



Reslizumab and mepolizumab for moderate-to-severe poorly controlled asthma: an indirect comparison meta-analysis

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Aim: A systematic literature review and network meta-analysis assessed the efficacy and safety of reslizumab 3.0 mg/kg and mepolizumab 100 mg. **Materials & methods:** Eligible studies evaluated reslizumab and mepolizumab in patients with inadequately-controlled severe eosinophilic asthma. Using a Bayesian network meta-analysis, 95% credible intervals and posterior probabilities were reported. **Results:** Of 19 indirect efficacy comparisons performed in base-case (Global Initiative for Asthma 4/5 patients with ≥ 2 exacerbations in the previous year) and overall populations, significant differences favoring reslizumab were observed for severe exacerbations, FEV₁ at 4 weeks and eosinophil counts at 4, 16 and 24 weeks, with no other significant differences including risk of adverse events. **Conclusion:** Indirect comparison of reslizumab and mepolizumab largely showed no significant differences in efficacy or safety.

First draft submitted: 9 July 2019; Accepted for publication: 16 October 2019; Published online: 5 November 2019

Keywords: eosinophilic asthma • indirect comparison • mepolizumab • network meta-analysis • reslizumab

Asthma is a major public health concern that affects over 235 million individuals worldwide, a number that is expected to grow by an additional 100 million people by 2025 [1–3]. Asthma is a heterogeneous disease, with different underlying biological mechanisms. In 40–60% of asthmatics, a significant mechanism contributing to the disease process is enhanced recruitment of eosinophils into the lungs. This has emerged as a distinctive asthma phenotype known as eosinophilic asthma [4,5], which is associated with key pathophysiological and clinical features of asthma, including airway remodeling with associated persistent airflow limitation, as well as poor clinical control [6,7]. A recent study has shown that asthma patients with blood eosinophil counts >400 cells/ μ l experience more severe exacerbations, and that a count–response relationship exists between blood eosinophil counts and asthma-related outcomes [8]. Sputum eosinophil count also has utility as both a biomarker of airway inflammation and a marker to assess disease severity and treatment outcome [9].

Understanding the underlying pathophysiology of certain asthma phenotypes has led to the development of novel therapies aimed at targeting specific intra- and extra-cellular pathways. The recruitment, growth and survival of eosinophils are regulated in part by the cytokine IL-5 [6,10]. Therefore an important approach to the treatment of eosinophilic asthma has been the development of humanized monoclonal antibodies that inhibit IL-5 which include reslizumab and mepolizumab. Their neutralizing effect reduces blood and sputum eosinophil counts and can contribute to the improvement of symptoms [11–14]. In 2015, mepolizumab was authorized for use in the USA for patients aged ≥ 12 years, and in Canada and EU for the treatment of adult patients (age ≥ 18 years), with severe eosinophilic asthma based on data in patients with blood eosinophils ≥ 150 cells/ μ l at initiation or

Table 1. Population, interventions, comparators, outcomes and study design.

Population	Patients ≥ 12 years of age with moderate-to-severe inadequately controlled eosinophilic asthma
Interventions	• Reslizumab • Mepolizumab
Comparators	• Placebo, BSC
Outcomes	Primary outcomes: • Rate and/or number of severe asthma exacerbations • Rate and/or number of any asthma exacerbations • Number of patients experiencing an exacerbation Secondary outcomes: • Change in FEV₁ (liters or percent predicted) • Number of hospitalizations • Number of emergency department visits • Change in eosinophil count • Time to first exacerbation Safety outcomes: • Any adverse events • Serious adverse events • Discontinuations due to adverse events
Study design	RCTs
Other	English language publications
BSC: Best supportive care; RCT: Randomized controlled trial.	

≥ 300 cells/ μ l in the past 12 months [11,13]. In 2016, reslizumab was approved in USA, Canada and EU as an add-on maintenance treatment of adults (age ≥ 18 years) with severe eosinophilic asthma based on studies in patients with blood eosinophils ≥ 400 cells/ μ l [12].

Since no head-to-head comparisons of reslizumab and mepolizumab exist, we conducted a systematic review and network meta-analysis (NMA) to assess the comparative efficacy and safety of these treatments in patients with moderate-to-severe inadequately-controlled eosinophilic asthma.

Materials & methods

Systematic literature review

Eligibility criteria

We included randomized controlled trials (RCTs) in patients with moderate-to-severe inadequately controlled eosinophilic asthma aged ≥ 12 years (Table 1). Eligible studies were those that compared the interventions, reslizumab 3.0 mg/kg (intravenous infusion) and mepolizumab 100 mg (subcutaneous injection), with placebo or best supportive care. The primary outcomes were rates of any exacerbations and severe exacerbations. To minimize the variability between studies in definitions of clinically significant asthma exacerbations, the study-specific definitions were re-categorized based on guideline specified definitions [15–17] and discussion with clinical experts. Severe exacerbations required the use of systemic or oral corticosteroids for at least 3 days, or required asthma-related emergency treatment. Secondary outcomes included time to first exacerbation, change in forced expiratory volume in 1 second (FEV₁) and FEV₁ % predicted, change in eosinophil counts, adverse events (total and serious) and discontinuations due to adverse events.

Search strategy & selection criteria

A comprehensive literature search was performed in August 2017 and updated in March 2019 in three databases: Embase, MEDLINE and the Cochrane Central Register of Controlled Trials (Supplementary Tables 1–3). Additional searches were conducted on ClinicalTrials.gov to supplement the evidence base. Unpublished data from clinical study reports and submissions by originator companies to the US FDA were also obtained. Study selection, data extraction and screening were conducted by two independent reviewers on the basis of a review protocol developed by Precision Xtract. Study screening and data extraction were performed in duplicate, and any discrepancies between the reviewers were resolved by arbitration by the third reviewer.

Data extraction

From each eligible study identified, study characteristics (design, phase, site, duration and population), treatment characteristics (dosage, route of administration and duration) and patient baseline characteristics were extracted.

Exacerbation outcomes were extracted as rates, defined as the number of events per patient per year and safety outcomes were defined as the proportion of patients with an event. The quality of included trials was examined using the Cochrane Collaboration's Risk of Bias tool [18].

Analytic approach

The rate of exacerbation, time to first exacerbation and safety outcomes were analyzed at the end of study time points. For all other outcomes, where possible, separate analyses were conducted at 4 weeks, 16 weeks (± 2 weeks), 6 months/26 weeks (± 2 weeks) and 12 months/52 weeks (± 2 weeks).

Patient populations

Comparability of the reslizumab and mepolizumab trials was assessed on the basis of baseline characteristics. If trial populations were not directly comparable because of differences in baseline characteristics, the base-case analysis selected a patient subgroup to provide similar patient populations for analysis. For this NMA, the base-case population comprised Global Initiative for Asthma (GINA) step 4/5 patients who had ≥ 2 exacerbations in the previous year.

