

Real-World Effectiveness of Mepolizumab in Severe Eosinophilic Asthma: A Systematic Review and Meta-analysis

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ABSTRACT

Purpose: Mepolizumab is a human monoclonal antibody against interleukin 5 (IL-5) used to treat severe eosinophilic asthma. Several studies have evaluated the effectiveness of mepolizumab in the real world. We conducted a systematic review and meta-analysis in the context of heterogeneity among patients, clinicians, and treatment regimens to study the effectiveness of mepolizumab in the real world.

Methods: We searched the PubMed and Embase databases for real-world studies on severe asthma treatment with mepolizumab as of June 30, 2020. Exacerbations, asthma-related hospitalizations, forced expiratory volume in 1 second (FEV₁), Asthma Control Questionnaire (ACQ) or Asthma Control Test (ACT), corticosteroid use, peripheral blood eosinophil counts, and the fraction of exhaled nitric oxide were selected as indicators to evaluate the effectiveness. Standardized mean differences by the Cohen method and mean differences were chosen as indicators of effect size. Cohen *d* values of 0.2, 0.5, and 0.8 are considered as small, medium, and large effects, respectively. We used the Dersimonian-Laird random-effect model to quantify pooled effectiveness estimates.

Findings: A total of 1457 patients from 13 studies were included in this review. At all time points, mepolizumab was associated with reductions in exacerbations (2.92 and 2.73 events per patient per year fewer at 6 and 12 months, respectively) and hospitalizations (0.36 events per patient per year fewer at 12 months); improvements in asthma control (ACQ scores reductions of 1.32 and 1.03 at 6 and 12 months, respectively; ACT scores increase of 6.52

at 6–12 months); slight improvements in pulmonary function (FEV₁ increase of 0.23 L at 1–3 months and 6–12 months, respectively); reductions in oral corticosteroid use (9.02- and 7.68-mg decrease at 6 and 12 months, respectively); and reductions in peripheral blood eosinophil counts (decreases of 559.11 cells/ μ L and 599.17 cells/ μ L at 1–3 months and 6–12 months, respectively) and fraction of exhaled nitric oxide (13-ppb reduction at 6–12 months).

Implications: Our study suggests that mepolizumab is associated with improvements in several clinically meaningful real-world outcomes. This study is a supplement to and extension of the efficacy of randomized controlled trials of mepolizumab. (*Clin Ther.* 2021;XX:XXX-XXX) © 2021 Elsevier HS Journals, Inc. (*Clin Ther.* 2021;000:1–17.) © 2021 Published by Elsevier Inc.

Key words: effectiveness, mepolizumab, meta-analysis, real world, severe eosinophilic asthma.

INTRODUCTION

Severe eosinophilic asthma (SEA) is a subgroup of severe asthma, often with elevated blood and/or airway eosinophils, accompanied by the most significant risk of severe deterioration and bronchial obstruction. Patients with SEA usually need high doses of inhaled corticosteroids plus long-acting β -agonists and other

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treatments, including oral corticosteroids (OCSs), long-acting muscarine anticholinergic, or biotherapy.¹ A large number of randomized clinical trials (RCTs) have found that biotherapy can improve asthma symptoms, exacerbation rates, and lung function and decrease OCS use.^{2,3} However, studies have found that >80% of patients with severe asthma are excluded from recent studies evaluating biotherapy.^{4,5} This finding limits RCT data application in the real world and challenges the real-world effectiveness of biotherapy in severe asthma. Data from real-world observational research can be used to solve this challenge.^{6,7}

Mepolizumab is a human monoclonal antibody against interleukin 5 (IL-5) for the treatment of SEA.⁸ Clinical studies have found that they reduce asthma exacerbations, OCS dosages, improve asthma control, pulmonary function, and cut down peripheral blood eosinophil (PBE) counts.^{9–14} To assess whether the data from RCTs apply to a broader population, real-world data on mepolizumab in patients with SEA are needed. Several studies have found that mepolizumab has positive clinical outcomes in people with SEA in the real world.^{15–27} Our research attempts to evaluate the real-world effectiveness of mepolizumab under the conditions of significant heterogeneity in patients, clinicians, and treatment regimens.

METHODS

Search Strategy

We searched the PubMed and Embase databases for relevant articles published before July 30, 2020, using the keywords *asthma*, *mepolizumab*, *real-world study*, and *observational*. We included observational studies of patients with SEA exposed to mepolizumab that reported acute exacerbation and/or hospitalization data. All English-language articles were included. Studies that did not report acute exacerbation and/or hospitalizations data, nonobservational studies, and duplicate records were excluded.

