Adv Ther (2023) 40:2944–2964
https://doi.org/10.1007/s12325-023-02514-0

REVIEW

Efficacy of Biologics in Severe, Uncontrolled Asthma Stratified by Blood Eosinophil Count: A Systematic Review

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Received: February 6, 2023 / Accepted: April 3, 2023 / Published online: May 26, 2023

ABSTRACT

Introduction: Randomized controlled trials (RCTs) of biologics in patients with severe, uncontrolled asthma have shown differential results by baseline blood eosinophil count (BEC). In the absence of head-to-head trials, we describe the effects of biologics on annualized asthma exacerbation rate (AAER) by baseline BEC in placebo-controlled RCTs. Exacerbations associated with hospitalization or an emergency room visit, pre-bronchodilator forced expiratory volume in 1 s, Asthma Control Questionnaire score, and Asthma Quality of Life Questionnaire score were also summarized.

Methods: MEDLINE (via PubMed) was searched for RCTs of biologics in patients with severe, uncontrolled asthma and with AAER reduction as a primary or secondary endpoint. AAER ratios and change from baseline in other outcomes versus placebo were compared across baseline BEC subgroups. Analysis was limited to US Food and Drug Administration-approved biologics.

Results: In patients with baseline BEC ≥ 300 cells/μL, AAER reduction was demonstrated with all biologics, and other outcomes were generally improved. In patients with BEC 0 to < 300 cells/μL, consistent AAER reduction was demonstrated only with tezepelumab; improvements in other outcomes were inconsistent across biologics. In patients with BEC 150 to < 300 cells/μL, consistent AAER reduction was demonstrated with tezepelumab and dupilumab (300 mg dose only), and in those with BEC 0 to < 150 cells/μL, AAER reduction was demonstrated only with tezepelumab.

Conclusion: The efficacy of all biologics in reducing AAER in patients with severe asthma increases with higher baseline BEC, with varying profiles across individual biologics likely due to differing mechanisms of action.

Keywords: Biologic; Blood eosinophil; Efficacy; Exacerbations; Randomized placebo-controlled trial; Severe asthma; Systematic review

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12325-023-02514-0.

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Key Summary Points

Randomized controlled trials (RCTs) of biologics in patients with severe asthma have demonstrated that efficacy varies according to blood eosinophil count (BEC), with increased efficacy demonstrated in patients with high baseline BECs and reduced or no efficacy demonstrated in those with low baseline BECs.

In the absence of head-to-head trials, a systematic literature review was conducted to describe the effects of biologics on the annualized asthma exacerbation rate (AAER) by baseline BEC in placebo-controlled RCTs.

The efficacy of biologics in reducing AAER in patients with severe asthma increases with higher baseline BEC; efficacy profiles varied between individual biologics, likely due to differing mechanisms of action.

These results may help clinicians to compare efficacy data across biologics for severe asthma.

INTRODUCTION

Severe asthma that remains uncontrolled despite maximal use of controller medications and treatment of modifiable risk factors poses a significant health and economic burden to patients and society [1]. Controller medications for severe asthma recommended by the Global Initiative for Asthma (GINA) strategy document are high-dose inhaled corticosteroids (ICS), for which the daily dosage varies according to patient age, plus a long-acting β_2 agonist [2]. A long-acting muscarinic antagonist may also be prescribed in patients over 12 years of age as an additional inhaled controller [2]. Some patients with severe, uncontrolled asthma may be prescribed maintenance oral corticosteroids (OCS); however, these are associated with side effects such as hypertension, bone fractures, and diabetes [3, 4]. As a result, GINA guidance recommends that maintenance OCS are prescribed at a low dose and as short term as possible to reduce the risk of serious side effects [2]. Biologic therapies are recommended at GINA step 5 as an adjunctive treatment in eligible patients with severe, uncontrolled asthma who require additional therapies to high-dose maintenance ICS and other controller medications to prevent exacerbations and control symptoms [2].

Biologic therapies for severe asthma are monoclonal antibodies that specifically inhibit molecular targets involved in asthma inflammation to improve disease control [5]. Examples of biologics that have been well studied in patients with severe asthma include omalizumab (anti-immunoglobulin E), mepolizumab and reslizumab [both anti-interleukin (IL)-5], benralizumab (anti-IL-5 receptor), dupilumab (anti-IL-4 receptor), and tezepelumab [anti-thymic stromal lymphopoietin (TSLP)] [2]. The majority of these biologics target type 2 (T2) inflammatory pathways, whereas tezepelumab targets TSLP, which has been shown to play a role in T2 inflammation and other disease pathways [6].

For all biologics, differential efficacy has been shown based on patients' baseline blood eosinophil count (BEC), with increased efficacy in patients with high baseline BEC and reduced or no efficacy in patients with low baseline BEC [7–11]. However, these data have not been comprehensively summarized across the relevant clinical trials. Additionally, to date, there have been no randomized, head-to-head trials comparing different biologics to allow direct comparisons. In the absence of such trials, and to contextualize the observed results across biologics by baseline BEC, we sought to systematically and quantitatively summarize biologic efficacy in patients with severe, uncontrolled asthma as a function of baseline BEC. Our primary focus was the endpoint of asthma exacerbation rate reduction.

METHODS

Literature Search

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12]. We performed a comprehensive search of MEDLINE (via PubMed) on 27 May 2021, using a search string containing terms related to severe, uncontrolled asthma, as well as biologic therapies, eosinophils, and clinical outcomes (Table S1). There were no publication date or language restrictions. Two reviewers independently screened the results based on the titles and abstracts, and then assessed the eligibility of the records according to specific inclusion criteria. A search of www.clinicaltrials.gov was also performed to find any additional unpublished trial data from studies identified in the literature search.

Inclusion Criteria

We included peer-reviewed publications reporting placebo-controlled RCTs of biologic therapies in patients with severe, uncontrolled asthma with a primary or secondary endpoint of annualized asthma exacerbation rate reduction. The definition of severe asthma had to be consistent with the GINA 2020 guidelines (i.e., receipt of medium- to high-dose ICS with additional controllers) [13]. Eligible publications reported data for asthma exacerbation rate or other secondary outcomes of interest as a function of baseline BEC for US Food and Drug Administration (FDA)-approved biologics and their approved doses or bioequivalents; tezepelumab was also included because phase 3 trials were completed and FDA approval was anticipated at the time of the literature search (FDA approval was granted on 17 December 2021). When available to the authors, unpublished data from studies identified in the systematic search were included if they enabled comparison with published data from other studies. This included results posted on www.clinicaltrials.gov and unpublished trial data for tezepelumab. To enhance comparability with the BEC subgroup data obtained from other studies, we report subgroup data from PATHWAY for the common BEC thresholds of 150, 300, and 450 cells/μL rather than the original published subgroups based on BEC thresholds of 250 and 400 cells/μL [14].

The purpose of this review was to aggregate and summarize published RCT efficacy data across the biologics studied. Indirect treatment comparisons, meta-analyses, congress materials, real-world safety studies, open-label extension studies, OCS reduction trials, and data for non-FDA approved doses or biologics for which development has been discontinued were excluded. Studies of mild or moderate asthma populations (i.e., those not receiving medium- to high-dose ICS with additional controllers) were also excluded from this review, as were studies conducted solely in OCS-dependent patients, given that this patient population has a unique biology and that maintenance OCS use affects BEC [15] (i.e., the analysis by BEC category would be skewed). Racial/ethnic subgroup analyses were also out of scope for this review.

Data Extraction and Summary

Data were extracted from eligible sources into a standardized data extraction table by one reviewer, and the second reviewer verified the entry of data into the table. The data extracted were study design details, baseline characteristics of the overall study population, and any BEC subgroup data for the primary outcome of interest [annualized asthma exacerbation rate (AAER) ratio versus placebo] and for all secondary outcomes reported (as rate ratio versus placebo, change from baseline versus placebo, or responder rates, as appropriate). When summarizing the data, demonstration of efficacy in AAER reduction or improvement in other outcomes with a given biologic was determined based on the reported 95% confidence interval (CI) for the estimated rate ratio, or change from baseline with treatment versus placebo; *p* values were not used because they were not reported consistently. For example, for the AAER ratio, the 95% CI for the BEC subgroup estimate for

active versus placebo must have been below 1 to demonstrate efficacy in reducing exacerbations. For a given BEC subgroup, wherever available, reported data from single trials and single doses are presented in preference to pooled data (trials or doses). Additionally, to avoid redundancy or conflict within results, data from a single trial were not reported more than once within any specific BEC subgroup.

