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In an indirect treatment comparison with matched populations, benralizumab and mepolizumab had comparable efficacy http://ow.ly/e5kC30md39F

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ABSTRACT Benralizumab is an interleukin-5 receptor α-directed cytolytic monoclonal antibody that directly depletes eosinophils. Its relative efficacy *versus* other IL-5-targeted treatments for patients with severe, uncontrolled asthma is not yet fully characterised.

We performed a matching-adjusted indirect comparison (MAIC) of benralizumab *versus* mepolizumab and reslizumab. Trials were selected through systematic review and evaluation of trial methods. Benralizumab patient-level data were weighted to match treatment-effect-modifying patient characteristics of comparator trials before indirect efficacy comparisons.

After matching adjustment, benralizumab and mepolizumab reduced exacerbations *versus* placebo by 52% and 49%, respectively (rate ratio [RR] 0.94, 95% CI 0.78–1.13; n=1524) and reduced the rate of exacerbations requiring hospitalisation/emergency department visit by 52% and 52%, respectively (RR 1.00, 95% CI 0.57–1.75; n=1524). Benralizumab and mepolizumab similarly improved pre-bronchodilator forced expiratory volume in 1 s at 32 weeks (difference 0.03 L, 95% CI −0.06–0.12; n=1443). Benralizumab and reslizumab patient populations were too dissimilar to generate a sufficient effective sample size to produce a reliable estimate for MAIC.

MAIC is a robust way to indirectly compare treatment efficacies from trials with heterogeneous patient populations. When baseline patient characteristics were matched across asthma trials, benralizumab and mepolizumab yielded similar efficacy.

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Introduction

Patients with severe asthma have frequent exacerbations and hospitalisations [1, 2], a substantial cost burden [3, 4] and residual symptoms despite use of high-dosage inhaled corticosteroids (ICS) plus a second controller medication [2, 5]. The anti-interleukin (IL)-5 monoclonal antibodies reslizumab [6] and mepolizumab [7] and the IL-5 receptor α (IL-5Rα)-directed cytolytic monoclonal antibody benralizumab [8] have demonstrated efficacy for patients with severe, uncontrolled asthma with an eosinophilic phenotype [9–13].

Data on the comparative efficacy of treatments would be valuable for clinicians making decisions about patients who are potential candidates for IL-5Rα or anti-IL-5 treatments. However, these biologics have not been compared in head-to-head clinical trials, limiting interpretations regarding their relative benefits and harms. In lieu of direct comparisons, indirect treatment comparisons (ITCs), including network meta-analyses (NMAs), can be performed to estimate effects using a common comparator, such as standard-of-care treatment and/or placebo. Meta-analyses have also been used to indirectly compare the efficacy and safety of benralizumab, mepolizumab and reslizumab, and concluded that no treatment was clearly superior [14, 15].

One important limitation in the interpretation of recent attempts at indirect comparison of IL-5Rα or anti-IL-5 therapies [16] is that the studies used aggregate data sources that may lead to biased estimates, because they do not take into account important between-trial differences. A key requirement of ITCs (and NMAs) is that included studies have sufficiently similar designs, treatment durations and patient baseline characteristics to justify cross-study comparisons. Baseline asthma severity, eosinophil count and exacerbation history, for example, are all important modulators of asthma treatment efficacy. If these differ across trials for each IL-5Rα or anti-IL-5 monoclonal antibody development programme because of different inclusion or exclusion criteria, the indirect comparison estimate may be erroneous or biased.

Matching-adjusted indirect comparisons (MAICs) are a form of population-adjusted ITC that attempt to reduce bias in treatment comparisons by matching patient-level data from the clinical trials of one treatment to aggregate data reported for comparator trials [17]. Treatment-effect-modifying variables that differ across studies, *e.g.* baseline exacerbation history, are used to weight the patient-level data to reflect the characteristics of the comparator's patient population. Data from patients who had exacerbation rates similar to the aggregate of the comparator population are weighted more heavily when modelling study outcomes, similar to a propensity score. Data from patients who are quite different from the comparator population would have less weight on the outcome. This matching adjustment simulates the results as if the treatments being compared were both tested in the same patient population [17].

MAIC analyses have been conducted for biologics across a variety of therapeutic areas, including haemophilia [18], psoriasis [19] and multiple myeloma [20]. The objective of this study was to perform a MAIC of benralizumab *versus* IL-5-directed monoclonal antibodies for the treatment of patients with severe, uncontrolled asthma and with an eosinophilic phenotype.

Methods

Overview

This MAIC analysis was conducted according to the National Institute for Health and Care Excellence (NICE) Technical Support Document (TSD) guidance [21] for a robust, population-adjusted ITC. This required the identification of randomised controlled studies of IL-5Rα/anti-IL-5 treatments with similar study methods. Studies were identified through systematic review. We then applied stringent requirements for MAIC analysis, which required narrowing the selection of trials, as described below. To perform matching of the benralizumab population to the comparator treatment populations, we used several steps to identify variables that were known to modify treatment effects. Data from patients in the benralizumab population were then weighted to reflect the treatment-effect-modifying characteristics in the comparator populations. To evaluate the success of the weighting techniques, we compared the benralizumab population's adjusted baseline characteristics with the comparator's characteristics, as reported in the literature. Relative treatment effects could then be evaluated across comparators in ITCs.

Study selection and data extraction

Further details on the methods for the systematic review are detailed in appendix 1. The systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [22], and the requirements of health technology appraisal organisations in the UK, Germany, France and the USA. MEDLINE, EMBASE, MEDLINE In-Process and CENTRAL databases were searched using a combination of medical subject headings and free-text terms to identify English-language articles of relevant studies of biologics in moderate to severe uncontrolled asthma. Searches were conducted from database

inception to August 2016 (search date). Conference abstracts were included and identified *via* EMBASE or hand searching of the relevant conference website.