As a sensitivity analysis, we also indirectly compared the outcomes in patients who received mepolizumab with those who received reslizumab in the overall population (i.e., not restricting patients to the base-case analysis) and in adults (age ≥ 18 years) from the base-case population.

Network meta-analysis

Data from the included RCTs were used to perform an NMA by population for each outcome. A Bayesian hierarchical model was used for the NMA, as this preserves the randomization of each trial [19], and all analyses were performed in a Bayesian statistical framework. Although the assumptions of random-effects models may be more plausible, both fixed- and random-effects models were considered, and the deviance information criterion and assessment of variability in study and patient characteristics were used to guide the model selection. Noninformative priors were used for analyses of all outcomes. Statistical uncertainty around the parameters was reported using 95% credible intervals (95% CrI), and statistical significance was declared when the 95% CrI excluded 0 for values expressed as a mean difference (MD) or 1 for rate ratio (RR).

The posterior probability (Pr) that reslizumab is superior to mepolizumab was expressed as a percentage, according to Bayesian inference conventions. For each parameter of interest, the prior probability was assumed to follow a noninformative distribution so that the observed data from RCTs were the main determinants of the estimated treatment effects. A Markov Chain Monte Carlo algorithm was used to calculate the probability of a certain value of the parameter being observed given the RCT data and prior probability. This algorithm was implemented with the software package OpenBUGS in accordance with methods described by the National Institute for Health and Care Excellence in UK [20]. This yielded a Pr distribution which was summarized as a point estimate and 95% CrI. The probability of a treatment having a certain ranking (i.e., First, Second or Third most efficacious) was also presented for each outcome.

For exacerbation rates, a Poisson regression model with a log link function and a Poisson likelihood was used. For this approach, observed person-years had to be estimated to transform rates to events in the study period. Person-years were estimated by using the study period times the average of the number of patients randomized and number of patients that completed the study. For the continuous outcomes, linear regression models were used with an identity link and normal likelihood. Safety outcomes were analyzed using a generalized linear model with logit link function and binomial likelihood. All analyses were performed using R version 3.2.0 (<http://www.r-project.org/>) and OpenBUGS and JAGS version 3.2.3 (OpenBUGS/JAGS Project Management Group).

Results

Study selection

A total of 551 citations were identified from bibliographic databases and two additional citations through other sources. After the removal of duplicate citations, 435 abstracts were screened, of which 28 full-text citations were assessed. Nineteen full-text articles were further excluded (Population: $n = 7$; Intervention: $n = 4$; Study Design: $n = 7$; Other: $n = 1$), leaving nine citations that met the inclusion criteria. Two of the nine included citations were mepolizumab clinical briefing documents [21,22]. In addition, four reslizumab clinical study reports [23–26], including a supplementary *post hoc* analysis [Teva, data on file], were included. A total of 13 citations, representing eight

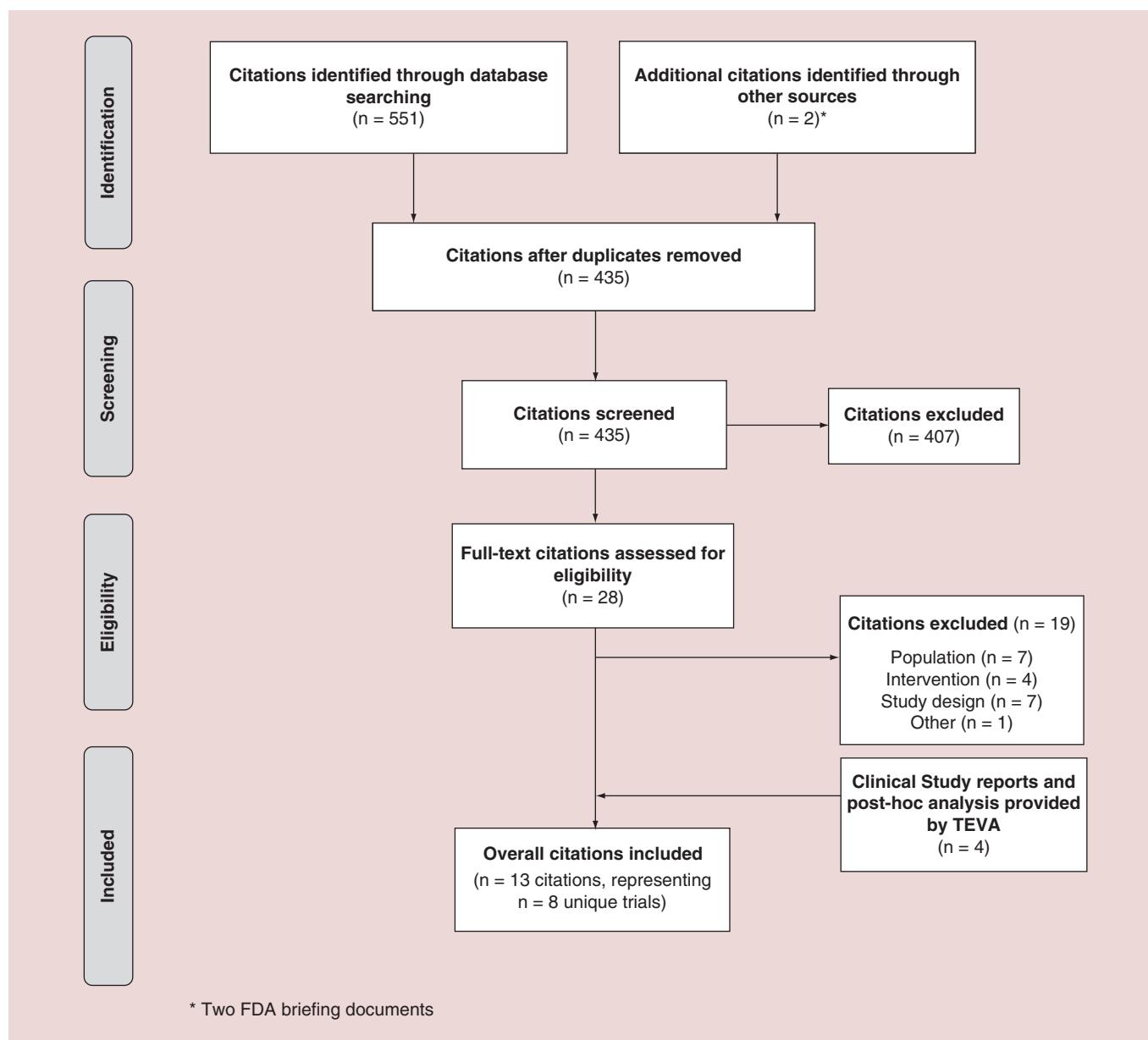


Figure 1. PRISMA study flow diagram.

unique RCTs (five assessing reslizumab [12,23–29] [Teva, data on file] and three assessing mepolizumab [11,21,22,30,31]) were included in the analysis. The study flow diagram is presented in [Figure 1](#).