Risk of Bias Assessment

The Cochrane Collaboration's revised tool for assessing the risk of bias in randomized trials [16, 17] was applied to the included publications (specifically, to the BEC subgroup AAER data extracted from that publication or, if the AAER was not reported, to the trial's primary outcome data that were extracted for BEC subgroups). The tool assessed the risk of bias arising from the following sources: the randomization process; deviations from the intended interventions (effect of assignment to intervention); missing outcome data; measurement of the outcome; and selection of the reported result.

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

RESULTS

Literature Search, Screening, and Selection

The MEDLINE literature search identified 298 results (Fig. 1; Table S2). Of these, 265 were excluded, the majority because they did not report RCTs (212 records). A further 29 and 11 were excluded for ineligible study population and ineligible RCT design, respectively. In addition, five publications did not have AAER reduction as a primary or secondary endpoint, four publications reported a discontinued drug, two reported only non-approved doses, and two reported study protocols only. Of the 33 remaining publications assessed in full, seven were excluded because no eligible data were presented and a further six were excluded because they reported data that were duplicated in publications already included. A final total of 20 publications met the inclusion criteria for the review, and all relevant data were extracted.

Characteristics of the Included Studies

Characteristics of the included studies and analyses are summarized in Table 1. Tezepelumab studies were the NAVIGATOR phase 3 and PATHWAY phase 2b trials, with data coming from two publications plus unpublished data [9, 14]. Dupilumab studies were the LIBERTY ASTHMA QUEST phase 3 trial and a phase 2b trial, with data coming from three publications and www.clinicaltrials.gov [10, 18–20]. Benralizumab studies were the ANDHI, SIROCCO, and CALIMA phase 3 trials, with data coming from seven publications [7, 21–26]. Reslizumab studies were two phase 3 trials and a phase 2b trial, with data coming from two publications [27, 28]. Mepolizumab studies were the MENSA and MUSCA phase 3 trials and the DREAM phase 2b trial, with data coming from five publications [11, 29–32]. The only eligible omalizumab study was the EXTRA phase 3 trial, with data coming from one publication [8].

All efficacy outcome data for BEC subgroups contained in the records were extracted, although not all outcomes were consistently reported across studies. In addition to AAER, the outcomes most commonly reported for BEC subgroups were AAER for exacerbations that required hospitalization or an emergency room (ER) visit, and change from baseline in pre-bronchodilator (BD) forced expiratory volume in 1 s (FEV_1), Asthma Control Questionnaire (ACQ) score, and Asthma Quality of Life Questionnaire (AQLQ) score. Outcomes that were inconsistently reported included change from baseline in post-BD FEV_1, St George's Respiratory Questionnaire score, asthma symptom diary score, total asthma symptom score or asthma symptom utility index, short-acting β_2 agonist use for symptom relief, fractional exhaled nitric oxide levels, and BEC.

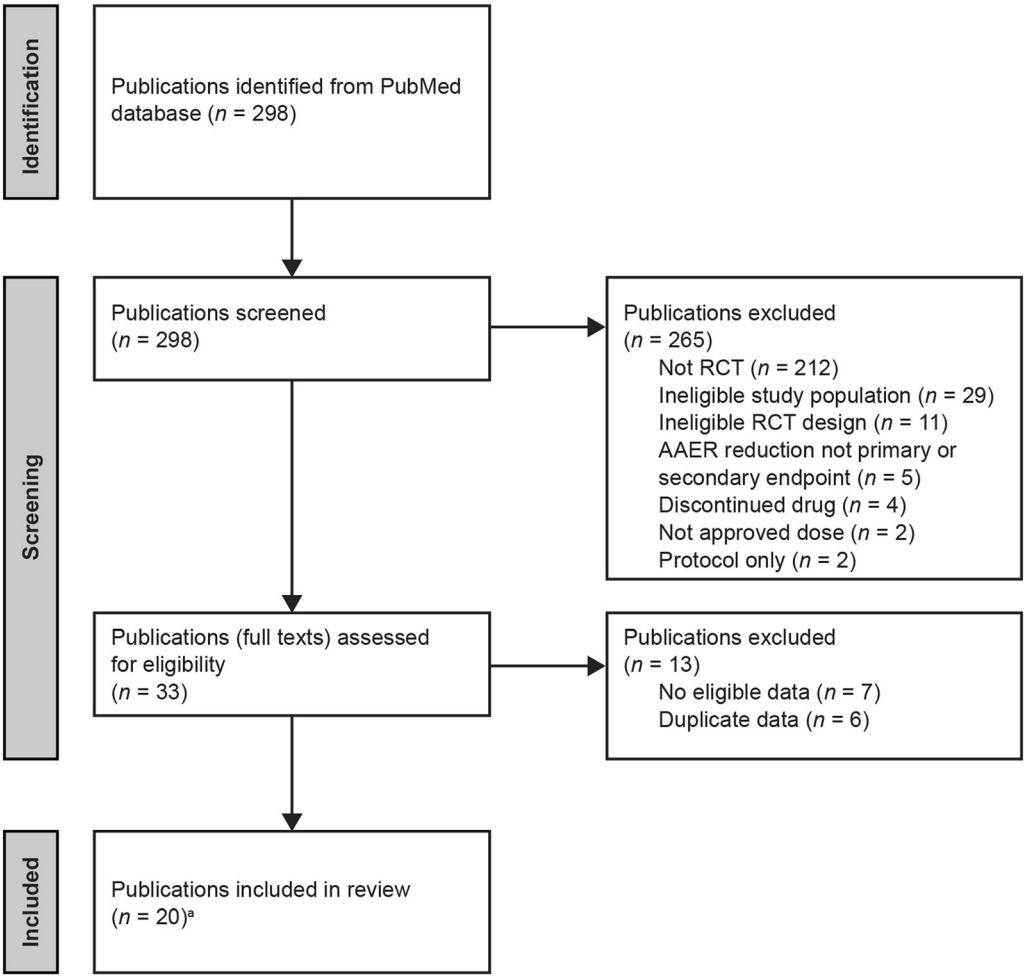

Fig. 1 PRISMA flow diagram illustrating publication selection process. [a]Including previously unpublished tezepelumab data, and dupilumab data posted on www.clinicaltrials.gov (see Table 1 for details). *AAER* annualized asthma exacerbation rate, *PRISMA* Preferred Reporting Items for Systematic Reviews and Meta-Analyses, *RCT* randomized controlled trial

To examine differences between the study populations and provide context for the AAER by BEC subgroup data, the mean number of exacerbations that patients experienced in the 12 months before study commencement, both in the overall population and by BEC subgroup where available, were also extracted from the included publications (Table 2). This number ranged from 1.9 to 3.0 exacerbations across the active and placebo groups of the overall study populations (1.7–3.8 exacerbations when considering BEC subgroups). Patients participating in trials of tezepelumab, benralizumab, and mepolizumab generally had a higher mean number of exacerbations in the 12 months before study commencement than those participating in trials of dupilumab, reslizumab, and omalizumab. For the majority of studies, in the 12 months before study commencement and post-randomization in the placebo group, the rate of exacerbations was slightly higher among patients with baseline BEC $\geq$ 300 cells/μL than those with baseline BEC 0 to < 300 cells/μL.