All studies included the following outcomes, which were chosen to reflect their clinical significance in severe asthma, inclusion as primary endpoints in severe asthma trials and availability of data across trials: annual rate of clinically significant exacerbations, annual rate of exacerbations requiring emergency department (ED) visit or hospitalisation, and pre-bronchodilator forced expiratory volume in 1 s (FEV_1). Because definitions of exacerbation might differ, we included only trials in which the definition of exacerbation included worsening of asthma symptoms leading to use of systemic corticosteroids and an urgent care/ED visit or hospitalisation.

Citations identified through literature searches were screened for inclusion on the following prospectively defined criteria: randomised controlled trials comparing IL-5Rα/anti-IL-5 treatments with placebo for patients with severe, uncontrolled asthma receiving medium- or high-dosage ICS plus an additional controller medication. Two independent reviewers performed screening and data extraction activities with discrepancies reconciled by a third independent reviewer.

Assessment of risk of bias

The risk of bias was assessed using a NICE checklist [23]. Sources of clinical heterogeneity were summarised and assessed. Each study was graded as having a high, low or unclear risk of bias.

Data analysis

Exacerbation rate outcomes were estimated as rate ratios (RR) for monoclonal antibody treatments *versus* placebo. Change in FEV_1 was estimated as the mean difference between monoclonal antibody treatments and placebo. Studies were evaluated in detail for differences in study methods, presence of potential treatment-effect-modifying patient characteristics, and availability of variables and outcomes of interest in the treatment comparisons. Variables that we believed made findings uninterpretable because of between-trial variability were identified through elicitation of opinion from asthma experts, a literature review, and univariate and multivariate analyses of SIROCCO [9] and CALIMA data [11]. Eligibility criteria were then refined to increase the face validity of comparisons.

All analyses were conducted using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA) and R version 3.0.3 (R Foundation for Statistical Computing, Vienna).

Matching-adjusted indirect comparison analyses

To enable valid treatment comparison across trials, we used matching procedures to weight benralizumab patient characteristics to reflect the comparator populations. An anchoring method was used for the population-adjusted indirect comparisons, which is further described in appendix 1, figure S2. Matching variables were selected for their clinical and statistical importance in explaining variability in the outcomes of interest and their demonstrated imbalance between the SIROCCO/CALIMA [9, 11] and comparator populations, as described in appendix 1.

Data adjustments

SIROCCO/CALIMA [9, 11] individual patient data were weighted based on the relevant aggregate baseline characteristics from the mepolizumab or reslizumab studies. Variables were adjusted by estimating a logistic propensity score model that was conditional on the treatment-effect modifiers identified previously for comparison with either mepolizumab or reslizumab. Individuals were weighted by the inverse of their propensity score [21].

Effective sample size

After matching, and as part of the treatment comparison for each outcome, we evaluated effective sample size (ESS). A small ESS is an indication that the weighted population (*i.e.* from the benralizumab trials) and non-weighted population (*i.e.* from the mepolizumab or reslizumab trials) have little overlap, which may result in unstable, invalid estimates [21].

Treatment comparisons

The final step was to estimate the relative treatment effects of benralizumab and the comparator included in the MAIC using standard ITC methodologies [24]. For the MAIC analysis, treatment differences of each intervention against placebo were used to derive the anchored ITCs for each outcome, rate of exacerbations, rate of exacerbations resulting in hospitalisation or ED visits and change in FEV_1.

Sensitivity analysis

The mepolizumab MUSCA trial [25] was not included in the systematic review because it was unpublished at the time. However, MUSCA data were included in a set of sensitivity analyses at week 24 (appendix 1).

Results

Study selection and variability assessment

This systematic review identified 32 studies. Figure 1 presents the flow of studies for eligibility in the systematic review and ITC. We identified important variability across study methods, including patient selection criteria (such as disease severity, exacerbation history and eosinophil count), primary outcome measure, sample size, study length, ICS dosage during the studies and oral corticosteroid (OCS) background. Therefore, additional criteria were applied to narrow the studies, treatment arms or patients included in the analysis. Only phase 3 studies with a primary endpoint of reduction in asthma exacerbations were included.

For each pairwise treatment comparison, we established a standard ICS dosage. For the benralizumab *versus* mepolizumab comparison, only patients who received high-dosage ICS (fluticasone propionate (FP) $\geqslant$880 μg·day^{-1}) were included; patients in the benralizumab trials who received smaller dosages were excluded. Because no reslizumab studies used high-dosage ICS, we widened the criterion for the benralizumab *versus* reslizumab comparison. Reslizumab Study 3082 and Study 3083 [10] were included, in which patients received medium- to high-dosage ICS. For this analysis only, patients in the benralizumab CALIMA study [11] who received medium- to high-dosage ICS were also included.

Evidence networks for MAIC analysis

The evidence networks generated for the placebo-anchored comparison of benralizumab *versus* mepolizumab included the benralizumab SIROCCO [9] and CALIMA [11] trials and the mepolizumab MENSA [12] and DREAM [13] trials. The evidence network for the placebo-anchored comparison of benralizumab *versus* reslizumab included the benralizumab SIROCCO [9] and CALIMA [11] trials and the reslizumab Study 3082 and Study 3083 trials [10] (appendix 2, figure S3). In studies with several treatment arms, only active treatment arms that used licenced (European and USA) dosages were included. Mepolizumab 75 mg administered intravenously every 4 weeks is bioequivalent to the approved dosage of 100 mg administered subcutaneously every 4 weeks. Therefore, these two dosages were pooled. Data for benralizumab were obtained by pooling the individual patient data from the SIROCCO and CALIMA trials (patients who received FP $\geqslant$880 μg·day^{-1} for the mepolizumab comparison and patients who received FP $\geqslant$500 μg·day^{-1} for the reslizumab comparison). Aggregate data for mepolizumab were pooled from the clinical study reports for MENSA and DREAM (mepolizumab 75-mg data pooled from MENSA and DREAM; mepolizumab 100-mg data from MENSA). Aggregate results for reslizumab came from publications of Study 3082 and Study 3083 [10]. Study details for benralizumab, mepolizumab and reslizumab are presented in appendix 2, table S4.