Data Extraction

At least 2 reviewers evaluated each study. We extracted each study's main characteristics, including the first author's last name, published year, study time, study areas, study types, number of participants, patient demographic characteristics, outcomes, effect size, and 95% CI. Any discrepancies were reconciled among the reviewers or, if not reconciled, escalated to a third person.

Outcomes

Acute exacerbations and hospitalizations were used to evaluate the health care resource utilization outcomes. Four studies did not mention the definition of acute exacerbations. In the other 5 studies, acute exacerbations were defined as the need for additional systemic corticosteroids for >2 to 5 days, and 3 of the studies required emergency treatment or hospitalization. Exacerbations and asthma-related hospitalizations were reported in annualized incidence rates. The Asthma Control Questionnaire (ACQ) and Asthma Control Test (ACT) are tools to evaluate asthma control.^{28,29} ACT scores range from 5 to 25 (higher is better). ACQ scores range from 0 to 6 (higher is worse). Lung function, especially forced expiratory volume in 1 second (FEV₁), is critical to the evaluation of asthma therapy.³⁰ Blood eosinophils and the fraction of exhaled nitric oxide (FeNO) are common biomarkers for assessing eosinophilic inflammation.³¹ The proportion and dose of OCSs required were also included in this meta-analysis.

Statistical Analysis

Two effect size types were extracted from the literature: number of patients requiring OCSs before and after mepolizumab treatment and odds ratios (ORs). Continuous measures, such as exacerbations, asthma-related hospitalizations, FEV₁, OCS dosages, PBE counts, FeNO, ACQ score, and ACT score, were extracted as pretreatment and posttreatment means (SDs). If the study provided only medians, interquartile ranges, or maximum and minimum values, we estimated the means and SDs according to the method of Luo et al.³² and Wan et al.³³ Standardized mean differences (SMDs) by the Cohen method and mean differences (MDs) were selected as effect size. SMDs by the Cohen method of 0.2, 0.5, and 0.8 are considered small, medium, and large effects, respectively. Considering the paucity of studies providing some outcomes (such as the ACT score, FEV₁, FeNO, and PBE counts), we conducted a meta-analysis of these studies from 1 to 3 months or 6 to 12 months together.

Considering the differences and diversity of the participants, clinicians, and measurement results, we used the Dersimonian-Laird random-effect model to quantify pooled effectiveness estimates in this meta-analysis. Weighted pooled effectiveness estimates and 95% CIs were reported. We use Q and I^2 statistics

to assess heterogeneity. The Q statistic corresponds to $P < 0.1$ or $I^2 \geq 50$, which means significant statistical heterogeneity among different studies.³⁴ The Egger test³⁵ and the trim-and-fill test were used to estimate publication bias and evaluate publication bias's impact on the results. Sensitivity analysis was used to assess the influence of a single study on the overall meta-analysis estimate. Our meta-analysis followed the recommendations of the meta-analysis of observational studies in epidemiology.³⁶ All statistical analyses were performed with Stata software, version 15.0 (StataCorp, College Station, Texas).

RESULTS

A total of 92 studies were initially screened out, of which 15 were excluded for duplicates, 10 for reviews, 5 for editorials, 31 for conference abstracts, and 18 for unrelated studies. Finally, 13 studies were included in this meta-analysis.^{15–27} (Figure 1).

Study Design

Patient demographic and clinical data are presented in Table I. The 13 studies were from 8 countries and 69 centers, including 10 retrospective studies^{15–17,20–24,26,27} and 3 prospective studies.^{18,19,25} All the included patients received mepolizumab 100 mg subcutaneously every 4 weeks. The follow-up time ranged from 6 to 36 months. Four studies lasted for 6 months,^{16–18,23} and 7 lasted for 12 months.^{15,19–22,24,27} Taillé et al²⁶ prospectively followed up the patients for 24 months. Pertzov et al²⁵ reviewed the condition of patients treated within 36 months. The primary time points for evaluation were 3,^{16,19,21,25,26} 6,^{16–19,21,23,26,27} and 12 months^{15,19–22,24,27} after treatment, and a few studies assessed the time points at 1,^{16,18,23} 18,²⁶ and 24 months²⁶ after treatment.

Because of the difference in experimental designs and research centers, evaluation of outcome indicators in different studies is also different. Asthma exacerbations and hospitalizations are the most commonly used outcomes. Most studies also reported the use of OCS, lung function, FeNO, PBE count, ACT score, and ACQ score as the clinical outcomes to evaluate mepolizumab's effectiveness. A few studies also assessed quality of life^{19,20,25} and adverse events^{15,17,19,21,26,27}. Time points of assessments and effectiveness assessments are reported in Table II and Table III.