Study characteristics

The eligible studies, including predominantly adult men and women, were primarily multicenter with sample sizes ranging from 106 to 551 patients, and treatment durations from 12 to 52 weeks (Supplementary Table 4). In the reslizumab trials, the mean ages across the studies ranged from 43 to 47.5 years, the studies included a higher proportion of females in all treatment groups and the majority of patients were of Caucasian ethnicity ([Table 2](#)). The mean blood eosinophil counts for reslizumab trials ranged from 281 to 696 cells/ μ l ([Table 2](#)). All of the patients on reslizumab were using inhaled corticosteroids at baseline and more than 80% were using long-acting β -agonists ([Table 2](#)). In the mepolizumab trials, the mean ages were around 50 years, the studies included a higher proportion of females, and the majority of patients were of Caucasian ethnicity ([Table 2](#)). The mean blood eosinophil counts for mepolizumab trials ranged from 344 to 451 cells/ μ l ([Table 2](#)). There were some notable differences between

Table 2. Baseline patient characteristics.

Trial (Ref.)	Interventions	Patients (n)	Mean age (years)	Females (%)	Caucasians (%)	Africans (%)	Asians (%)	Blood eosinophil count (cells/ μ l)	IgE levels (IU/ml)	Disease duration (years)	Previous smokers (%)	Exacerbations in the past year (n/patient)	ICS use at baseline (%)	LABA use at baseline (%)	OCS use at baseline (%)
Reslizumab															
Res-5-0010 [28]	Placebo	53	45.8	55	–	–	–	500	–	26.1	–	–	100	96	0 [†]
	Reslizumab 3.0 mg/kg IV	53	44.9	64	–	–	–	500	–	23.3	–	–	100	94	0 [†]
Study 3081 [24,27]	Placebo	105	44.2	59	81	7	0	592	–	20.7	–	–	100	80	0 [†]
	Reslizumab 3.0 mg/kg IV	106	43	58	85	5	2	648	–	20.4	–	–	100	75	0 [†]
Study 3082 [12,23]	Placebo	244	46.7	66	75	8	14	624	–	18.8	–	2.1	100	85	19
	Reslizumab 3.0 mg/kg IV	245	46.6	58	71	6	20	696	–	19.7	–	1.9	100	87	19
Study 3083 [12,25]	Placebo	232	47.5	65	73	2	9	688	–	18.7	–	2	100	83	12
	Reslizumab 3.0 mg/kg IV	232	46.4	62	72	3	7	610	–	18.2	–	1.9	100	82	12
Study 3084 [26,29]	Placebo	98	45.1	55	74	21	2	277	–	25.8	–	–	100	82	0 [†]
	Reslizumab 3.0 mg/kg IV	398	44.9	66	65	28	3	281	–	26.2	–	–	100	77	0 [†]
Mepolizumab															
MENSA [13]	Mepolizumab 100 mg SC	194	51	60	78	4	18	451	150	20.5	26	3.8	–	–	27
	Placebo	191	49	56	77	2	20	460	150	19.5	30	3.6	–	–	23
SIRIUS [11]	Mepolizumab 100 mg SC	66	49.8	64	97	0	1	344	117	17.4	41	3.3	100	–	100 [‡]
	Placebo	62	49.9	45	92	0	3	408	114	20.1	38	2.9	100	–	100 [‡]
MUSCA [31]	Mepolizumab 100 mg SC	274	49.8	54	–	–	–	–	–	19.5	26	2.9	>99	>99	23
	Placebo	277	52.1	64	–	–	–	–	–	19.6	27	2.7	100	99	24

[†]Use of maintenance systemic corticosteroids was a pre-specified exclusion criterion for this study.[‡]Patients were required to have ≥ 6 -month history of maintenance treatment with systemic corticosteroids for study eligibility.

ICS: Inhaled corticosteroids; IV: Intravenous; LABA: Long-acting beta-agonist; OCS: Oral corticosteroids; SC: Subcutaneous.

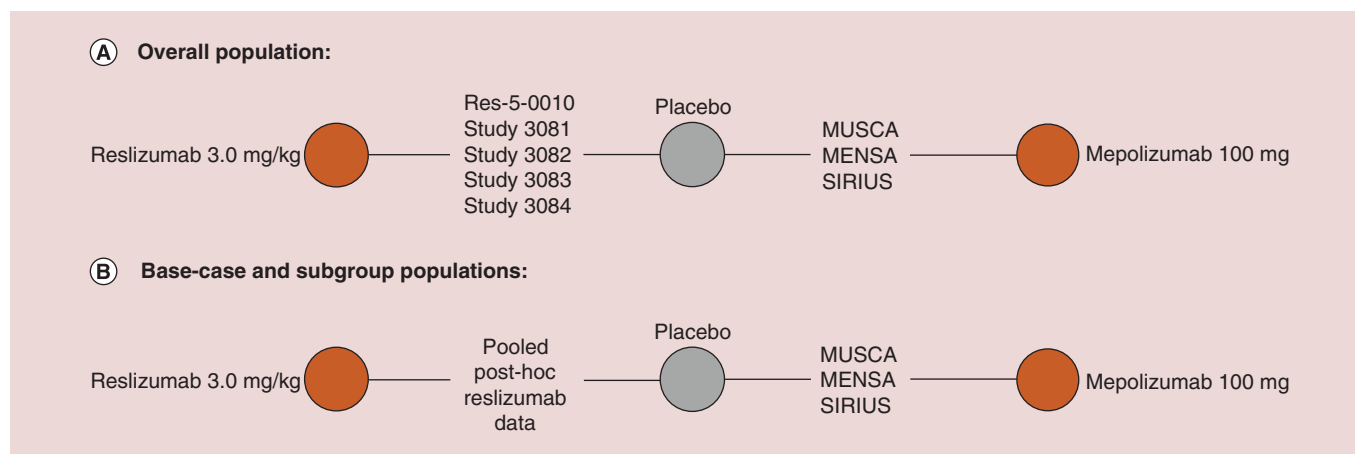


Figure 2. Evidence network. (A) The base-case population consisted of GINA step 4/5 patients who had ≥ 2 exacerbations in the previous year. (B) The subgroup consisted of adults from the base-case population. GINA: Global initiative for asthma.

reslizumab and mepolizumab study populations. The mean number of exacerbations in the previous year was approximately 2 for reslizumab patients, and ranged from 2.7 (placebo; MUSCA) to 3.8 (mepolizumab 100 mg; MENSA) for mepolizumab patients (Table 2). Also, the inclusion criteria for reslizumab and mepolizumab trials were different with regards to eosinophil count (reslizumab: ≥ 400 cells/ μ l and mepolizumab: ≥ 150 cells/ μ l).