Risk of Bias Assessment

Of the 20 included studies, 12 were assessed to have a low risk of bias (Fig. S1). In the remaining eight studies, there was some potential bias in

Table 1 Characteristics of the included trials and publications

Drug	Trial name (NCT number)	Total study population, *n*	Age range, years	Intervention[a]	Treatment period	Publication
Tezepelumab	NAVIGATOR (NCT03347279)	1059	12–80	Tezepelumab 210 mg SC Q4W	52 weeks	Menzies-Gow et al. [9] supplemented with unpublished data
	PATHWAY phase 2b (NCT02054130)	550	18–75	Tezepelumab 210 mg SC Q4W	52 weeks	Corren et al. [14] supplemented with unpublished data
	PATHWAY phase 2b and NAVIGATOR pooled (NCT03347279 and NCT02054130)	1334	12–80	Tezepelumab 210 mg SC Q4W	52 weeks	Unpublished data
Dupilumab	LIBERTY ASTHMA QUEST (NCT02414854)	1902	≥ 12	Dupilumab 200 mg SC Q2W Dupilumab 300 mg SC Q2W	52 weeks	Castro et al. [19] Castro et al. [10] supplemented with data posted on www.clinicaltrials.gov [20]
	Phase 2b trial (NCT01854047)	776	≥ 18	Dupilumab 200 mg SC Q2W Dupilumab 300 mg SC Q2W	24 weeks	Wenzel et al. [18]

Table 1 continued

Drug	Trial name (NCT number)	Total study population, *n*	Age range, years	Intervention[a]	Treatment period	Publication
Benralizumab	ANDHI (NCT03170271)	656	18–75	Benralizumab 30 mg SC Q8W	24 weeks	Harrison et al. [22]
	SIROCCO and CALIMA pooled (NCT01928771 and NCT01914757)	1537 (BEC ≥ 300 cells/μL), 1941 (BEC ≥ 150 cells/μL)	12–75	Benralizumab 30 mg SC Q8W	48 weeks and 56 weeks	O'Quinn et al. [23]
		2295	12–75	Benralizumab 30 mg SC Q8W	48 weeks and 56 weeks	FitzGerald et al. [24] Bleecker et al. [25]
	SIROCCO and CALIMA assessed separately (NCT01928771 and NCT01914757)	1204 (SIROCCO), 1306 (CALIMA)	12–75	Benralizumab 30 mg SC Q8W	48 weeks and 56 weeks	Goldman et al. [26]
	SIROCCO (NCT01928771)	1204	12–75	Benralizumab 30 mg SC Q8W	48 weeks	Bleecker et al. [21]
	CALIMA (NCT01914757)	1306	12–75	Benralizumab 30 mg SC Q8W	56 weeks	FitzGerald et al. [7]
Reslizumab	Study 1 and Study 2 assessed separately (NCT01287039 and NCT01285323)	489 (Study 1), 464 (Study 2)	12–75	Reslizumab 3.0 mg/kg IV Q4W	52 weeks	Castro et al. [27]
	Phase 2b trial (NCT00587288)	106	18–75	Reslizumab 3.0 mg/kg IV Q4W	15 weeks	Castro et al. [28]

Table 1 continued

Drug	Trial name (NCT number)	Total study population, *n*	Age range, years	Intervention[a]	Treatment period	Publication
Mepolizumab	MENSA and MUSCA assessed separately; pooled doses for MENSA (NCT01691521 and NCT02281318)	576 (MENSA), 556 (MUSCA)	12–82	Mepolizumab 75 mg IV Q4W Mepolizumab 100 mg SC Q4W	24–52 weeks	Yancey et al. [32]
	MUSCA (NCT02281318)	551	≥ 12	Mepolizumab 100 mg SC Q4W	24 weeks	Chupp et al. [29]
	DREAM phase 2b and MENSA assessed separately; pooled doses for MENSA (NCT01000506 and NCT01691521)	621 (DREAM), 576 (MENSA)	12–82	Mepolizumab 75 mg IV Q4W Mepolizumab 100 mg SC Q4W	32–52 weeks	Ortega et al. [11]
	MENSA (NCT01691521)	576	12–82	Mepolizumab 75 mg IV Q4W Mepolizumab 100 mg SC Q4W	32 weeks	Ortega et al. [30]
	DREAM phase 2b (NCT01000506)	621	12–74	Mepolizumab 75 mg IV Q4W	52 weeks	Pavord et al. [31]
Omalizumab	EXTRA (NCT00314574)	850	12–75	Minimum dose of 0.008 mg/kg/IgE [IU/mL] SC Q2W or 0.016 mg/kg/IgE [IU/mL] SC Q4W	48 weeks	Hanania et al. [8]

All data are from phase 3 trials unless otherwise specified

BEC blood eosinophil count, *FDA* US Food and Drug Administration, *IgE* immunoglobulin E, *IV* intravenous, *Q2W* every 2 weeks, *Q4W* every 4 weeks, *Q8W* every 8 weeks, *SC* subcutaneous

[a]Extracted data only (i.e., FDA-approved dose for each drug)

Table 2 Exacerbations in the 12 months before study commencement and in placebo-treated patients during the studies

Study	Intervention	Population	Exacerbations in 12 months before study, mean ± SD (*n*)		AAER during study, mean (95% CI)	Publication
			Active	Placebo	Placebo	
NAVIGATOR	Tezepelumab 210 mg SC Q4W	Overall	2.8 ± 1.4 (528)	2.7 ± 1.4 (531)	2.10 (1.84–2.39)	Menzies-Gow et al. [9] supplemented with unpublished data
		BEC ≥ 450 cells/μL	3.1 ± 1.8 (120)	3.0 ± 1.6 (127)	3.00 (2.34–3.84)	
		BEC ≥ 300 cells/μL	3.0 ± 1.7 (219)	2.9 ± 1.5 (222)	2.66 (2.19–3.23)	
		BEC 0 to < 300 cells/μL	2.6 ± 1.2 (309)	2.6 ± 1.2 (309)	1.73 (1.46–2.05)	
		BEC ≥ 150 cells/μL	2.9 ± 1.5 (390)	2.8 ± 1.4 (393)	2.24 (1.93–2.60)	
		BEC 0 to < 150 cells/μL	2.6 ± 1.0 (138)	2.6 ± 1.2 (138)	1.70 (1.32–2.19)	
		BEC ≥ 150 to < 300 cells/μL	2.7 ± 1.3 (171)	2.6 ± 1.3 (171)	1.75 (1.40–2.19)	
PATHWAY phase 2b	Tezepelumab 210 mg SC Q4W	Overall	2.4 ± 1.2 (137)	2.5 ± 1.2 (138)	0.72 (0.61–0.86)	Corren et al. [14] supplemented with unpublished data
		BEC ≥ 450 cells/μL	2.6 ± 1.5 (53)	2.6 ± 1.5 (55)	0.82 (0.57–1.13)	
		BEC ≥ 300 cells/μL	2.5 ± 1.3 (84)	2.5 ± 1.3 (82)	0.65 (0.48–0.87)	
		BEC 0 to < 300 cells/μL	2.4 ± 1.1 (86)	2.4 ± 1.1 (85)	0.80 (0.59–1.04)	
		BEC ≥ 150 cells/μL	2.4 ± 1.2 (114)	2.5 ± 1.3 (117)	0.66 (0.52–0.84)	
		BEC 0 to < 150 cells/μL	2.4 ± 1.4 (39)	2.4 ± 1.2 (44)	0.92 (0.61–1.32)	
		BEC ≥ 150 to < 300 cells/μL	2.3 ± 0.9 (56)	2.4 ± 1.0 (58)	0.68 (0.43–1.03)	
LIBERTY ASTHMA QUEST	Dupilumab 200 mg SC Q2W	Overall	2.07 ± 2.66 (631)	2.07 ± 1.58 (317)	0.87 (0.72–1.05)	Castro et al. [10]
		BEC ≥ 300 cells/μL	NR	NR	1.08 (0.85–1.38)	
		BEC 0 to < 300 cells/μL	NR	NR	0.68 (0.52–0.88)	
		BEC ≥ 150 cells/μL	NR	NR	1.01 (0.81–1.25)	
		BEC 0 to < 150 cells/μL	NR	NR	0.51 (0.35–0.76)	
		BEC ≥ 150 to < 300 cells/μL	NR	NR	0.87 (0.59–1.27)	
	Dupilumab 300 mg SC Q2W	Overall	2.02 ± 1.86 (633)	2.31 ± 2.07 (321)	0.97 (0.81–1.16)	
		BEC ≥ 300 cells/μL	NR	NR	1.24 (0.97–1.57)	
		BEC 0 to < 300 cells/μL	NR	NR	0.73 (0.56–0.95)	
		BEC ≥ 150 cells/μL	NR	NR	1.08 (0.88–1.33)	
		BEC 0 to < 150 cells/μL	NR	NR	0.64 (0.45–0.93)	
		BEC ≥ 150 to < 300 cells/μL	NR	NR	0.84 (0.58–1.23)	