Patients

A total of 1457 patients were included in the study. The mean age was approximately 50 years, ranging from 49 to 60 years. Bagnasco et al¹⁵ and Caminati et al¹⁶ enrolled patients ranging in age from 21 to 81 years. Harvey et al¹⁹ and Llanos et al²² enrolled people older than 12 years with severe asthma, whereas Pertzov et al²⁵ and Van Toor et al²⁷ enrolled people older than 18 years. The number of female patients was slightly higher (57.6%). A total of 9 studies reported body mass index,^{16–21,24,26,27} with the mean body mass index ranging from 24.0 to 30.5 kg/m². According to the report, between 15.9% and 50.0% of patients were current or former smokers.^{17–20,24,26,27} Between 42.5% and 67.7% of patients reported allergies.^{17,19,20,23,26,27} Four studies reported baseline IgE levels, and 5 reported that some patients had used omalizumab before mepolizumab (Table I).

Health Care Resource Utilization Outcomes

There was a total of 9 studies related to asthma exacerbations. There was a significant and considerable reduction in exacerbations after 6 (SMD = 1.39; 95% CI, 0.77–2.02; mean, 2.92 events per patient per year fewer exacerbations)^{16,17,23} and 12 months of therapy (SMD = 1.23; 95% CI, 0.88–1.58; mean, 2.73 events per patient per year fewer exacerbations)^{15,20–22,24–27} (Figure 2). For the 12-month subgroup, the Egger test suggested publication bias ($P = 0.048$), but asthma exacerbations remained significantly and substantially reduced by the trim-and-fill test (SMD = 0.92; 95% CI, 0.61–1.22). Removing the studies of Kavanagh et al²⁰ and Llanos et al²² from the 12-month subgroup, the number of exacerbations was still significantly reduced compared with the baseline (SMD = 1.45; 95% CI, 1.30–1.59), and no significant heterogeneity between studies was found ($I^2 = 8.7\%$).

Regarding the number of asthma-related hospitalizations, there was a significant reduction after 12 months of therapy with mepolizumab (SMD = 0.51; 95% CI, 0.27–0.75; mean, 0.36 events per patient per year fewer hospitalizations) (Figure 3).^{15,22,26,27}

Clinical Outcomes

Two scales were used for assessing asthma control. At 4 weeks after the first injection, the ACQ score had improved significantly (mean [SD], –1.1 [0.8]),¹⁸ and the ACT score also increased from a mean (SD) of 13.64 (3.00) to 18.86 (3.15).²³ Langton et

Table I. Patient demographic characteristics and clinical status data.

Study	Design	No. of Centers (n = 69)	Country	Follow-up, mo	Evaluable No. at baseline (mepolizumab- treated)	Age, y	Female, No. (%)	BMI, kg/m ²	Smokers, No. (%)	IgE, IU/mL	Allergies, No. (%)	Previous Omalizumab Treatment, No. (%)
Bagnasco et al, ¹⁵ 2019	Retrospective	11	Italy	12	138	58 (10)*	78 (56.5)		22 (15.9)			18 (13.0)
Caminati et al, ¹⁶ 2019	Retrospective	6	Italy	6	69	55.4 (11.9)*	42 (60.9)	24 (3.8)*				
Drick et al, ¹⁷ 2018	Retrospective	1	Germany	6	42	51 (45–59) [†]	19 (45.2)	28 (24–34) [†]	21 (50.0)	128 (77– 1222) [†]	24 (57.1)	
Farah et al, ¹⁸ 2019	Prospective	1	Australia	6	20	60 (16)*	8 (40.0)	29.6 (6.1)*	4 (20.0)			
Harvey et al, ¹⁹ 2020	Prospective	20	Australia	12	309	59.55 (49.99– 68.28) [†]	178 (57.6)	29.45 (25.30–34.46) [†]	118 (38.2)	137.5 (53.0– 479.0) [†]	156 (50.5)	16 (5.2)
Kavanagh et al, ²⁰ 2020	Retrospective	1	United Kingdom	12	99	53.47 (13.18)*	52 (52.5)	29.88 (5.76)*	36 (36.4)		67 (67.7)	20 (20.2)
Langton et al, ²¹ 2020	Retrospective	1	Australia	12	47	61.3 (12.6)*	26 (55.3)	30.5 (6.0)*		288 (595)*		
Llanos et al, ²² 2020	Retrospective	1	United States	12	346	49.3 (12)*	213 (61.6)					
Pelaia et al, ²³ 2018	Retrospective	1	Italy	6	14	56.79 (9.68)*	11 (78.6)				8 (57.1)	
Pelaia et al, ²⁴ 2020	Retrospective	4	Italy	12	88	54.51 (10.8)*	57 (64.8)	26.85 (22.78–30.00) [†]	23 (26.1)			
Pertzovet al, ²⁵ 2019	Prospective	1	Israel	12	61	57.46 (13.23)*	35 (57.4)					
Taillé et al, ²⁶ 2020	Retrospective	20	French	24	146	58.2 (13.6)*	66 (45.2)	27.2 (5.1)*	68 (46.6)	563.4 (773.0)*	62 (42.5)	91 (62.3)
van Toor et al, ²⁷ 2020	Retrospective	1	Netherlands	12	78	54 (20–83) [‡]	54 (69.2)	28.4 (20.9–57.7) [†]	27 (34.6)		34 (43.6)	18 (23.1)