Network of evidence

The overall evidence network shows that reslizumab and mepolizumab are connected at placebo, which allows for indirect comparisons to be made between them (Figure 2A). The placebo treatment was accompanied by best supportive care that was based on conventional therapy as recommended by GINA or the National Heart, Lung and Blood Institute. The study quality assessment using the Cochrane risk of bias assessment is summarized in Supplementary Table 5.

The specific trials from which the data were used for the comparison of each outcome and population are described in Supplementary Table 6. As all of the patients included in the mepolizumab trials were required to have ≥ 2 exacerbations in the previous year, we selected to compare them in the base-case analyses with similar patients who received reslizumab treatment, in other words, GINA step 4/5 patients who had ≥ 2 exacerbations in the previous year (as the inclusion criteria for reslizumab trials required patients to have ≥ 1 exacerbations in the previous year). This was accomplished by analyzing the outcomes for these patients in a pooled *post hoc* analysis of reslizumab trial data (Figure 2B).

Results for the direct comparisons of reslizumab or mepolizumab with placebo from the included trials are summarized in Supplementary Table 6.

Exacerbations

Severe exacerbations

Indirect comparison of reslizumab with mepolizumab suggested no significant difference in the rate of severe exacerbations in the base-case population, in other words, all GINA step 4/5 patients with ≥ 2 exacerbations in the previous year (RR: 0.77; 95% CrI: 0.54–1.11; Pr = 92%) (Figure 3). In adult (age ≥ 18 years) GINA step 4/5 patients with ≥ 2 exacerbations in the previous year, indirect comparison suggested a significantly greater reduction in the rate of severe exacerbations with reslizumab compared with mepolizumab (RR: 0.70; 95% CrI: 0.53–0.95; Pr = 99%) (Figure 3).

In the overall population, in other words, patients with no restriction of ≥ 2 exacerbations in the previous year, indirect comparison of reslizumab with mepolizumab suggested no significant difference in the rate of severe exacerbations (RR: 0.90; 95% CrI: 0.38–2.04; Pr = 68%) (Figure 3).

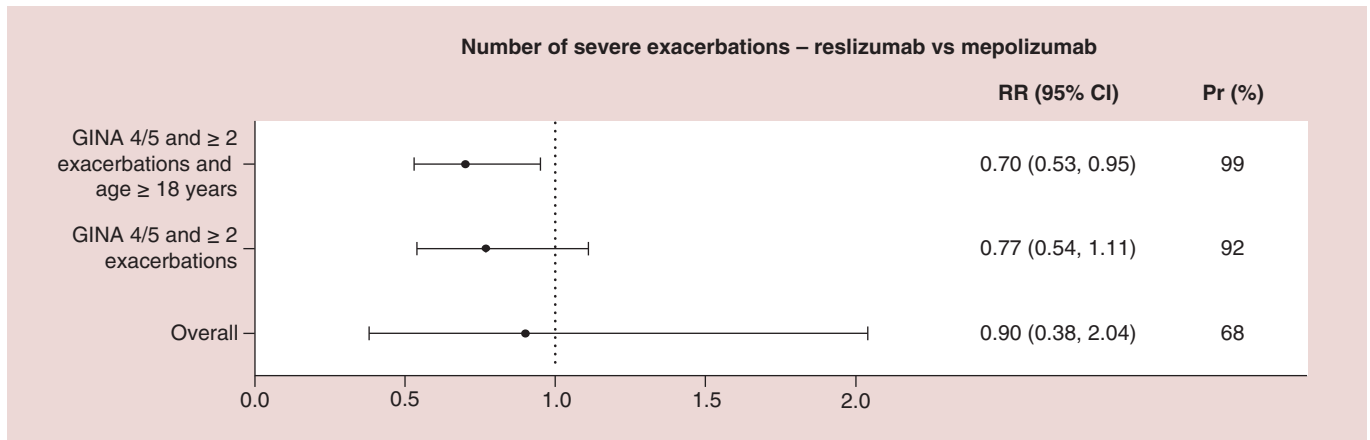


Figure 3. Indirect comparisons of reslizumab and mepolizumab for number of severe exacerbations.

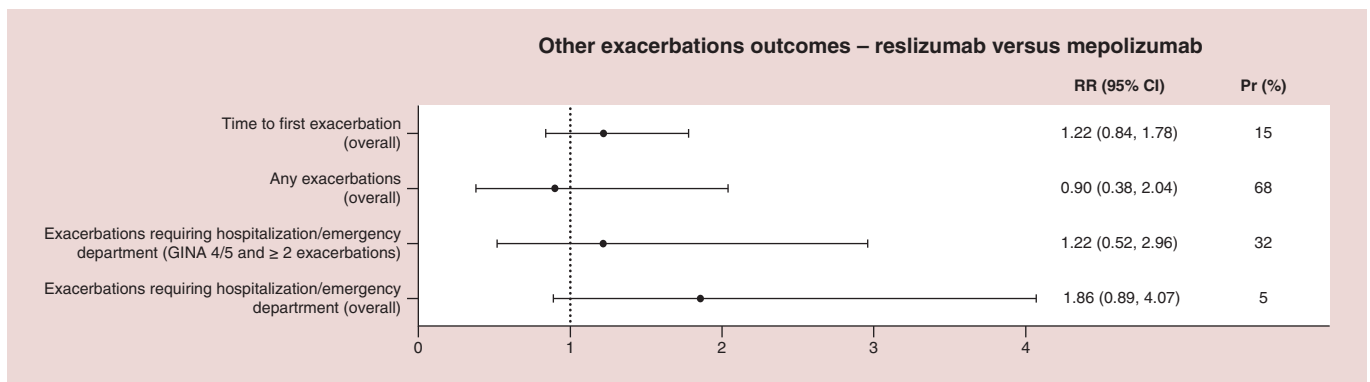


Figure 4. Indirect comparison of reslizumab and mepolizumab for other exacerbation outcomes.

Any exacerbations

Indirect comparison of reslizumab with mepolizumab suggested no significant difference in the rate of any exacerbations in the overall population (RR: 0.90; 95% CrI: 0.38–2.04; Pr = 68%) (Figure 4).

Exacerbations requiring hospitalization/ED visit

In the base-case population, indirect comparison suggested no significant difference with reslizumab compared with mepolizumab in the rate of exacerbations requiring hospitalization or ED visit at 16 weeks (RR: 1.22; 95% CrI: 0.52–2.96; Pr = 32%) (Figure 4). Similar results were observed in the overall population (RR: 1.86; 95% CrI: 0.89–4.07; Pr = 5%) (Figure 4).