Table 2 continued

Study	Intervention	Population	Exacerbations in 12 months before study, mean ± SD (*n*)		AAER during study, mean (95% CI)	Publication
			Active	Placebo	Placebo	
Phase 2b trial	Dupilumab 200 mg SC Q2W	Overall	1.85 ± 1.43 (150)	2.27 ± 2.25 (158)	0.90 (0.62–1.30)	Wenzel et al. [18]
		BEC ≥ 300 cells/μL	2.08 ± 1.67 (65)	2.41 ± 2.77 (68)	1.04 (0.57–1.90)	
		BEC 0 to < 300 cells/μL	1.67 ± 1.19 (85)	2.17 ± 1.77 (90)	0.78 (0.49–1.23)	
	Dupilumab 300 mg SC Q2W	Overall	2.37 ± 2.29 (157)	2.27 ± 2.25 (158)	0.90 (0.62–1.30)	
		BEC ≥ 300 cells/μL	2.83 ± 2.79 (64)	2.41 ± 2.77 (68)	1.04 (0.57–1.90)	
		BEC 0 to < 300 cells/μL	2.05 ± 1.82 (93)	2.17 ± 1.77 (90)	0.78 (0.49–1.23)	
SIROCCO	Benralizumab 30 mg SC Q8W	Overall	2.8 ± 1.5 (398)	3.0 ± 1.8 (407)	NR	Goldman et al. [26]
		BEC ≥ 300 cells/μL	2.8 ± 1.5 (267)	3.1 ± 2.0 (267)	1.33 (1.12–1.58)	Bleecker et al. [21]
		BEC 0 to < 300 cells/μL	2.6 ± 1.3 (131)	2.7 ± 1.5 (140)	1.21 (0.96–1.52)	
		BEC ≥ 150 cells/μL	2.9 ± 1.6 (325)	3.1 ± 1.9 (306)	1.50 (1.27–1.76)	
		BEC 0 to < 150 cells/μL	2.4 ± 0.8 (48)	2.7 ± 1.6 (74)	1.34 (1.00–1.79)	
CALIMA	Benralizumab 30 mg SC Q8W	Overall	2.7 ± 1.4 (441)	2.7 ± 1.6 (440)	NR	Goldman et al. [26]
		BEC ≥ 300 cells/μL	2.7 ± 1.3 (239)	2.8 ± 1.7 (248)	0.93 (0.77–1.12)	FitzGerald et al. [7]
		BEC 0 to < 300 cells/μL	2.7 ± 1.7 (125)	2.7 ± 1.9 (122)	1.21 (0.96–1.52)	
		BEC ≥ 150 cells/μL	2.7 ± 1.2 (300)	2.7 ± 1.5 (315)	1.10 (0.94–1.28)	
		BEC 0 to < 150 cells/μL	3.1 ± 2.4 (48)	2.5 ± 1.3 (40)	1.55 (1.06–2.28)	
ANDHI	Benralizumab 30 mg SC Q8W	Overall (BEC ≥ 150 cells/μL)	**≤ 2:** 206 (48%)[a]	**≤ 2:** 113 (49%)[a]	NR	Harrison et al. [22]
			≥ 3: 221 (52%)[a]	**≥ 3:** 116 (51%)[a]		
Study 1	Reslizumab 3.0 mg/kg IV Q4W	Overall (BEC ≥ 400 cells/μL)	1.9 ± 1.6 (245)	2.1 ± 2.3 (244)	1.80 (1.37–2.37)	Castro et al. [27]
Study 2	Reslizumab 3.0 mg/kg IV Q4W	Overall (BEC ≥ 400 cells/μL)	1.9 ± 1.6 (232)	2.0 ± 1.8 (232)	2.11 (1.33–3.37)	
Phase 2b trial	Reslizumab 3.0 mg/kg IV Q4W	Overall	NR	NR	NR	Castro et al. [28]
DREAM phase 2b	Mepolizumab 75 mg IV Q4W	Overall (BEC ≥ 300 cells/μL)	3.7 ± 3.1 (153)	3.7 ± 3.8 (155)	2.40 (0.11[b])	Pavord et al. [31]
MUSCA	Mepolizumab 100 mg SC Q4W	Overall (BEC ≥ 150 cells/μL)	2.9 ± 1.9 (274)	2.7 ± 1.5 (277)	1.21 (NR)	Chupp et al. [29]

Table 2 continued

Study	Intervention	Population	Exacerbations in 12 months before study, mean ± SD (*n*)		AAER during study, mean (95% CI)	Publication
			Active	Placebo	Placebo	
MENSA	Mepolizumab 75 mg IV Q4W	Overall (BEC ≥ 150 cells/μL)	3.5 ± 2.2 (191)	3.6 ± 2.8 (191)	1.74 (NR)	Ortega et al. [30]
	Mepolizumab 100 mg SC Q4W	Overall (BEC ≥ 150 cells/μL)	3.8 ± 2.7 (194)			
EXTRA	Omalizumab 0.008 mg/kg/IgE (IU/mL) SC Q2W or 0.016 mg/kg/IgE (IU/mL) SC Q4W	Overall	2.0 ± 2.2 (427)	1.9 ± 1.5 (421)	0.88 (NR)	Hanania et al. [8]
		BEC ≥ 260 cells/μL		2 ± 2 (414)	1.03 (NR)	Hanania et al. [43]
		BEC < 260 cells/μL		2 ± 1 (383)	0.72 (NR)	

All data are from phase 3 trials unless otherwise specified

AAER annualized asthma exacerbation rate, *BEC* blood eosinophil count, *CI* confidence interval, *IgE* immunoglobulin E, *IV* intravenous, *NR* not reported, *Q2W* every 2 weeks, *Q4W* every 4 weeks, *Q8W* every 8 weeks, *SC* subcutaneous, *SD* standard deviation, *SE* standard error

[a]Mean (SD) not reported; *n* (%) of patients with ≤ 2 and ≥ 3 exacerbations, respectively, in the 12 months before the study are provided here

[b]SE log

the reported results because the BEC subgroup analyses were not pre-specified. In addition, one study examining the efficacy of mepolizumab in patients with baseline BEC of ≥ 150 to 300 cells/μL [32] was reported with insufficient detail to allow assessment of the appropriateness of the analysis used to estimate the effect of assignment to intervention (e.g., intention-to-treat or per protocol). There was little risk of bias arising from other aspects of the analyses in these eight studies.

Exacerbations

In patients with baseline BEC ≥ 300 cells/μL, efficacy in AAER reduction versus placebo was demonstrated with all biologics in all trials for which this subgroup was reported (studies of tezepelumab, dupilumab, benralizumab, mepolizumab, and omalizumab) (Figs. 2, S2) [7–10, 14, 18, 21, 22, 31]. The greatest AAER reductions versus placebo (≥ 60%) were observed with dupilumab and tezepelumab [9, 10, 14, 18]. Similarly, reductions were demonstrated with all biologics in patients with baseline BEC ≥ 150 cells/μL where reported (studies of tezepelumab, dupilumab, benralizumab, and mepolizumab) [9, 10, 14, 26, 29, 30] and ≥ 450 cells/μL where reported (studies of tezepelumab, benralizumab, reslizumab, and mepolizumab) [9, 11, 14, 24, 27].

In patients with BEC 0 to < 300 cells/μL, AAER reduction versus placebo was consistently demonstrated only with tezepelumab (in both NAVIGATOR and PATHWAY) [9, 14]. With benralizumab and dupilumab, AAER reduction was observed in one each of the two trials in which they were studied (CALIMA for benralizumab and the phase 2b study for dupilumab) [7, 18]. In patients with BEC 150 to < 300 cells/μL, AAER reduction was only demonstrated consistently with tezepelumab (NAVIGATOR and PATHWAY) [9, 14], although this outcome was also observed with dupilumab (QUEST 300 mg dose only) [10]. In patients with BEC 0 to < 150 cells/μL, AAER reduction was only demonstrated with tezepelumab (NAVIGATOR and PATHWAY) [9, 14].