Benralizumab versus *mepolizumab comparison*

Baseline characteristics and ESS

For the benralizumab *versus* mepolizumab comparison, the following variables were selected for matching: eosinophil count ($\geqslant$300 cells·μL^{-1} *versus* <300 cells·μL^{-1}), IgE count (<30 IU·mL^{-1} *versus* >30–$\leqslant$700 IU·mL^{-1} *versus* >700 IU·mL^{-1}), exacerbations in the previous 12 months (two *versus* more than two), presence of nasal polyps, mean body mass index, sex and maintenance OCS use (table 1).

For change in FEV_1 for benralizumab *versus* mepolizumab, the main analysis was conducted from baseline to week 32 because each of the four trials included had FEV_1 data at week 32. Because the MENSA trial was shorter than the other trials (32 weeks *versus* 52 weeks for DREAM, 48 weeks for SIROCCO and 56 weeks for CALIMA), two additional analyses of change in FEV_1 were conducted, one evaluating change from baseline to the end of each trial and the other evaluating change from baseline to the end of each trial after excluding the MENSA study from the analysis.

After adjustment for the mepolizumab MENSA/DREAM population characteristics, benralizumab SIROCCO/CALIMA baseline characteristics were well matched to the mepolizumab population for the analyses of exacerbations (table 2) and the analyses of change in FEV_1 at week 32 (table 3), end of each study (appendix 2, table S5) and end of each study excluding MENSA (appendix 2, table S6).

As a result of matching, the benralizumab population ESS decreased from 959 to 639 in the exacerbation comparison. When the benralizumab population was matched for the FEV_1 comparisons, ESS was reduced from 863 to 559 (32-week comparison), from 838 to 540 (end-of-study comparison) and 838 to 402 (end-of-study comparison excluding MENSA). These adjusted ESSs were adequate for robust MAIC analyses according to the NICE TSD [21].

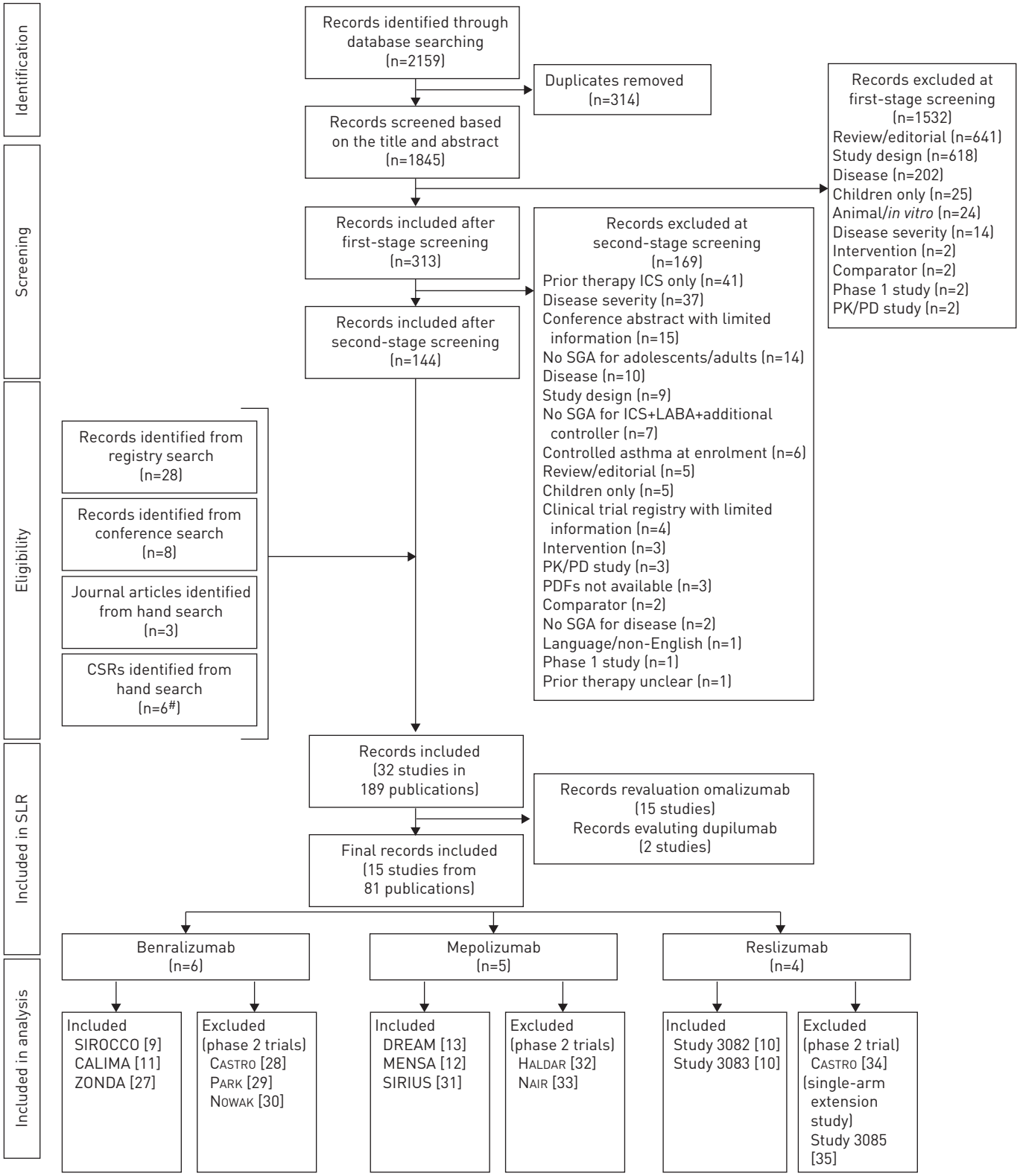

FIGURE 1 Flow of citations for inclusion in matching-adjusted indirect comparison. PK: pharmacokinetics; PD: pharmacodynamics; PDF: portable document format; ICS: inhaled corticosteroid; SGA: subgroup analysis; LABA: long-acting β_2-agonist; CSR: clinical study report; SLR: systematic literature review. #: includes benralizumab clinical study reports (SIROCCO, CALIMA, ZONDA).