Time to first exacerbation

Indirect comparison suggested that time to first exacerbation was similar for reslizumab compared with mepolizumab in the overall population (RR: 1.22; 95% CrI: 0.84–1.78; Pr = 15%) (Figure 4).

Change in FEV₁

In the base-case population, indirect comparison suggested a significantly greater improvement in FEV₁ with reslizumab compared with mepolizumab at 4 weeks (MD: 0.14 l; 95% CrI: 0.03–0.24; Pr = 99%), but not at 16 or 24 weeks (Figure 5). Indirect comparison in the overall population suggested no significant difference with reslizumab compared with mepolizumab for change in FEV₁ at all time points (Figure 5).

In the overall population, the indirect comparison of change in FEV₁ % predicted suggested no significant difference with reslizumab compared with mepolizumab at 4, 16 and 24 weeks (Figure 6).

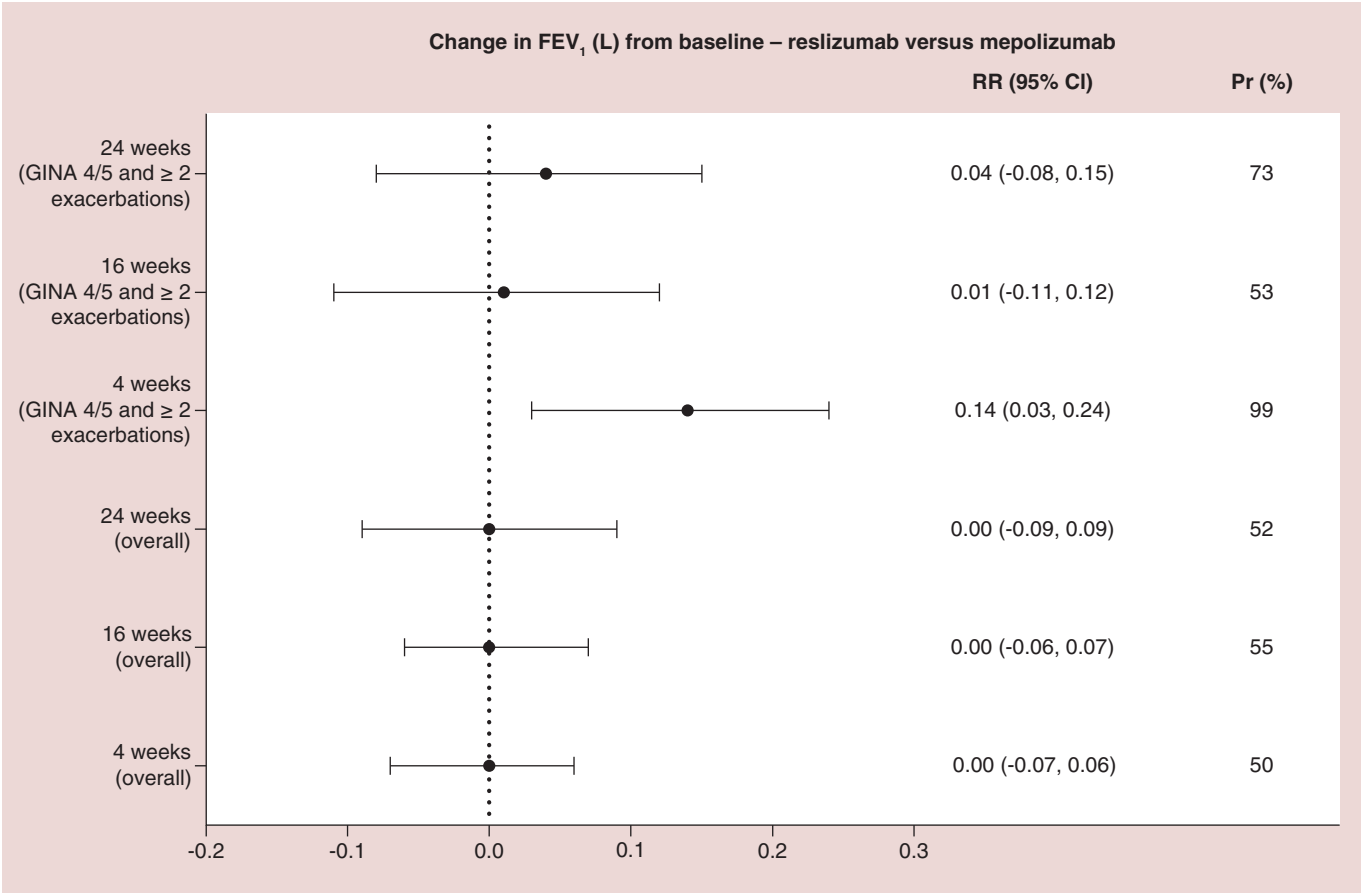


Figure 5. Indirect comparisons of reslizumab and mepolizumab for changes from baseline FEV₁ (L).

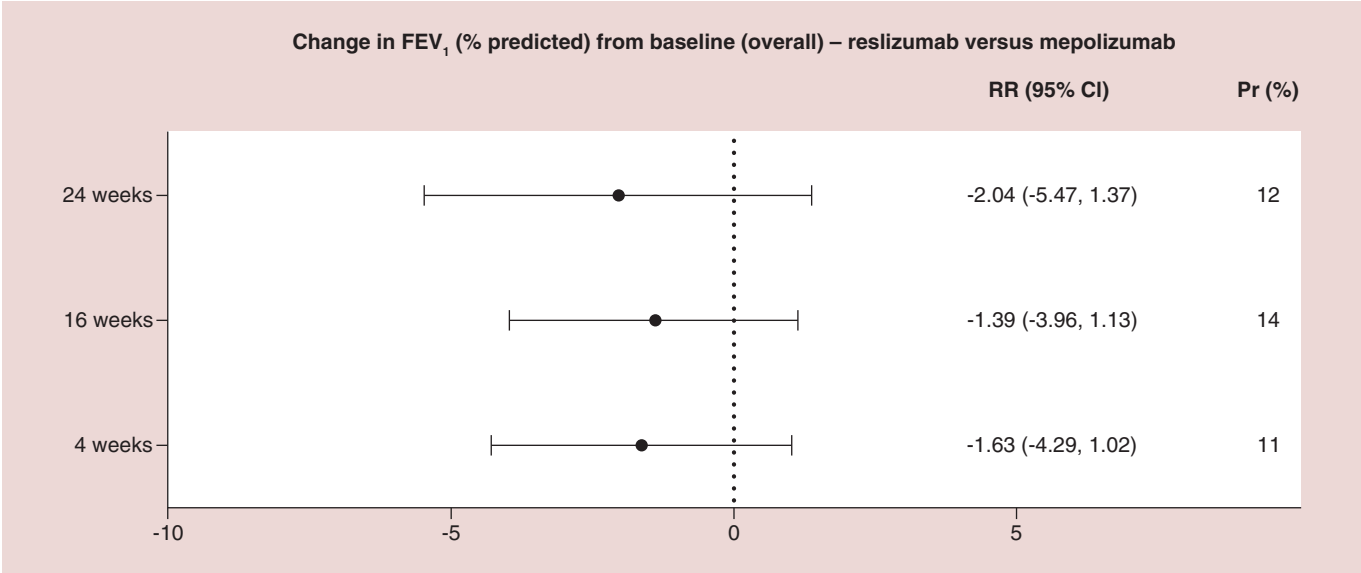


Figure 6. Indirect comparisons of reslizumab and mepolizumab for changes from baseline in FEV₁ % predicted.