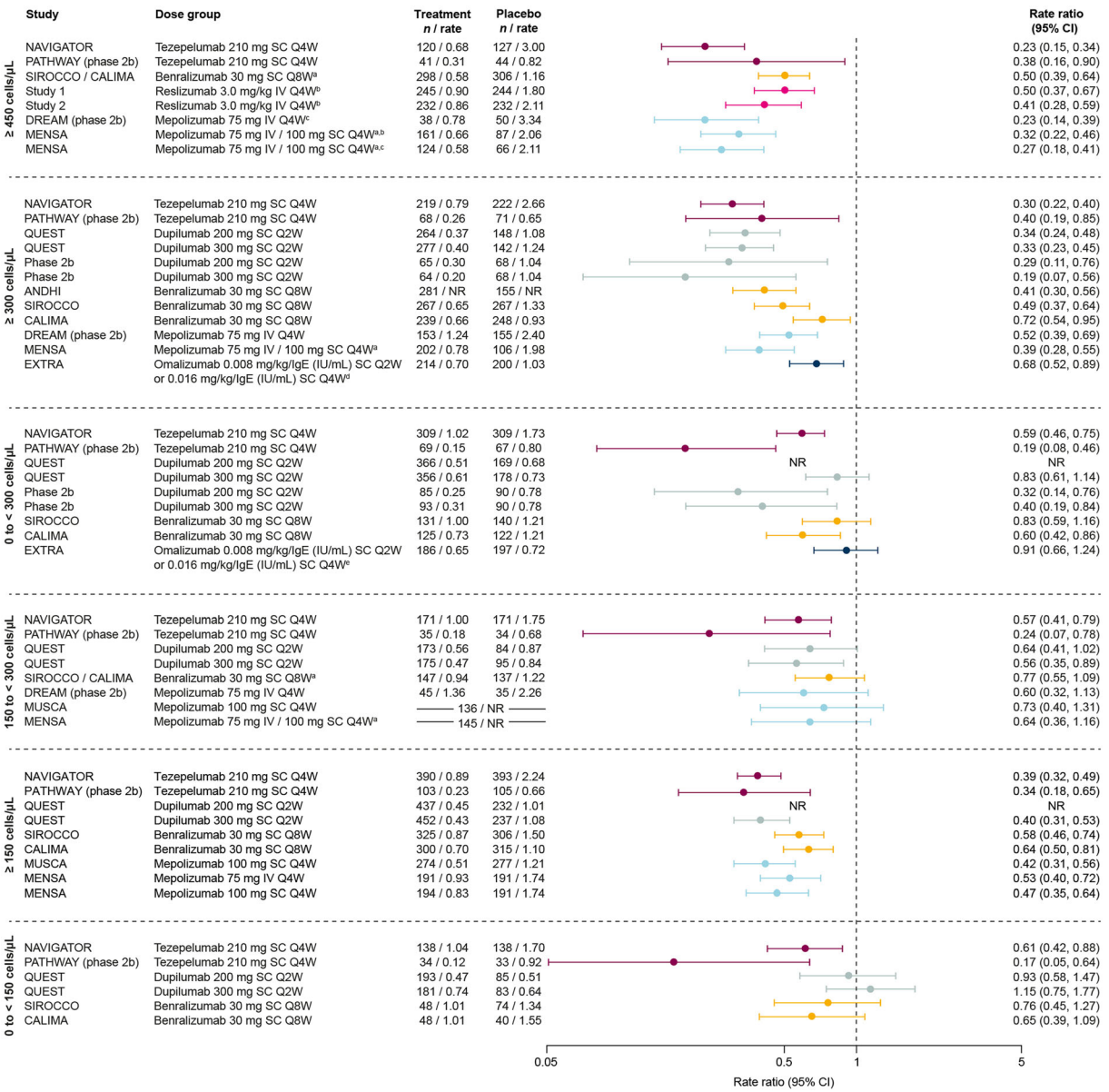

Fig. 2 AAER by biologic therapy across baseline BEC subgroups. Data are phase 3 unless otherwise specified. In the 0 to < 300 cells/µL panel, QUEST data are from www.clinicaltrials.gov [20]; reported for the 300 mg dose only. Patient numbers for MUSCA and MENSA in the 150 to < 300 cells/µL panel are for the overall population (breakdown by treatment group not given). In the ≥ 150 cells/µL panel, MUSCA and MENSA data are for patients with BEC > 150 cells/µL at screening (rather than baseline). [a]Pooled trials or doses; [b]BEC ≥ 400 cells/µL; [c]BEC ≥ 500 cells/µL; [d]BEC ≥ 260 cells/µL; [e]BEC < 260 cells/µL. *AAER* annualized asthma exacerbation rate, *BEC* blood eosinophil count, *CI* confidence interval, *IgE* immunoglobulin E, *IV* intravenous, *NR* not reported, *Q2W* every 2 weeks, *Q4W* every 4 weeks, *Q8W* every 8 weeks, *SC* subcutaneous

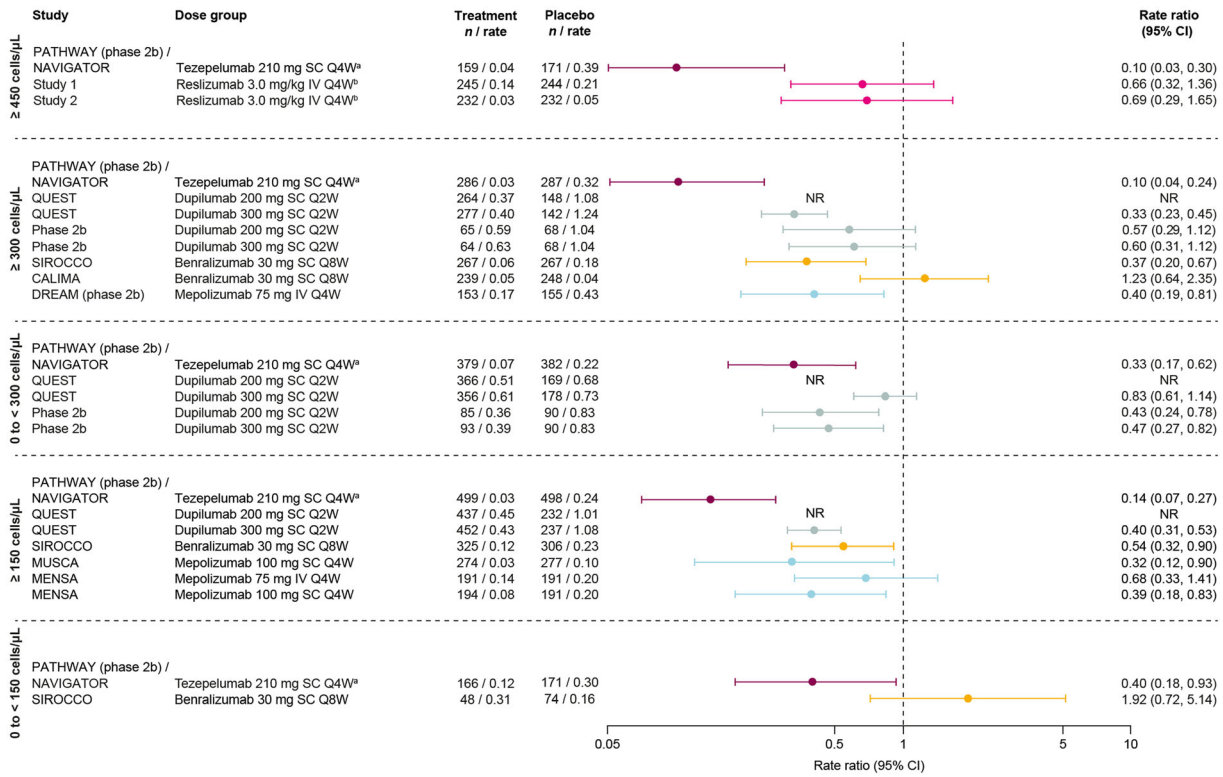

Fig. 3 Exacerbations that required hospitalization or an ER visit by biologic therapy across baseline BEC subgroups. Data are phase 3 unless otherwise specified. QUEST data are from www.clinicaltrials.gov [20]. In the ≥ 150 cells/µL panel, MUSCA and MENSA data are for patients with BEC > 150 cells/µL at screening (rather than baseline). [a]Pooled trials or doses; [b]BEC ≥ 400 cells/µL. *BEC* blood eosinophil count, *CI* confidence interval, *ER* emergency room, *IV* intravenous, *Q2W* every 2 weeks, *Q4W* every 4 weeks, *Q8W* every 8 weeks, *SC* subcutaneous

Exacerbations Requiring Hospitalization or an ER Visit

In patients with BEC ≥ 300 cells/µL, reductions in the annualized rate of exacerbations requiring hospitalization or an ER visit versus placebo were demonstrated with tezepelumab (pooled NAVIGATOR and PATHWAY), dupilumab (QUEST 300 mg dose only), benralizumab (SIROCCO), and mepolizumab (DREAM) (Fig. 3) [20, 21, 31]. In patients with BEC ≥ 150 cells/µL, a reduction was demonstrated across all trials for which this subgroup was reported, comprising studies of tezepelumab (pooled NAVIGATOR and PATHWAY), dupilumab (QUEST 300 mg dose), benralizumab (SIROCCO), and mepolizumab (MUSCA and MENSA, 100 mg subcutaneous arm only) [20, 26, 29, 30]. The greatest reductions in exacerbations requiring hospitalization or an ER visit in both the BEC ≥ 300 cells/µL and BEC ≥ 150 cells/µL subgroups were observed with tezepelumab, at 90% and 86%, respectively. Of the two biologics with data reported for patients with BEC 0 to < 150 cells/µL, a reduction was demonstrated only with tezepelumab (pooled NAVIGATOR and PATHWAY).

