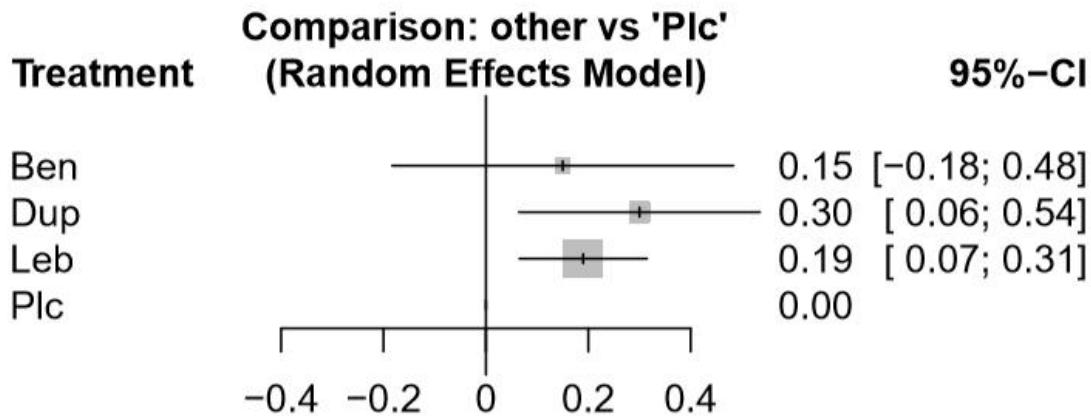
Biomarker-low sub-group:



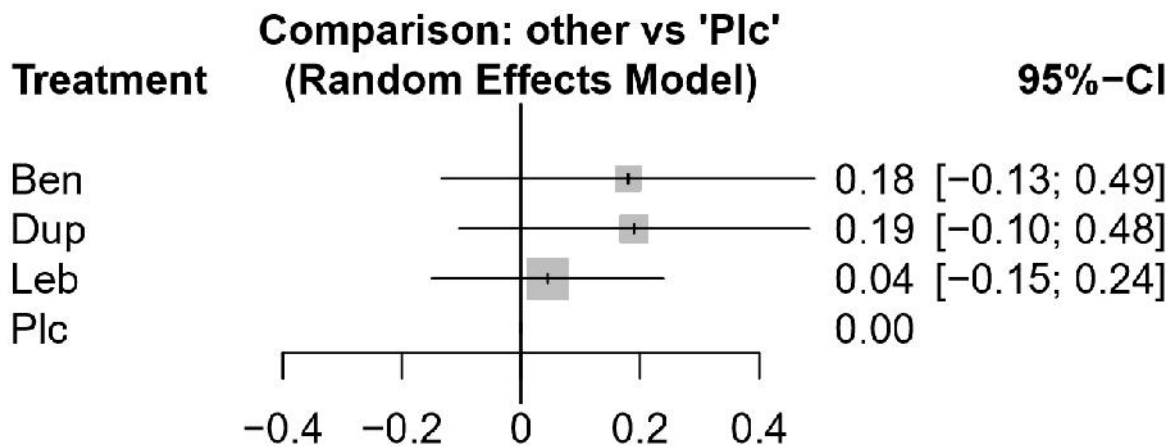
The size of the square indicates the weight of the effect size as determined by the number of studies and participants. CI, confidence interval; 'Ben', benralizumab; 'Dup', dupilumab; 'Leb', lebrikizumab; 'Plc', placebo; 'Res', reslizumab. Total number of studies analyzed for benralizumab: 3; for dupilumab: 1; for lebrikizumab: 2; for reslizumab: 1

Figure E6: AQLQ subgroup analyses

Biomarker-high sub-group:



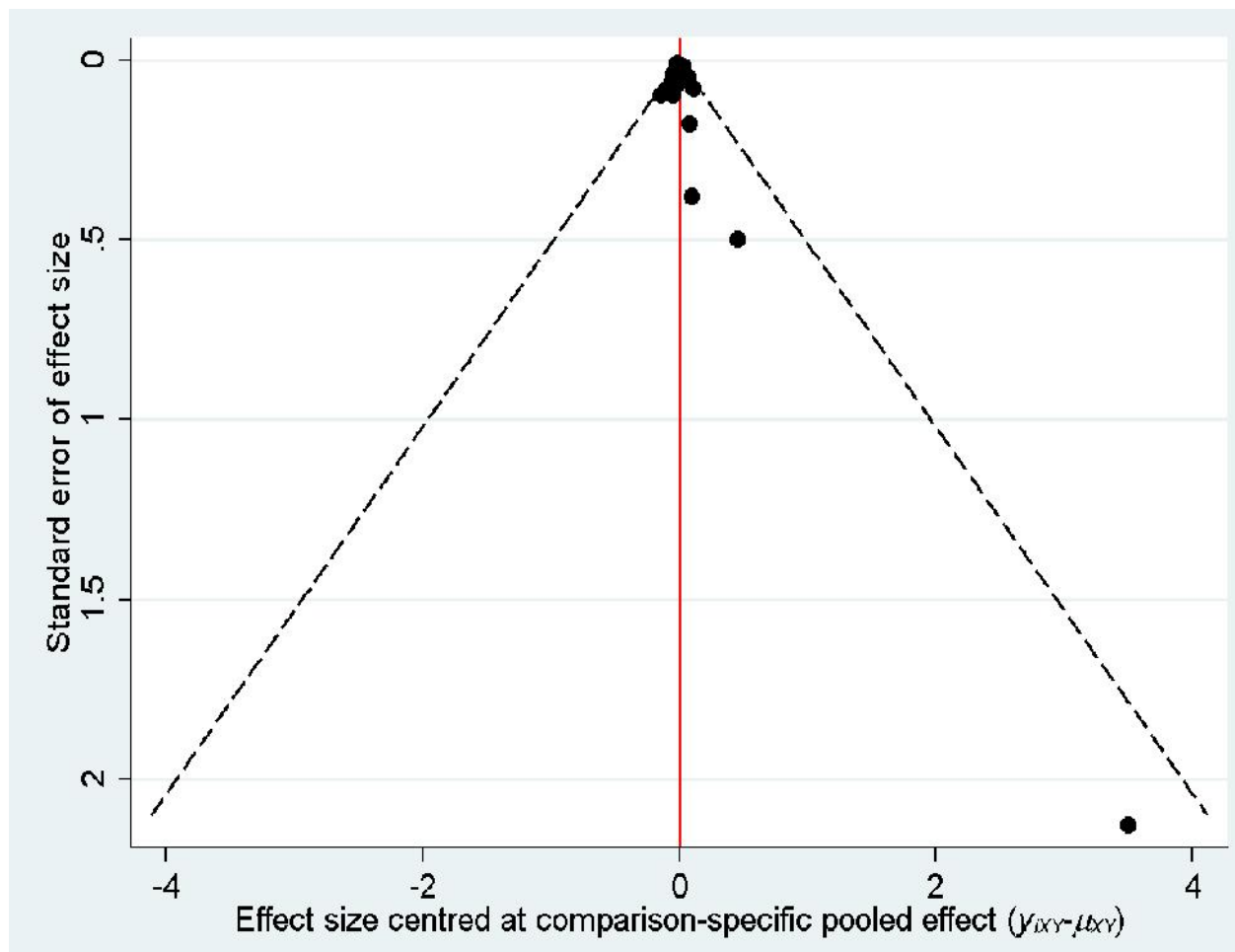
Biomarker-low sub-group:



The size of the square indicates the weight of the effect size as determined by the number of studies and participants.

CI, confidence interval; 'Ben', benralizumab; 'Dup', dupilumab; 'Leb', lebrikizumab; 'Plc', placebo. Total number of studies analyzed for benralizumab: 1; for dupilumab: 1; for lebrikizumab: 1

Figure E7: Publication bias assessment



E-REFERENCES:

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