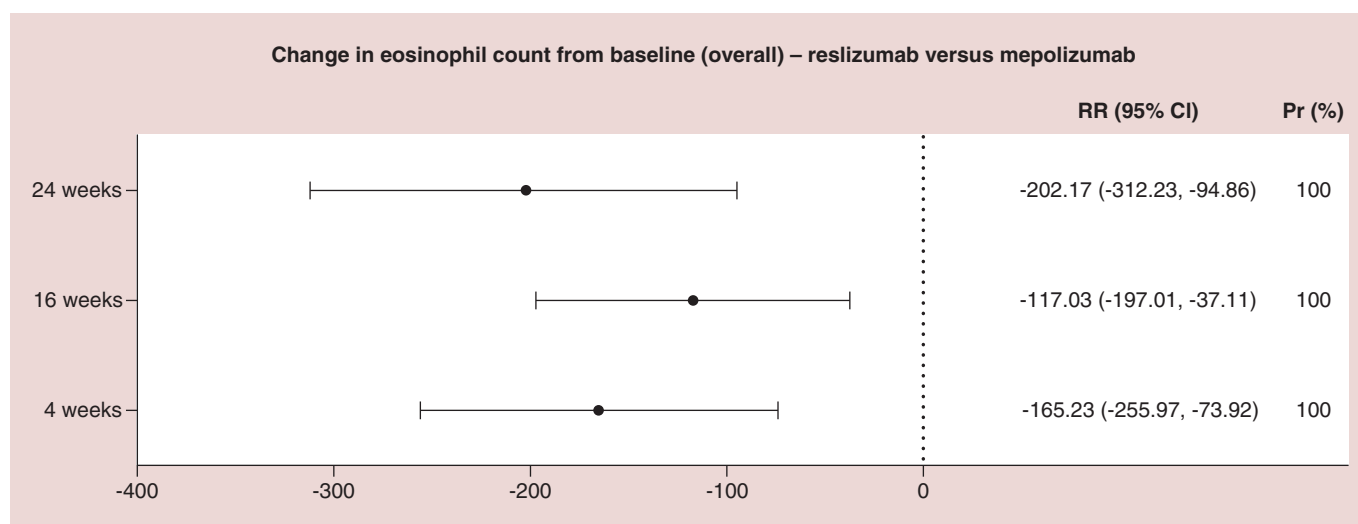


Figure 7. Indirect comparisons of reslizumab and mepolizumab for changes from baseline in blood eosinophil counts.

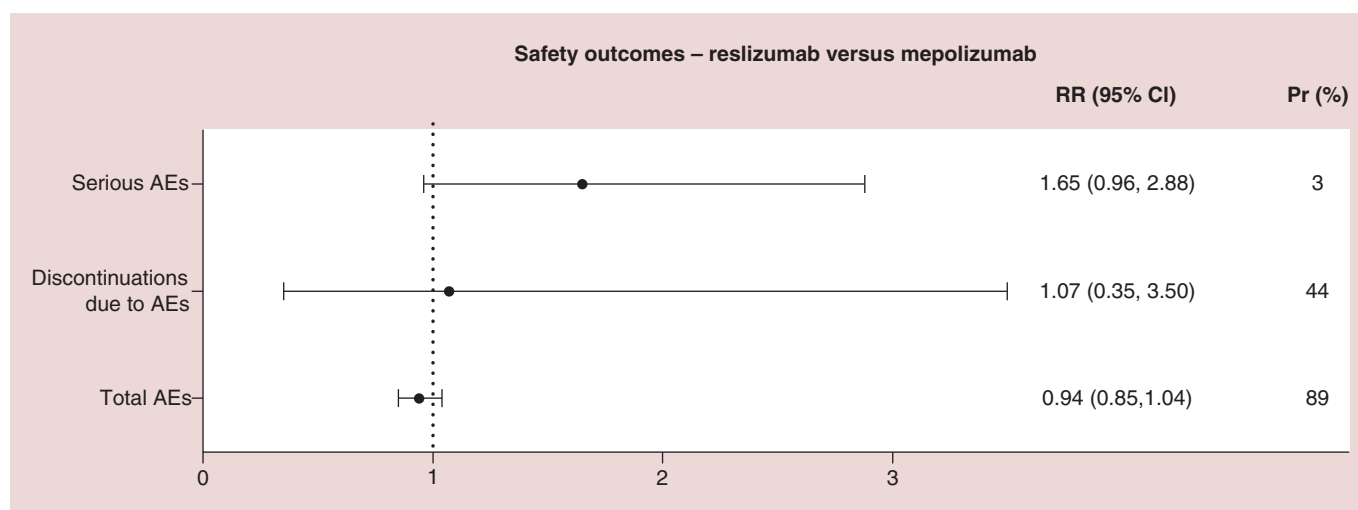


Figure 8. Indirect comparisons of reslizumab and mepolizumab for safety outcomes.

Eosinophil counts

In the overall population, indirect comparison suggested that reslizumab resulted in significantly greater reductions in eosinophil counts compared with mepolizumab at 4 weeks (MD: -165.23; 95% CrI: -255.97 to -73.92; Pr = 100%), 16 weeks (MD: -117.03; 95% CrI: -197.01 to -37.11; Pr = 100%) and 24 weeks (MD: -202.17; 95% CrI: -312.23 to -94.86; Pr = 100%) (Figure 7).

Safety

Indirect comparison of reslizumab with mepolizumab in the overall population suggested a similar risk of any adverse events (RR: 0.94; 95% CrI: 0.85–1.04; Pr = 89%), discontinuations due to adverse events (RR: 1.07; 95% CrI: 0.35–3.50; Pr = 44%) and serious adverse events (RR: 1.65; 95% CrI: 0.96–2.88; Pr = 3%) (Figure 8).