Pre-bronchodilator FEV_1

Efficacy in improving pre-BD FEV_1 versus placebo in patients with BEC ≥ 300 cells/µL or ≥ 150 cells/µL was demonstrated by all biologics across all trials that reported these subgroups (studies of tezepelumab, dupilumab, benralizumab, and mepolizumab), except for the BEC ≥ 300 cells/µL subgroup in DREAM

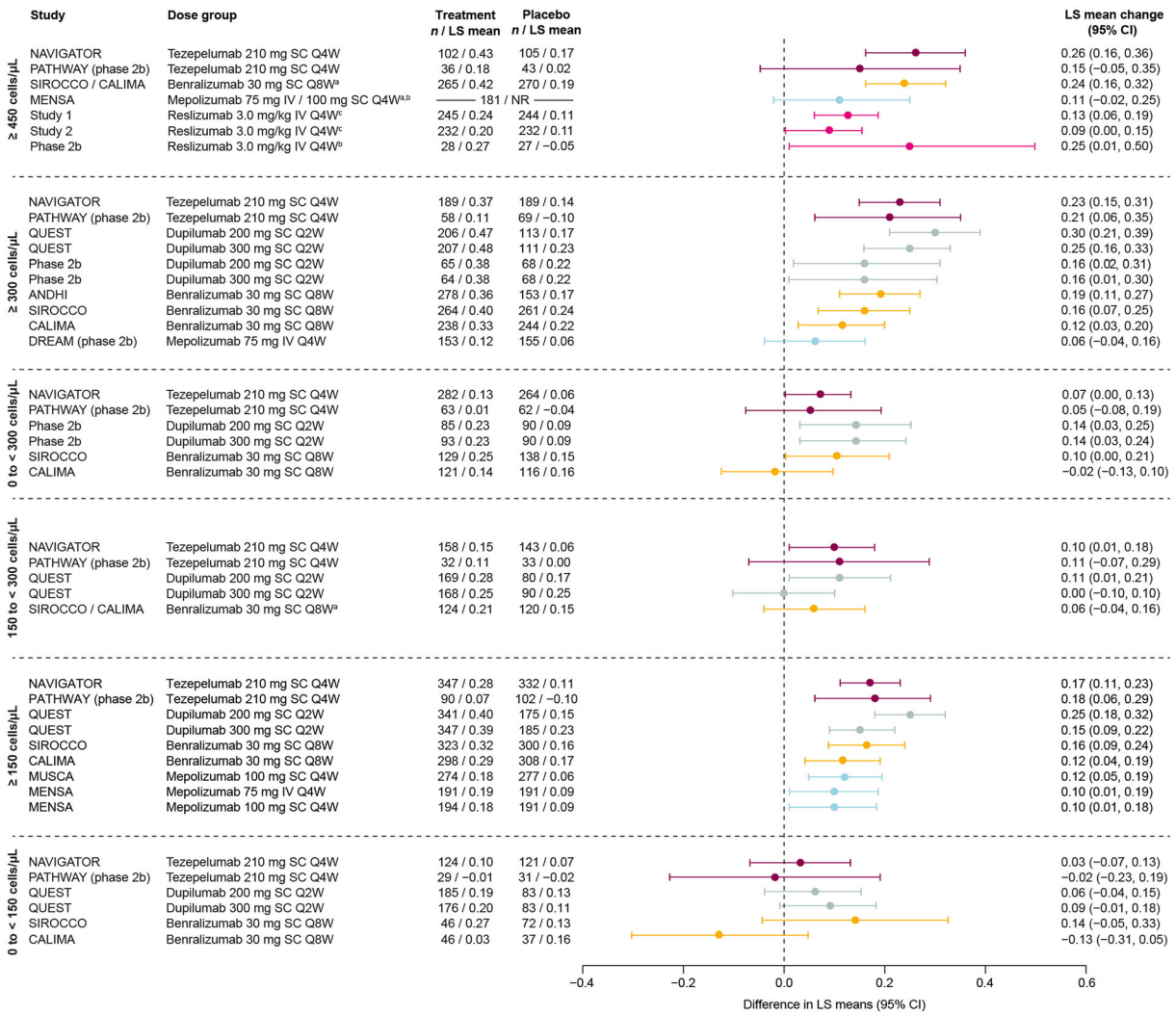

Fig. 4 Change from baseline versus placebo in pre-bronchodilator FEV_1 (L) by biologic therapy across baseline BEC subgroups. Data are phase 3 unless otherwise specified. MENSA patient numbers are for the overall population (≥ 450 cells/μL panel). QUEST 200 mg and 300 mg data in the 150 to < 300 cells/μL and 0 to < 150 cells/μL panels are from study week 12. MUSCA and MENSA data in the BEC ≥ 150 cells/μL panel are from screening (rather than baseline). [a]Pooled trials or doses; [b]BEC ≥ 500 cells/μL; [c]BEC ≥ 400 cells/μL. *BEC* blood eosinophil count, *CI* confidence interval, *FEV_1* forced expiratory volume in 1 s, *IV* intravenous, *LS* least-squares, *Q2W* every 2 weeks, *Q4W* every 4 weeks, *Q8W* every 8 weeks, *SC* subcutaneous

(mepolizumab) (Fig. 4) [7, 9, 14, 18, 19, 21, 22, 26, 29–31]. Where data were available for patients with BEC ≥ 450 cells/μL, improvements were demonstrated in the majority of trials (studies of tezepelumab, benralizumab, and reslizumab) [9, 14, 27, 28].

Of studies that reported data from patients with BEC 0 to < 300 cells/μL, tezepelumab, dupilumab, and benralizumab demonstrated efficacy in improving pre-BD FEV_1 in one trial each (NAVIGATOR, dupilumab phase 2b, and SIROCCO, respectively) [9, 18, 21]. Improvements in patients with BEC 150 to < 300 cells/μL were observed in one trial each of tezepelumab (NAVIGATOR) and dupilumab (QUEST 200 mg dose only) [9, 10]. No biologic demonstrated a significant improvement compared with

placebo in pre-BD FEV_1 in patients with BEC 0 to < 150 cells/μL.

ACQ Score

Efficacy in improving ACQ score versus placebo in patients with BEC ≥ 300 cells/μL was demonstrated in all trials that reported this subgroup (studies of tezepelumab, dupilumab, benralizumab, and mepolizumab), with the exception of mepolizumab in DREAM (Fig. 5) [7, 9, 11, 14, 18, 21, 22, 31]. The greatest improvements (> 0.4-point improvement in mean score versus placebo) were observed with tezepelumab, dupilumab, benralizumab (ANDHI), and mepolizumab (MENSA) [9, 11, 14, 18, 22]. Where data were available, improvements were also demonstrated in the majority of trials reporting BEC ≥ 450 cells/μL subgroup data (studies of tezepelumab, benralizumab, mepolizumab and reslizumab) [9, 11, 14, 24, 27, 28]. Improvements in ACQ score in patients with BEC ≥ 150 cells/μL were demonstrated in all but one trial [benralizumab (SIROCCO)] that reported this subgroup (studies of tezepelumab, benralizumab, and mepolizumab) [9, 14, 26, 29, 30].

In trials reporting BEC 0 to < 300 cells/μL subgroup data, tezepelumab and dupilumab (200 mg dose only) were the only biologics to demonstrate efficacy in improving ACQ scores, in one trial each (NAVIGATOR and dupilumab phase 2b, respectively) [9, 18]. In patients with BEC 0 to < 150 cells/μL, only benralizumab in the SIROCCO trial demonstrated efficacy in improving ACQ score [26].