BMI = body mass index.

* Mean (SD).

† Median (interquartile range).

‡ Mean (range).

Table II. Time points of assessments reported and effectiveness assessments reported.

Study	Response			Exacerbations		Hospitalizations at 12 mo	Asthma Control: ACQ				Asthma Control: ACT				Quality of Life (Mini-AQLQ, HRQoL)		
	1 mo	6 mo	12 mo	6 mo	12 mo		1 mo	3 mo	6 mo	12 mo	1 mo	3 mo	6 mo	12 mo	3 mo	6 mo	12 mo
Bagnasco et al, ¹⁵ 2019					✓	✓								✓			
Caminati et al, ¹⁶ 2019	✓	✓		✓							✓	✓	✓				
Drick et al, ¹⁷ 2018		✓			✓								✓				
Farah et al, ¹⁸ 2019							✓		✓				✓				
Harvey et al, ¹⁹ 2020		✓	✓		✓			✓	✓	✓					✓	✓	✓
Kavanagh et al, ²⁰ 2020			✓		✓					✓							✓
Langton et al, ²¹ 2020				✓	✓			✓	✓	✓							
Llanos et al, ²² 2020					✓	✓											
Pelaia et al, ²³ 2018				✓							✓		✓				
Pelaia et al, ²⁴ 2020					✓									✓			
Pertsov et al, ²⁵ 2019		✓			✓												✓
Taillé et al, ²⁶ 2020					✓	24 mo					*						
van Toor et al, ²⁷ 2020		✓	✓		✓	✓			✓	✓				✓			

ACQ = Asthma Control Questionnaire; ACT = Asthma Control Test; HRQoL = health-related quality of life; mini-AQLQ, mini-Asthma Quality of Life Questionnaire.

* No specific values were provided.

Table III. Time points of assessments reported and effectiveness assessments reported.

Study	Lung Function: FEV ₁				Lung Function: Other Objective				Peripheral Blood Eosinophil Counts					FeNO				Oral Corticosteroid Use			Adverse Events	
	1 mo	3 mo	6 mo	12 mo	1 mo	3 mo	6 mo	12 mo	1 mo	3 mo	6 mo	12 mo	Other	1 mo	3 mo	6 mo	12 mo	6 mo	12 mo	Other	6 mo	12 mo
Bagnasco et al, ¹⁵ 2019				✓								✓					✓					✓
Caminati et al, ¹⁶ 2019	✓	✓	✓		✓	✓	✓		✓		✓			✓	✓	✓		✓			✓	
Drick et al, ¹⁷ 2018			✓															✓			✓	
Farah et al, ¹⁸ 2019	✓		✓		✓		✓							✓		✓						
Harvey et al, ¹⁹ 2020		✓	✓	✓						✓		✓*						✓	✓			✓
Kavanagh et al, ²⁰ 2020				✓				✓				✓					✓		✓			
Langton et al, ²¹ 2020			✓	✓			✓	✓											✓		✓	
Llanos et al, ²² 2020																			✓			
Pelaia et al, ²³ 2018	✓		✓		✓		✓		✓		✓							✓				
Pelaia et al, ²⁴ 2020				✓								✓					✓		✓			
Pertzovet al, ²⁵ 2019		✓		✓						✓									✓			
Taillé et al ²⁶ 2020		*					✓			✓		✓	24 mo					✓		3 mo, 18 mo, 24 mo	✓	
van Toor et al ²⁷ 2020			✓	✓			✓	✓				✓				✓*	✓*	✓	✓		✓	✓

FeNO = fraction of exhaled nitric oxide = FEV₁, forced expiratory volume in 1 second.