Discussion

This analysis assessed the relative efficacy and safety of reslizumab and mepolizumab for the treatment of moderate-to-severe inadequately-controlled eosinophilic asthma; it is an indirect comparison and should be interpreted in this context. A total of 19 indirect efficacy analyses were conducted, of which 16 of these showed no statistically

significant differences between reslizumab and mepolizumab. Three analyses showed statistically significant benefit of reslizumab when indirectly compared with mepolizumab: the rate of severe exacerbations in the base-case analysis of adult GINA step 4/5 patients with ≥ 2 exacerbations in the previous year was significantly lower with reslizumab versus mepolizumab; the improvement in FEV₁ at 4 weeks with reslizumab was significantly greater compared with mepolizumab in the base-case analysis; and reslizumab showed significantly greater reductions in eosinophil counts compared with mepolizumab at 4, 16 and 24 weeks in the overall population. The safety analysis suggested that the tolerability of reslizumab is similar to that of mepolizumab.

It has been well documented that asthma exacerbations are associated with increased morbidity and mortality, reduced quality of life, increased direct and indirect healthcare costs and loss of productivity [32]. Patients with severe eosinophilic asthma, based on an eosinophil blood count >400 cells/ μ l, have been strongly associated with an increased risk of future and more severe exacerbations [33], and poorer asthma symptom control compared with those with a blood eosinophil count of ≤ 400 cells/ μ l [8]. Thus, the observations that both biologics improved exacerbations compared with placebo, and that, in this NMA, reslizumab showed a statistically significantly lower rate of severe exacerbations in GINA step 4/5 adults with ≥ 2 prior exacerbations (base-case population) when compared with mepolizumab, are interesting, as the majority of patients requiring anti-IL-5 therapy are in this category [34]. A direct relationship between the number of exacerbations in patients with severe eosinophilic asthma and decline in their lung function has been reported [29]. Repeated exacerbations may be associated with accelerated loss of lung function [29]. As such, reduction of exacerbation rates could potentially confer substantial benefits in terms of reduction in the rate of decline of lung function in exacerbation-prone patients [35].

The second outcome for which statistical significance was observed in this indirect analysis, also in the base-case population, suggested that in a subpopulation of patients with a history of more frequent exacerbations, those treated with reslizumab may have earlier evidence of clinical effect than those treated with mepolizumab as demonstrated by earlier FEV₁ response, with beneficial effects observed as early as 4 weeks following the first dose. Both monoclonal antibodies have the same target (IL-5 ligand) and similar mechanisms of action. This could therefore suggest a relationship between weight-based intravenous dosing and speed of onset of action. Compared with the subcutaneous route, intravenous administration may enable faster absorption, greater bioavailability and a shorter time to maximum serum concentration with similar elimination half-life [36], a finding that warrants further investigation.

In addition, we report significantly greater reductions in eosinophil counts for reslizumab as early as 4 weeks, and at 16 and 24 weeks, compared with mepolizumab. These rapid reductions in blood eosinophil counts have been observed as early as within 2–3 days following the first intravenous infusion of reslizumab [37], which supports the more rapid onset of action relative to mepolizumab. While it must be considered that no direct comparison has been conducted, our indirect analysis supports this proposal of early onset of action as significant differences in eosinophil counts were observed at 4 weeks.

Limitations of the present analysis preclude definitive conclusions on the relative impact of reslizumab and mepolizumab on eosinophilia. One such limitation is the lack of documented airway or sputum eosinophil response. Mukherjee *et al.* showed that both reslizumab and mepolizumab can normalize blood eosinophils, but that the weight-based dosing of reslizumab (i.e., a higher dose) was more effective than fixed-dose mepolizumab (i.e., a lower dose) in terms of reduction in sputum eosinophils [14]. This is likely to be due to the inability of the lower doses of mepolizumab to effectively neutralize airway IL-5 and control airway eosinophilia despite normalizing blood eosinophil counts [38]. Recent publications have highlighted the issue of underdosing and the importance of the correct dose of anti-IL-5 biologics [39,40]. More specifically, an increase in sputum IL-5 despite anti-IL-5 biologics can be indicative of immune complexes, which can form when the administered anti-IL-5 biologic is not in excess of the target antigen. Importantly, immune complexes can act as cytokine depots and increase *in vivo* potency and biological activity of the bound IL-5 [41]. Furthermore, to the impact of dosing, it is intriguing to recognize that despite the same mechanism of action and therapeutic target, mepolizumab and reslizumab have difference potencies. For instance, an *in vitro* analysis by Liddament *et al.* demonstrated that reslizumab has a 12-fold higher affinity to IL-5 than mepolizumab, attributed to a faster association rate [42]. The clinical impact of these differences warrants further investigation.

Indirect comparisons of monoclonal antibodies targeting the IL-5 pathway have been reported by other authors. Cabon *et al.* concluded that reslizumab 3.0 mg/kg was most likely to be effective at reducing exacerbation rates and improving FEV₁, when compared with mepolizumab and benralizumab, in patients with eosinophilic asthma [43]. A pair-wise and Bayesian NMA suggested that reslizumab was most likely to result in benefits for pulmonary

function, reducing adverse events and improving quality of life scores compared with placebo, and mepolizumab presented the best benefits for reducing asthmatic exacerbations [44]. An NMA by Casale *et al.* indirectly compared reslizumab and benralizumab and suggested that reslizumab may be more efficacious than benralizumab in patients with eosinophilic asthma in GINA step 4/5 with elevated blood eosinophil levels and ≥ 2 exacerbations in the previous year [45]. Similar to our NMA, Casale *et al.* used a Bayesian statistical framework and identified a base-case population that allowed for a robust and fair analysis. A recent indirect comparison by Busse *et al.* suggested that mepolizumab was associated with greater improvements in clinically significant exacerbations and asthma control, compared with reslizumab and benralizumab, in patients with Asthma Control Questionnaire scores ≥ 1.5 and stratified by baseline blood eosinophils [46]. However, it has been argued that the methodology of this meta-analysis does not allow for robust and replicable results. In particular, the analysis did neither fully account for patient heterogeneity nor adjust for factors that can potentially modify treatment effect, meaning that it is likely that study populations were unbalanced [47]. Furthermore, exclusion of the pivotal DREAM study for mepolizumab was unwarranted as the study has clinical and methodological similarities with other studies included in the meta-analysis, leading to a selection bias [47]. The findings by Busse *et al.* are in contrast to those from our NMA, which largely showed no differences in efficacy or safety outcomes between reslizumab and mepolizumab, with statistically significant benefit with reslizumab in a few efficacy outcomes. Although the mechanism of action of reslizumab and mepolizumab are similar, differences in prior exacerbation history and cut-points for eosinophils could contribute to the differences in the relative efficacy and safety of these treatments.