TABLE 1 Comparison of baseline characteristics of patients included in benralizumab (SIROCCO, CALIMA) and mepolizumab (MENSA, DREAM) studies

Characteristics	SIROCCO		CALIMA (only high-dosage ICS subgroup)		MENSA			DREAM	
	Benralizumab Q8W	Placebo	Benralizumab Q8W	Placebo	Mepolizumab 100 mg SC	Mepolizumab 75 mg IV	Placebo	Mepolizumab 75 mg IV	Placebo
Patients n	398	407	364	370	194	191	191	153	155
Age mean±SD years	47.6±14.5	48.7±14.9	50.1±13.3	49.8±14.3	51.2±14.55	50.0±14.03	49.2±14.26	50.2±11.3	46.4±10.8
Male sex %	36.7	33.9	38.2	40.3	40.0	45.0	44.0	32.0	37.0
Race %									
White	72.1	74.2	85.2	86.8	77.0	79.0	77.0	91.0	90.0
Black	3.8	3.9	3.6	3.2	4.0	3.0	2.0	3.0	4.0
Asian	12.6	12.3	11.0	10.0	18.0	17.0	20.0	5.0	6.0
Other	11.6	9.6	0.3	0.0	1.0	1.0	1.0	1.0	0.0
BMI mean±SD kg·m^{-2}	28.21±6.18	28.93±7.07	29.0±6.5	29.25±6.54	27.60±5.58	27.68±5.68	28.04±5.58	28.4±6.0	28.3±6.1
FEV_1 % pred mean	56.1[#]	56.6[#]	56.9	57.5	59.3	61.4	62.4	60[#]	59[#]
Morning PEF mean L·min^{-1}	233.12	230.83	241.85	242.16	255.3	268.6	277	-	-
FEV_1/FVC %	65	66	64	65	63	64	64	68	67
FEV_1 pre-bronchodilator L	1.68	1.66	1.72	1.76	1.73	1.85	1.86	1.81[#]	1.90[#]
Reversibility %	27.2	25.5	25.1	27.2	27.9[#]	25.4[#]	27.4[#]	22.6[¶]	26.8[¶]
ACQ score[+]	2.8	2.87	2.82	2.73	2.26	2.12	2.28	2.2	2.5
Exacerbations in previous year									
Mean n	**2.8**	**3**	**2.7**	**2.8**	**3.8**	**3.5**	**3.6**	**>3[§]**	**>3[§]**
2 exacerbations %	**63.3**	**60**	**62.9**	**63.5**	**38**	**43**	**47**	**46**	**42**
⩾3 exacerbations %	**36.68**	**40**	**36.81**	**36.49**	**61.86**	**57.07**	**52.88**	**54**	**57**
Never smokers %	82.2	80.6	78.02[#]	78.92[#,f]	74[#,f]	73[#]	70[#]	80[#]	78[#]
OCS use %	**17.8**	**16.2**	**10.71[#]**	**11.08[#,f]**	**27[#,f]**	**25[#]**	**23[#]**	**30.07[#]**	**29.03[#]**
EOS ⩾300 cells·μL^{-1} %	**67.08**	**65.6**	**65.6**	**67.02**	**51.5**	**53.4**	**55.4**	**56.2**	**45.16**
EOS <300 cells·μL^{-1} %	**32.9**	**34.3**	**34.3**	**32.9**	**47.4**	**45.02**	**43.4**	**43.7**	**54.8**
EOS count mean cells·μL^{-1}	469.8	456.5	463.4	490.8	290[##]	280[##]	320[##]	250[##]	280[##]
IgE concentration IU·mL^{-1}	-	-	-	-	149.72[##]	180.32[##]	150.12[##]	-	-
Atopic status %	61.3	56.5	61.5	63.0	-	-	-	51.0	52.0
Nasal polyps %	19.0	19.0	16.8	18.1	14.4	16.7	17.2	7.0	10.0

Data in bold indicate differences across benralizumab and mepolizumab trials. For cells with no data listed, none were available. ICS: inhaled corticosteroid; Q8W: every 8 weeks (first three doses every 4 weeks); SC: subcutaneous; IV: intravenous; BMI: body mass index; FEV_1: forced expiratory volume in 1 s; PEF: peak expiratory flow; FVC: forced vital capacity; ACQ: Asthma Control Questionnaire; OCS: oral corticosteroid; EOS: eosinophil. [#]: data extracted from publications rather than clinical study reports; [¶]: data reported at screening visit; [+]: ACQ-6 in SIROCCO, CALIMA and DREAM, and ACQ-5 in MENSA; [§]: calculated from the reported frequency of exacerbations; [f]: calculated from the reported subgroup data; [##]: geometric means.