AQLQ Score

In patients with BEC ≥ 300 cells/μL, efficacy in improving AQLQ score versus placebo was demonstrated with tezepelumab (NAVIGATOR), dupilumab (phase 2b), and benralizumab (SIROCCO and CALIMA) (Fig. 6) [7, 9, 18, 21]. In patients with BEC ≥ 450 cells/μL, improvements were observed with tezepelumab (NAVIGATOR), benralizumab (SIROCCO/CALIMA pooled), and reslizumab (phase 3 studies 1 and 2) [9, 24, 27]. AQLQ data for patients with BEC ≥ 150 cells/μL were reported only for trials of tezepelumab (NAVIGATOR and PATHWAY) and benralizumab (SIROCCO and CALIMA), with efficacy demonstrated in all of these studies [9, 14, 26].

AQLQ improvements in patients with BEC 0 to < 300 cells/μL were demonstrated with tezepelumab in NAVIGATOR and with omalizumab in EXTRA [8, 27]. In patients with BEC 0 to < 150 cells/μL, no biologic demonstrated efficacy in improving AQLQ score.

Other Outcomes

Additional endpoints stratified by BEC subgroups were extracted for reference (summarized in Table S3). These include post-BD FEV_1, St George's Respiratory Questionnaire score, asthma symptom diary score, total asthma symptom score or asthma symptom utility index, short-acting β_2 agonist use for symptom relief, fractional exhaled nitric oxide levels, and mean change in BEC.

DISCUSSION

This systematic review of randomized, placebo-controlled clinical trial data evaluated the efficacy of biologics in patients with severe, uncontrolled asthma grouped by baseline BEC. A clear association between efficacy in reducing exacerbations and baseline BEC was demonstrated for all biologics assessed. Although they all demonstrated efficacy versus placebo in patients with baseline BEC ≥ 150, ≥ 300, or ≥ 450 cells/μL, with a clinically meaningful reduction in AAER (i.e., ≥ 20%) [33], biologics other than tezepelumab either demonstrated inconsistent efficacy across studies or did not demonstrate efficacy in reducing exacerbations in patients with lower BEC (either 0 to < 300 cells/μL or 0 to < 150 cells/μL). The association between baseline BEC and efficacy in reducing exacerbations associated with hospitalization or an ER visit was not as clear, largely owing to limited data availability; however, efficacy was generally demonstrated in patients with baseline BEC ≥ 150 cells/μL or ≥ 300 cells/μL for those biologics with data available (studies of tezepelumab, dupilumab, benralizumab, and mepolizumab). Tezepelumab uniquely

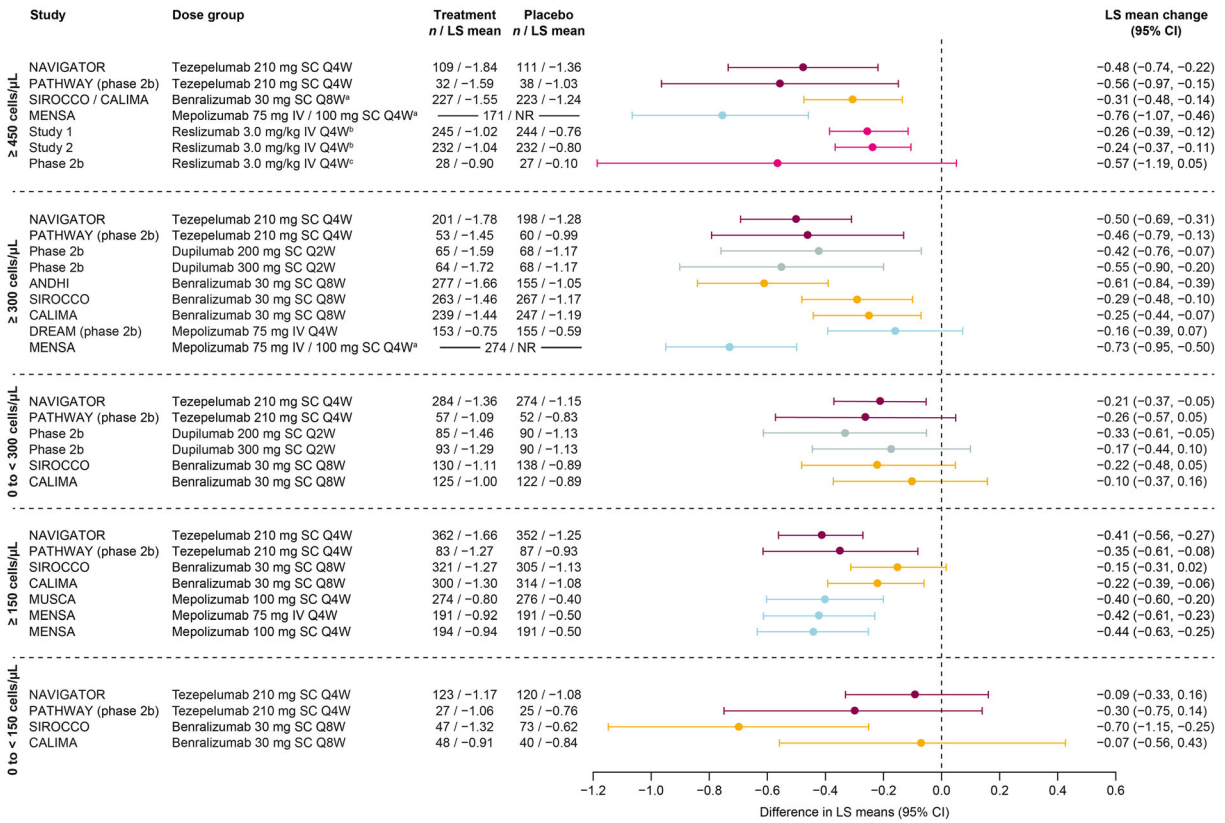

Fig. 5 Change from baseline versus placebo in ACQ score by biologic therapy across baseline BEC subgroups. Data are phase 3 unless otherwise specified. Data are ACQ-6, except for: dupilumab phase 2b (ACQ-5); all reslizumab studies (ACQ-7); and mepolizumab MUSCA and MENSA (ACQ-5). PATHWAY data are from study week 50. In the ≥ 300 cells/µL panel, patient numbers for MENSA are the overall population. In the ≥ 150 cells/µL panel, MUSCA and MENSA data are for patients with BEC > 150 cells/µL at screening (rather than baseline). [a]Pooled trials or doses; [b]BEC ≥ 400 cells/µL; [c]BEC ≥ 500 cells/µL. *ACQ* Asthma Control Questionnaire, *BEC* blood eosinophil count, *CI* confidence interval, *IV* intravenous, *LS* least-squares, *NR* not reported, *Q2W* every 2 weeks, *Q4W* every 4 weeks, *Q8W* every 8 weeks, *SC* subcutaneous

demonstrated efficacy in exacerbation reduction, overall and for those associated with hospitalization or an ER visit, in patients with BEC 0 to < 150 cells/µL.

The biologics studied all have different mechanisms of action. This fact underscores the importance of comparing results across their randomized, placebo-controlled studies, as providers must choose between biologics with different mechanisms to identify the biologic best suited for their patients. In fact, the differential efficacy of biologics in reducing exacerbations according to patients' BEC is likely a result of mechanistic differences between the treatments and the resulting impact of these on airway inflammation and physiology. The majority of FDA-approved biologics for severe asthma target specific elements of T2 inflammatory pathways (immunoglobulin E, IL-5, IL-5 receptor, or IL-4 receptor) and thus predominantly benefit patient phenotypes characterized by high levels of T2 inflammation, including high BEC. Tezepelumab, however, targets TSLP, an epithelial cytokine that has been shown to play a role in processes broader than strictly T2 inflammation in asthma pathophysiology [34]. The efficacy of tezepelumab in patients with low T2 inflammation may relate to the observed