The strengths and novelty of our NMA lie in its comprehensiveness, the robust methodology and the number of outcomes assessed. Despite these strengths, the validity of the NMA was restricted by a number of limitations related to the available evidence base, as well as different methodological approaches and clinical heterogeneity between the studies. We noticed some heterogeneity in patient characteristics between the trials. For instance, patients from the mepolizumab trials had a higher mean number of exacerbations in the previous year. We opted to use a base-case analysis (restricted to GINA 4/5 patients with ≥ 2 exacerbations in the previous year), which has been used previously [45] and minimized heterogeneity, allowing for a robust comparison of treatments. In addition, the use of posterior probabilities allowed us to interpret treatment differences based on specific assumptions, rather than the probability of a Type I Error using p-values. Eosinophil counts also differed between reslizumab (≥ 400 cells/ μL) and mepolizumab (≥ 150 cells/ μL) trials. However, the absence of patient-level data for mepolizumab patients with blood eosinophils ≥ 400 cells/ μL precluded stratification by baseline blood eosinophil count. These differences in baseline blood eosinophil levels may have in part influenced response to treatment in terms of improvement in FEV₁ and reduction in eosinophils. For instance, previous research has shown a positive relationship between higher blood eosinophil levels and greater improvements in FEV₁ with reslizumab [29]. Furthermore, sensitivity analyses in the overall population included a mix of studies with patients who had severe and moderate-to-severe eosinophilic asthma. Although the majority of the population within the included studies had severe eosinophilic asthma, the extent to which the slight variation in baseline severity affected the results could not be ascertained, as baseline adjustments were not possible. Despite our statistical adjustments, there remains a possibility that observed or unobserved differences between the study populations may have biased the results.

In this NMA, there was also variability in study characteristics across the trials. Various approaches, such as including or excluding certain trials in a sensitivity analysis and meta-regressions to adjust the baseline variability, could be explored to adjust for the baseline heterogeneity between studies. However, the sparsely informed comparisons and/or lack of contrast within the comparisons limited the ability to adjust for this heterogeneity during the analysis. This also limited the NMA modeling to fixed-effects models for some of the outcomes and, as a result, study variability could not be fully taken into account. Differences in defining asthma exacerbations was also an issue; although an attempt was made to match the exacerbation definitions across all included studies, some variability in the definitions used still remained due to differences in data reporting, which cannot be ignored. The comprehensive literature search to identify suitable trials for inclusion in the NMA was conducted in August 2017, and a repeat of the literature search in June 2019 did not identify any additional trials that met the eligibility criteria. As such, the evidence base used in this NMA is up to date.

Further limitations stem from the lack of data in some of the analyses. Comparisons in the two subgroups were informed by either a single trial or data from pooled analyses (for reslizumab); hence, these results do not provide a definitive estimate of efficacy and more studies in similar populations might strengthen the evidence to make it more robust. It should also be noted that while generating the pooled analysis from individual patient data in the reslizumab studies, randomization was broken such that selection bias could have affected all of these comparisons.

Conclusion

Given the small number of trials between each comparison, current data do not allow for clear conclusions to be drawn regarding the relative therapeutic benefit of any one treatment over another. Indirect comparison of reslizumab and mepolizumab largely showed no differences in efficacy or safety outcomes. However, reslizumab showed statistically significant benefit in three efficacy outcomes relating to greater reduction in the rate of severe exacerbations in adult (age ≥ 18 years) GINA step 4/5 patients with ≥ 2 exacerbations in the previous year; greater improvement in FEV₁ in GINA step 4/5 patients with ≥ 2 exacerbations in the previous year; and greater reductions in eosinophil count.

Future perspective

The advent of monoclonal antibodies that inhibit IL-5 has advanced the treatment of moderate-to-severe inadequately-controlled eosinophilic asthma. Direct comparison of IL-5 monoclonal antibodies in head-to-head clinical trials would be difficult to conduct and likely require thousands of patients to observe significant treatment differences [43]. In the absence of head-to-head clinical trials, indirect treatment comparisons have been reported; however, comparisons are challenging because of patient heterogeneity between trials. Future indirect comparisons using alternative methods, such as matching-adjusted indirect treatment comparison, are warranted for more conclusive results and to improve clinical insight into patient subtypes who may benefit most from specific IL-5 monoclonal antibodies.

Summary points

Background

- Reslizumab and mepolizumab are anti-IL5 biologics for the treatment of severe eosinophilic asthma. No head-to-head comparisons of the relative efficacy of reslizumab and mepolizumab exist.

Meta-analysis methodology

- A network meta-analysis (NMA) of data from randomized placebo-controlled trials (RCTs) was conducted, in a Bayesian statistical framework, to compare efficacy and safety outcomes with reslizumab and mepolizumab.
- Outcomes assessed in the NMA were exacerbation rates and severe exacerbation rates (primary outcomes) and time to first exacerbation, FEV₁, % predicted FEV₁, eosinophil counts and adverse events (secondary outcomes).
- A base case population was defined to provide similar patient populations for the NMA; this comprised patients meeting GINA step 4/5 criteria who had ≥ 2 exacerbations in the previous year.

Eligible studies

- Eight unique RCTs were included in the NMA, of which five assessed reslizumab and three assessed mepolizumab. The sample sizes of the RCTs ranged from 106 to 551 patients.

Efficacy findings

- A total of 19 indirect comparisons of efficacy outcomes were conducted in the base case and overall populations; of these, 16 showed no statistically significant difference between the two treatments.
- The three comparisons for which a statistically significant difference in favor of reslizumab was observed were severe exacerbations in the adult base-case population, FEV₁ improvement at 4 weeks in the base-case population and eosinophil counts in the overall population.

Safety findings

- No significant differences between the treatments with respect to safety outcomes were observed.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.future-science.com/doi/suppl/10.2217/imt-2019-0113

Financial & competing interests disclosure

This study was sponsored by Teva Pharmaceuticals. Teva Pharmaceuticals did not participate in study screening or data extraction. K Yan, E Druyts, C Balijepalli and R Sharma are former employees of Precision Xtract; all declare they have no conflicts of interest. SX Sun is a former employee of Teva Pharmaceuticals USA, and S Barakat and S Falcao are former employees of Teva Canada Innovations. JM Fitzgerald is a professor at University of British Columbia and serves on the advisory board of GSK, AstraZeneca, Boehringer Ingelheim, Novartis, and Sanofi Regeneron. JM Fitzgerald received research grants from GSK, AstraZeneca, Sanofi and Novartis through University of British Columbia. JM Fitzgerald also received honoraria from AstraZeneca, Boehringer Ingelheim, Novartis, Sanofi Regeneron, and GSK. The authors have no other relevant affiliations or financial involvement with any organization

or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Medical writing support was provided by IC Grieve of Ashfield Healthcare Communications, part of UDG Healthcare plc, and was funded by Teva Pharmaceuticals.

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