TABLE 2 Baseline characteristics of patients before and after matching for the analysis of annual rate of clinically significant exacerbations and annual rate of exacerbations leading to ED visit or hospitalisation

Baseline characteristics	SIROCCO/CALIMA (before adjustment)[#]	MENSA/DREAM (aggregate reported data)	SIROCCO/CALIMA (after adjustment)
	Benralizumab Q8, placebo	Mepolizumab 75 mg IV, mepolizumab 100 mg SC, placebo	Benralizumab Q8W, placebo
Patients n	959	884	639[¶]
Eosinophil count			
⩾300 cells·μL^{-1}	67.05	52.45	52.75
<300 cells·μL^{-1}	32.95	47.55	47.25
Maintenance oral corticosteroid use			
Yes	15.22	26.58[+]	30.18
No use	84.78	73.42[+]	69.82
IgE count			
<30 IU·mL^{-1}	11.55	13.29	14.66
⩾30–⩽700 IU·mL^{-1}	71.19	70.35	70.02
>700 IU·mL^{-1}	17.27	16.35	15.32
Sex			
Male	36.60	40.05	39.2
Female	63.40	59.95	60.8
Exacerbations in the previous year			
2	61.63	42.99	42.69
>2	38.38	56.79	57.31
Nasal polyps			
No	81.33	86.83	83.44
Yes	18.67	13.17	16.56
BMI mean±SD kg·m^{-2}	29.89±6.27	27.98±5.912	28.37±6.13

Data are presented as %, unless otherwise stated. ED: emergency department; Q8W: every 8 weeks (first three doses every 4 weeks); IV: intravenous; SC: subcutaneous; BMI: body mass index. [#]: includes only patients receiving fluticasone propionate ⩾880 μg·day^{-1}; [¶]: effective sample size; [+]: data extracted from publications rather than clinical study reports.

Annual rate of clinically significant exacerbations

Benralizumab treatment reduced the annual rate of clinically significant exacerbations *versus* placebo by 46% (RR=0.54) in SIROCCO/CALIMA before matching adjustment, and by 52% (RR=0.48) after matching adjustment to the mepolizumab patient population (table 4). Mepolizumab reduced the exacerbation rate in MENSA/DREAM by 49% (RR=0.51) *versus* placebo.

Indirect comparison of benralizumab *versus* mepolizumab after the matching adjustment indicated that benralizumab resulted in a comparable reduction in clinically significant exacerbations to mepolizumab (6% greater exacerbation reduction, RR=0.94, 95% CI 0.78–1.13, after adjustment). The two treatments were not statistically significantly different in their effects on exacerbations either before or after the matching adjustment (figure 2).

Annual rate of asthma exacerbations resulting in ED visit or hospitalisation

Benralizumab treatment reduced the rate of clinically significant exacerbations leading to ED visit or hospitalisation *versus* placebo by 35% (RR=0.65) in SIROCCO/CALIMA before matching adjustment to the mepolizumab patient population and by 52% (RR=0.48) after matching adjustment (table 4). Mepolizumab reduced the exacerbation rate in MENSA/DREAM by 52% (RR=0.48) *versus* placebo.

Indirect comparison of benralizumab *versus* mepolizumab after matching adjustment indicated comparable efficacy of benralizumab and mepolizumab for reducing exacerbations requiring ED visit or hospitalisation (RR=1.0) (figure 2).

Pre-bronchodilator FEV1

Before and after matching, benralizumab demonstrated a small improvement compared with mepolizumab in change in pre-bronchodilator FEV1 at all time points (table 4). For example, from baseline to week 32 for benralizumab, after matching, the improvement was 0.10 L (95% CI 0.04–0.17) *versus* 0.07 L (95% CI 0.02–0.13) for mepolizumab. The extent of FEV1 improvement associated with benralizumab treatment was comparable before and after matching for analyses at 32 weeks, at the end of the studies and at the end of the studies excluding MENSA (figure 2).

TABLE 3 Comparison of baseline characteristics of patients before and after matching for the analysis of change from baseline pre-bronchodilator FEV_1 at 32 weeks

Baseline characteristics	SIROCCO/CALIMA[#] (before adjustment)	MENSA/DREAM (aggregate reported data)	SIROCCO/CALIMA (after adjustment)
	Benralizumab Q8W, placebo	Mepolizumab 75 mg IV, mepolizumab 100 mg SC, placebo	Benralizumab Q8W, placebo
Patients n	863	884	559[¶]
Eosinophil count			
⩾300 cells·μL^{-1}	68.02	52.45	52.43
<300 cells·μL^{-1}	31.98	47.55	47.57
Maintenance OCS use			
Yes	15.06	26.58[+]	30.24
No	84.94	73.42[+]	69.76
IgE count			
<30 IU·mL^{-1}	11.40	13.29	14.62
⩾30–⩽700 IU·mL^{-1}	71.09	70.35	70.01
>700 IU·mL^{-1}	17.51	16.35	15.37
Sex			
Male	37.43	40.05	39.08
Female	62.57	59.95	60.92
Exacerbations in previous year			
2	62.34	42.99	42.82
>2	37.66	56.79	57.18
Nasal polyps			
No	81.23	86.83	83.09
Yes	18.77	13.17	16.91
BMI mean±SD kg·m^{-2}	28.89±6.27	27.98±5.912	28.38±6.15

Data are presented as %, unless otherwise stated. FEV_1: forced expiratory volume in 1 s; Q8W: every 8 weeks (first three doses every 4 weeks); IV: intravenous; SC: subcutaneous; OCS: oral corticosteroid; BMI: body mass index. [#]: includes only patients receiving fluticasone propionate ⩾880 μg·day^{-1}; [¶]: effective sample size; [+]: data extracted from publications rather than clinical study reports.

Sensitivity analyses

In the set of sensitivity analyses that included the MUSCA trial, relative efficacy results for exacerbations and FEV_1 were similar to those of the main MAIC analyses (appendix 2, tables S7 and S8).