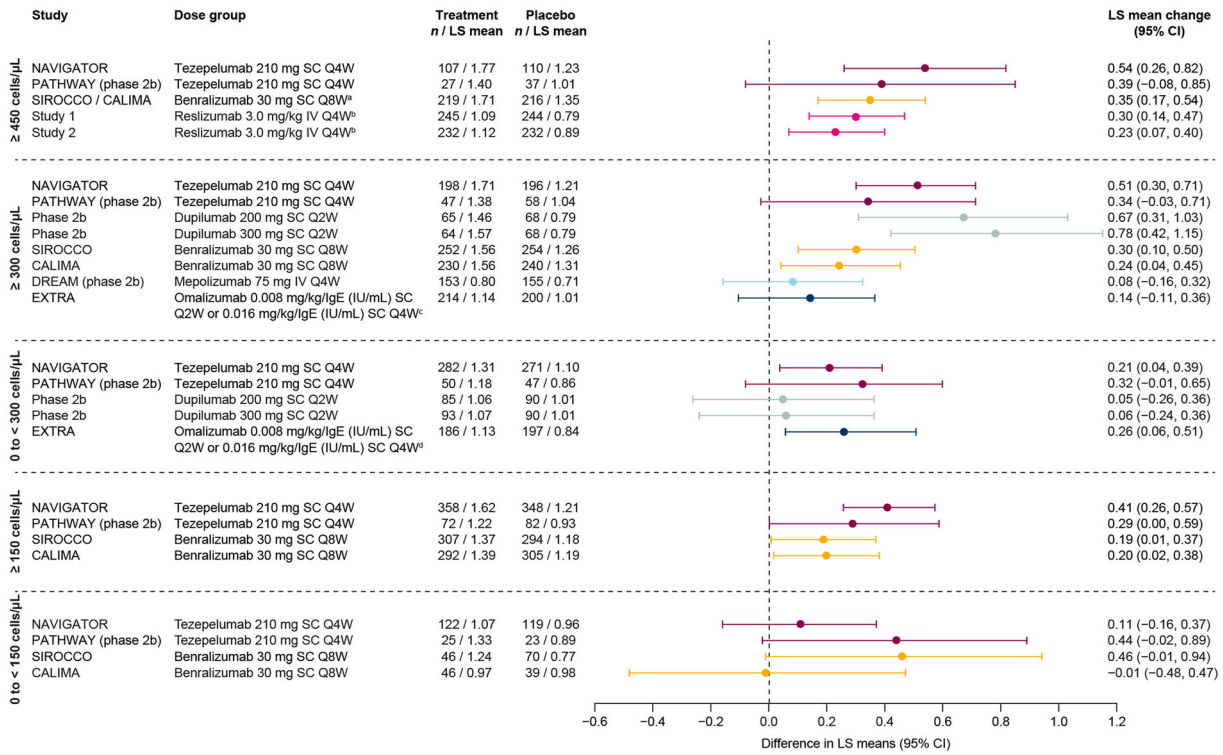

Fig. 6 Change from baseline versus placebo in AQLQ score by biologic therapy across baseline BEC subgroups. Data are phase 3 unless otherwise specified. PATHWAY data are from study week 48. [a]Pooled trials or doses; [b]BEC ≥ 400 cells/μL; [c]BEC ≥ 260 cells/μL; [d]BEC < 260 cells/μL. *AQLQ* Asthma Quality of Life Questionnaire, *BEC* blood eosinophil count, *CI* confidence interval, *IgE* immunoglobulin E, *IV* intravenous, *Q2W* every 2 weeks, *Q4W* every 4 weeks, *Q8W* every 8 weeks, *SC* subcutaneous

reduction in airway hyperresponsiveness (a largely T2-independent mechanism) with tezepelumab treatment and effects on other potential mediators, such as mast cell activity [35–37].

With regard to efficacy in improving lung function, asthma symptom control, and asthma-related quality of life, improvements were generally demonstrated across biologics in patients with baseline BEC ≥ 150 cells/μL and ≥ 300 cells/μL. In those with BEC 0 to < 300 cells/μL or 0 to < 150 cells/μL, inconsistent, reduced, or no efficacy in improving these outcomes was observed across biologics. In contrast to the mechanisms relevant to reducing asthma exacerbations, biologic mechanisms related to improvement of these secondary clinical trial endpoints of lung function and asthma symptoms may be more directly associated with T2 airway inflammation, given the similar results seen across biologics regardless of their mechanism. T2 inflammatory processes relevant to these clinical features include airway edema (secondary to inflammation), overproduction of airway mucus (driven by IL-13 activity), and airway mucus plugging (from IL-13 driven mucus production and IL-5 driven eosinophil recruitment and activation) [38–40]. Additionally, IL-13 can have a direct effect on airway smooth muscle tone [41, 42].

A primary limitation of this review is that the data are from different studies with different patient populations. For example, inclusion of adolescent patients, the specific dosage of ICS required for enrollment, inclusion of patients receiving daily OCS, study duration, and enrollment stratification methodologies varied across studies. We restricted the included studies to RCTs in severe, uncontrolled asthma with exacerbation rate reduction as the primary or a

secondary endpoint, in an attempt to obtain the most analogous data for the different biologics. We could not address the effects of study design differences in the current analysis, which was limited to published data. Given the differences across studies, comparisons are most robust between subgroups within a single study. Comparisons across studies are most valuable in describing what evidence exists and in which groups efficacy has been observed. Several of the subgroups reported are overlapping (e.g., BEC $\geq$ 150 cells/μL and BEC 150 to < 300 cells/μL), as we chose to report all available information for transparency and to avoid bias from prioritizing some subgroups over others. In the case of overlapping subgroups, the more specific subgroups are the most informative, because results from larger subgroups can obscure differences within the subgroup; for example, lower efficacy among patients with BEC 150 to < 300 cells/μL will not be perceptible in an analysis of patients with BEC $\geq$ 150 cells/μL where efficacy among patients with BEC $\geq$ 300 cells/μL is averaged with efficacy among patients with BEC 150 to < 300 cells/μL. Another limitation of our review is that many of the included studies were not prospectively powered for eosinophil subgroup analyses. Regarding minimum clinically important differences (MCIDs), this review acknowledges the available literature regarding the MCID for AAER reduction, which was the primary endpoint of interest. However, for the secondary outcomes of pre-BD FEV_1, ACQ, and AQLQ, the MCIDs are validated to be applied at the patient level for the change over time, and are best summarized in a population as the proportion achieving the MCID threshold response. The MCIDs for these outcomes are not validated to be applied to population mean responses with treatment versus placebo, which is how results are reported for randomized clinical trials and thus in this review. For this reason, our review does not discuss MCIDs for secondary outcomes. Lastly, data availability was a further issue, particularly for outcomes other than AAER, for which limited data were published for some BEC subgroups.

CONCLUSION

This systematic review of RCTs demonstrates that the efficacy of biologics in patients with severe, uncontrolled asthma in reducing exacerbations and improving lung function, asthma control, and health-related quality of life varies with baseline BEC. This differential efficacy was most pronounced for biologics targeting T2 inflammatory pathways (eosinophilic and/or allergic inflammation). All biologics generally demonstrated efficacy in reducing exacerbations and improving other outcomes in patients with baseline BEC $\geq$ 150, $\geq$ 300, or $\geq$ 450 cells/μL. However, efficacy was not generally observed in patients with baseline BEC 0 to < 300, 150 to < 300, or 0 to < 150 cells/μL. Tezepelumab was the only biologic to consistently demonstrate efficacy in lower BEC subgroups.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the contributions of J. Mark FitzGerald, MD, MB, FCCP, FRCPI, FRCPC, to the conception and development of this manuscript. Dr FitzGerald passed away before the manuscript was finalized.

Funding. This study and the journal's Rapid Service and Open Access Fees were funded by AstraZeneca, Wilmington, DE, USA, and Amgen Inc., Thousand Oaks, CA, USA.

Medical Writing Assistance. Medical writing support was provided by Richard Claes, PhD, of PharmaGenesis London, London, UK, with funding from AstraZeneca and Amgen Inc.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Author Contributions. Stephanie Korn, Bill Cook, Lisa J. Simpson, Jean-Pierre Llanos, and

Christopher S. Ambrose significantly contributed to development of the search string and manuscript content, and critically reviewed each draft of the manuscript. Lisa J. Simpson completed the literature search, article screen, and data extraction. All authors approved the final version of the submitted manuscript.

Prior Presentation. Findings from this systematic review were previously presented in a poster at the American College of Allergy, Asthma and Immunology Annual Meeting, 4–8 November 2021; New Orleans, LA, USA.

Disclosures. Stephanie Korn has received fees for lectures and/or advisory board meetings from AstraZeneca, GSK, Novartis, Roche, Sanofi-Aventis, and Teva Pharmaceuticals. Bill Cook and Christopher S. Ambrose are employees of AstraZeneca and may own stock or stock options in AstraZeneca. Lisa J. Simpson is an employee of PharmaGenesis London, a HealthScience communications consultancy. Jean-Pierre Llanos is an employee of Amgen and owns stock in Amgen.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data Availability. All data generated or analyzed during this study are included as supplementary information files.

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