TABLE 4 Benralizumab *versus* mepolizumab: matched and unmatched treatment comparisons of clinically significant asthma exacerbations and asthma exacerbations resulting in ED visit or hospitalisation, and change from baseline in pre-bronchodilator FEV_1

Efficacy outcome	Treatment comparison		
	SIROCCO/CALIMA[#]	MENSA/DREAM	SIROCCO/CALIMA
	Benralizumab Q8W *versus* placebo (no matching adjustment)[#]	Mepolizumab *versus* placebo	Benralizumab Q8W *versus* placebo (with matching adjustment)
Annualised rate of asthma exacerbations[¶]			
Clinically significant exacerbations	0.54 (0.47–0.61)	0.51 (0.44–0.58)	0.48 (0.43–0.55)
Exacerbations resulting in ED visit or hospitalisation	0.65 (0.46–0.93)	0.48 (0.31–0.73)	0.48 (0.33–0.68)
Change in pre-bronchodilator FEV_1 L[+]			
From baseline to week 32	0.11 (0.05–0.18)	0.07 (0.02–0.13)	0.10 (0.04–0.17)
From baseline to end of study[§]	0.11 (0.05–0.18)	0.09 (0.04–0.14)	0.11 (0.04–0.17)
From baseline to end of study, excluding data from MENSA	0.11 (0.05–0.18)	0.06 (–0.04–0.16)[f]	0.09 (0.03–0.14)[#]

ED: emergency department; FEV_1: forced expiratory volume in 1 s; Q8W: every 8 weeks (first three doses every 4 weeks). [#]: includes only patients receiving fluticasone propionate ⩾880 μg·day^{-1}; [¶]: data presented as rate ratio (95% CI); [+]: data presented as mean (95% CI); [§]: end of study was at the following time points: SIROCCO, 48 weeks; CALIMA, 56 weeks; MENSA, 32 weeks; DREAM, 52 weeks; [f]: comparison excludes MENSA, includes DREAM mepolizumab 75 mg intravenous *versus* placebo; [##]: comparison includes matching adjustment to DREAM only.

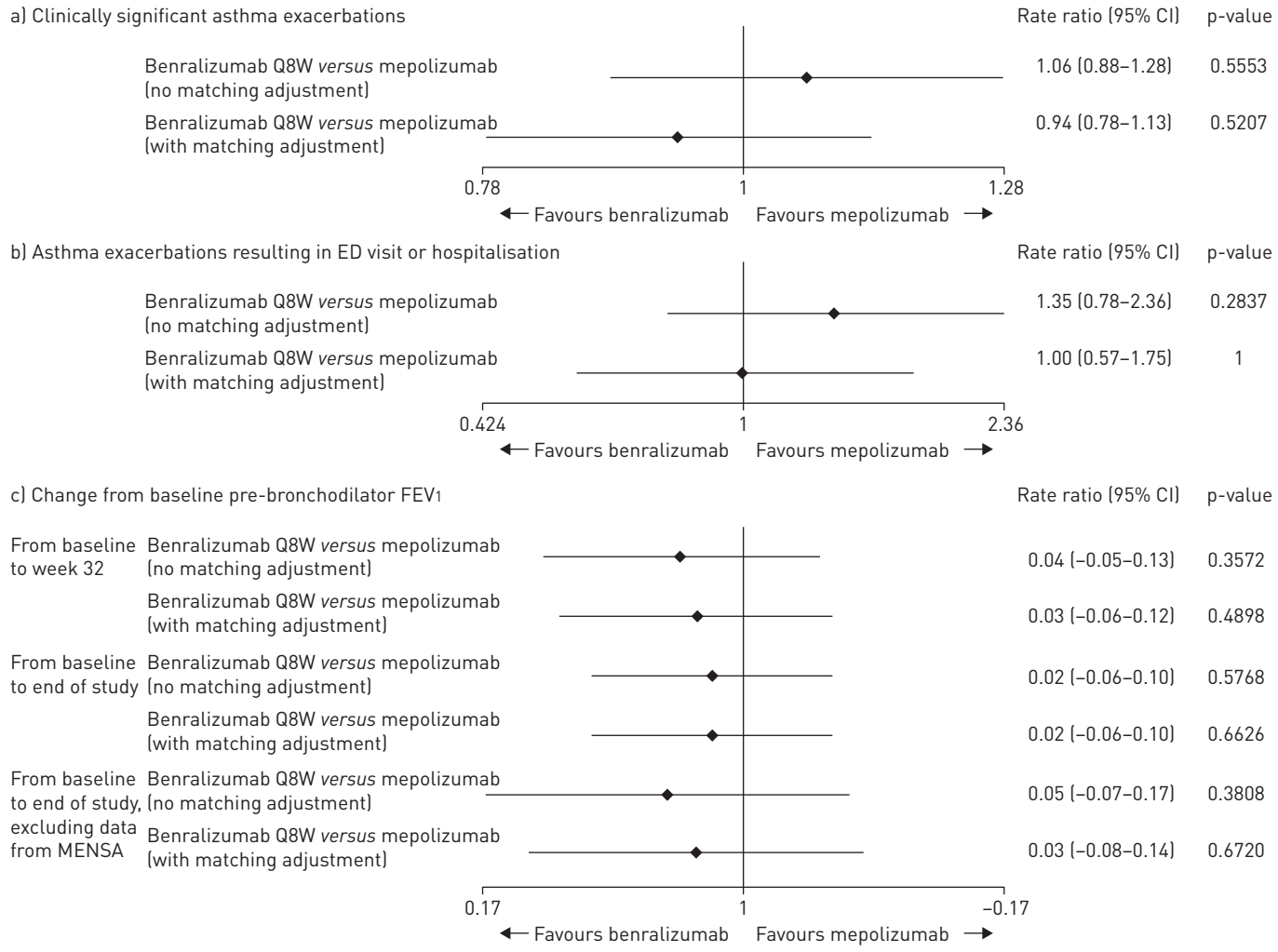

FIGURE 2 Rate ratios from indirect treatment comparisons of benralizumab and mepolizumab for a) clinically significant asthma exacerbations, b) asthma exacerbations resulting in emergency department (ED) visit or hospitalisation and c) change from baseline pre-bronchodilator forced expiratory volume in 1 s (FEV_1). Q8W: every 8 weeks (first three doses every 4 weeks).

Benralizumab versus *reslizumab comparison*

For the benralizumab *versus* reslizumab comparison, the following variables were selected for matching: mean baseline eosinophil count, mean number of exacerbations in the previous 12 months, sex and maintenance OCS use (table 5).

Matching the benralizumab SIROCCO/CALIMA dataset to the reslizumab population resulted in a 99% reduction in the ESS, from 1668 to 20 (table 6), indicating very little overlap in the treatment characteristics of the patient populations. The small ESS of 20 patients was not sufficient to support a robust MAIC between benralizumab and reslizumab.

Discussion

Our study compared exacerbation and lung function outcomes of benralizumab treatment with outcomes for other IL-5-directed biologics for severe, uncontrolled asthma. Results of the comparison between benralizumab and mepolizumab demonstrated comparable efficacy in reducing the annual rate of clinically significant exacerbations and exacerbations leading to ED visits or hospitalisation and improving pre-bronchodilator FEV_1. In most comparisons, benralizumab was numerically better than mepolizumab after matching adjustment balanced baseline characteristics between the two populations, although there were no significant differences. This analysis extends findings from recent systematic review methods [26] and expands upon evidence from a recent ITC of IL-5-directed monoclonal antibody treatments by Cabon *et al.* [15] that did not include the key benralizumab phase 3 SIROCCO [9] and CALIMA [11] trials used in our analysis and did not adjust for differences in baseline patient characteristics. Cabon *et al.* [15] also included heterogeneity across studies that was restricted in our analysis, including treatment arms with

TABLE 5 Comparison of baseline characteristics of patients included in benralizumab (SIROCCO, CALIMA) and reslizumab (Study 3082 and Study 3083) studies

Characteristics	SIROCCO (high-dosage ICS)		CALIMA (medium- to high-dosage ICS)		Study 3082 (medium- to high-dosage ICS)		Study 3083 (medium- to high-dosage ICS)		Study 3082 and Study 3083 (pooled) (medium- to high-dosage ICS)	
	Benralizumab Q8W	Placebo	Benralizumab Q8W	Placebo	Reslizumab 3 mg·kg^{-1}	Placebo	Reslizumab 3 mg·kg^{-1}	Placebo	Reslizumab 3 mg·kg^{-1}	Placebo
Patients n	398	407	441	440	245	244	232	232	477	476
Ag mean±SD years	47.6±14.5	48.7±14.9	49.0±14.3	48.8±15.1	46.6±13.8[¶]	46.7±14.8[¶]	46.4±13.8[¶]	47.5±13.6[¶]	-	-
Male sex %	36.7	33.9	38.1	40.0	42.0	34.0	38.0	35.0	40.04	34.45
BMI mean±SD kg·m^{-2}	28.21±6.18	28.93±7.07	29.0±6.5	29.25±6.54	27.7±6.3	28±6.2	27±5.1	27±5.3	-	-
FEV$_1$ % pred mean	56.1[+]	56.6[+]	57.9	58.0	63.6	65.0	70.4	68.0	-	-
Reversibility % mean	27.2	25.5	24.6	27.3	26.1	26.3	28.1	28.7	-	-
ACQ score mean[#]	2.8	2.87	2.82	2.73	2.66	2.76	2.57	2.61	-	-
Never smokers %	82.2	80.6	78.9	79.3	-	-	-	-	-	-
OCS use %	17.8	16.2	10.0	8.9	19.0	19.0	12.0	12.0	-	-
EOS count cells·μL^{-1} mean	**469.8**	**456.5**	**465.1**	**487.5**	**696.0**	**624.0**	**610.0**	**688.0**	-	-
Exacerbations in previous year										
Mean	2.8	3	2.7	2.8	1.9	2.1	1.9	2.0	-	-
1 exacerbation %	**0.0**	**0.0**	**0.2**[§]	**0.0**	-	-	-	-	**58.07**	**59.24**
2 exacerbations %	63.3	60.0	65.1	65.5	-	-	-	-	18.03	22.48
⩾3 exacerbations %	19.8	18.7	21.1	21.1	-	-	-	-	9.22	7.56
⩾4 exacerbations %	16.9	21.3	13.6	13.4	-	-	-	-	14.05	10.08
Omalizumab use %	7.0	7.6	2.7	3.8	-	-	-	-	-	-
Nasal polyps %	19.0[+]	19.0[+]	16.8	18.1	-	-	-	-	-	-

Data in bold indicate differences across benralizumab and reslizumab studies. For cells with no data listed, none were available. ICS: inhaled corticosteroid; Q8W: every 8 weeks (first three doses every 4 weeks); BMI: body mass index; FEV$_1$: forced expiratory volume in 1 s; ACQ: Asthma Control Questionnaire; OCS: oral corticosteroid; EOS: eosinophil. [#]: ACQ-5 in benralizumab trials and ACQ-7 in reslizumab trials; [¶]: extracted from reslizumab National Institute for Health and Care Excellence single technology appraisal, all other data for reslizumab trials are extracted from publications; [+]: data extracted from publications rather than clinical study reports; [§]: one patient in CALIMA had one exacerbation in the past year.

TABLE 6 Baseline characteristics of SIROCCO/CALIMA before and after matching to the population of reslizumab Study 3082 and Study 3083

Baseline characteristics	SIROCCO/CALIMA (before adjustment)	Study 3082 and Study 3083 (aggregate reported data)	SIROCCO/CALIMA (after adjustment)
	Benralizumab Q8W, placebo (medium- to high-dosage ICS)	Reslizumab 3 mg·kg^{-1}, placebo (medium- to high-dosage ICS)	
Patients n	1668	953	20[#]
Sex			
Male	37.35	37.25	37.25
Female	62.65	62.75	62.75
OCS use at baseline			
No	86.69	84.50	84.50
Yes	13.31	15.50	15.50
EOS count	456.22±402.28	654.68±628.74	654.68±247.39
Exacerbations in previous year	2.76±1.53	1.98±1.85	1.98±0.73

Data presented as % or mean±SD. Data for Study 3082 and Study 3083 were extracted from publications. Q8W: every 8 weeks (first three doses every 4 weeks); ICS: inhaled corticosteroid; OCS: oral corticosteroid; EOS: eosinophil. [#]: effective sample size.

monoclonal antibody dosages not licenced in Europe and the USA and widely varying treatment duration and patient selection criteria.

To conduct a standard ITC of published aggregate data, which is typically performed when researchers do not have access to individual patient data, the contributing studies should have homogeneous methods because differences across studies may result in biased comparisons of outcomes. Our assessment indicated considerable variation across studies of monoclonal antibody treatments for severe asthma, including differences in baseline patient characteristics, outcome definitions and inclusion and exclusion criteria, that would likely bias standard ITCs. Therefore, we used the MAIC approach, in which individual patient data for one treatment are adjusted to match important aggregate baseline characteristics from the comparator trial. The re-weighted, matching-adjusted data can then be used to provide an estimate of the outcomes that might have occurred if the comparator trial had included a benralizumab arm. Use of individual patient data for adjustment offers more information on patient-level associations than aggregate-level adjustments applied to standard ITCs, making MAIC a more powerful tool than meta-regression in adjusting for the impact of treatment-effect modifiers [17]. In situations with few trials and no head-to-head data, as with the current study of relatively new therapies, MAIC can be a particularly helpful approach to address evidence gaps and aid decision-making by payers and health technology assessment authorities [17].

When methods differ between studies, the placebo effect size can also differ. For example, the placebo group's annual exacerbation event rate was greater in the pooled MENSA/DREAM data than in the pooled SIROCCO/CALIMA data (2.0 and 1.27 events per year, respectively). This difference might have been caused by procedural differences between studies, such as permitted concomitant treatments. However, when the SIROCCO/CALIMA data were matched to the MENSA/DREAM patient population characteristics in our MAIC analysis, the placebo group's annual exacerbation event rate in SIROCCO/CALIMA increased from 1.27 to 1.63 (appendix 2), suggesting that at least part of this difference in the placebo effects for benralizumab *versus* mepolizumab was because of patient population differences. Inspection of patient baseline characteristics in each pooled dataset (table 1) also suggests that patients taking mepolizumab had somewhat more severe asthma than patients taking benralizumab, as indicated by differences in baseline eosinophil count, prior exacerbations and the percentage of patients using OCS at baseline.

Because the trial patient populations from the benralizumab (SIROCCO [9] and CALIMA [11]) and reslizumab (Study 3082 and Study 3083 [10]) trials had limited overlap in their sample characteristics, MAIC analysis was not possible, and no conclusion could be drawn about the relative efficacy of these two treatments using this methodology. Although we selected similar trials of benralizumab and reslizumab for indirect comparison, the patient populations were still different enough that robust MAIC could not be accomplished. The most notable difference in the baseline characteristics of the two studies was the number of exacerbations in the previous year. Whereas almost every patient in the benralizumab population had two or more exacerbations in the previous year, ~60% of patients in the reslizumab population had only one exacerbation in the previous year. This indicates a difference in disease severity, as specified in the inclusion criteria; SIROCCO/CALIMA enrolled patients with severe asthma, whereas

the two reslizumab studies enrolled patients with less severe asthma. A recent ITC analysis [16] used the same four phase 3 studies used in our analysis to evaluate comparative efficacy for several asthma outcomes, including the exacerbation and FEV_1 outcomes we analysed. However, they used no matching adjustment to balance population characteristics. Their NMA suggests a numeric advantage for reslizumab for several efficacy outcomes, with a statistically significant advantage in the reduction of clinically significant exacerbations. Given that exacerbation history was an important characteristic in which the benralizumab and reslizumab populations differed, our analysis suggests caution in drawing conclusions about relative efficacies from these trials.

Limitations

MAIC analysis has several advantages over traditional ITC, but it also has limitations. Although we balanced treatment-effect-modifying patient characteristics that were measured in the trials, there may have been unmeasured differences between trials that were not matched.

Another limitation is the occurrence of extreme weights for some patients during matching adjustment, which can lead to decreased statistical power to detect differences between treatments. ESS is a reliable indicator in such cases, and we did not perform MAIC when the ESS was insufficient for the benralizumab *versus* reslizumab comparison. All other comparisons had sufficient ESS.

To limit heterogeneity across studies, the current analysis included only trials with exacerbations as a key endpoint. OCS sparing is another important endpoint for patients with severe, uncontrolled asthma; however, trials evaluating OCS-sparing effects have important study design differences that warrant separate analysis. A MAIC analysis of the OCS-sparing properties of benralizumab *versus* IL-5 inhibitors could not be adequately addressed here but will be described in a future report.

The MUSCA trial [25] was unpublished at the time of this analysis. It was not retrospectively included in the MAIC analysis because it differed from the other benralizumab and mepolizumab studies in several ways, including study design and choice of health-related quality of life as the primary endpoint. Despite these differences, the MUSCA trial was included in a sensitivity analysis, and the overall pattern of significance did not change.

Conclusions

MAIC is an accepted method for comparing treatments in lieu of head-to-head trials and is less subject to biases than standard ITC. To our knowledge, this is the first MAIC comparing monoclonal antibodies for the treatment of severe asthma. The MAIC demonstrated that, after adjustment for baseline population characteristics that differed across benralizumab *versus* mepolizumab trials, reductions in asthma exacerbation rates were similar, and improvements in FEV_1 were slightly better but not statistically significant at all time points tested. Comparisons with reslizumab could not be performed because of insufficient ESS.

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