* No specific values were provided.

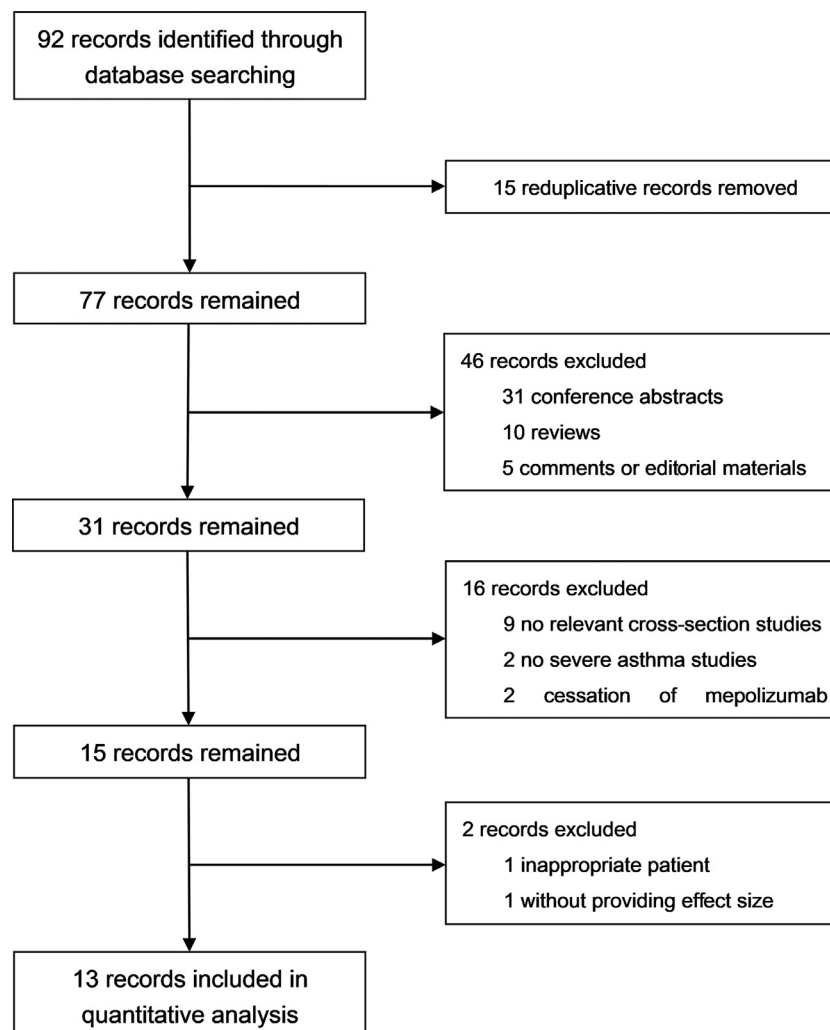


Figure 1. Flow diagram of research screening.

al²¹ found that after 3 months of treatment the ACQ score decreased significantly (from 3.7 [1.0] to 2.2 [1.1]), whereas Harvey et al¹⁹ found similar results (data not given). The ACQ scores were also significant and largely improved after 6 (SMD = 1.15; 95% CI, 0.61–1.70; mean, 1.32 score reduction)^{18,22,27} and 12 (SMD = 0.84; 95% CI, 0.23–1.45; mean, 1.03 score reduction) months of treatment (Figure 4A).^{20,21,27} In addition, significant and large ACT score improvements were found after 6 to 12 months of treatment (SMD = 1.83; 95% CI, 1.17–2.49; 6.52 score improvement)^{15,17,24} (Figure 4B).

Regarding pulmonary function, the FEV₁ was significantly improved after 1 to 3 (SMD = 0.29; 95%

CI, 0.01–0.58; 0.23-L increase)^{18,23,25} and 6 to 12 (SMD = 0.30; 95% CI, 0.07–0.53; 0.23-L increase) months of treatment with mepolizumab^{15,18,20,23,24} (Figure 5).

Large and significant improvements occurred in PBE counts after 1 to 3 (SMD = 1.83; 95% CI, 1.33–2.33; 559.11-cells/ μ L reduction)^{16,19,23,25,26} and 6 to 12 (SMD = 1.63; 95% CI, 1.15–2.11; 599.17-cells/ μ L reduction) months of treatment with mepolizumab^{15,16,20,24,26} (Figure 6A).

Regarding FeNO, van Toor et al²⁷ did not find significant improvement in FeNO after 6 and 12 months of treatment (data not given). Five studies were eventually included in the meta-analysis on FeNO. There were

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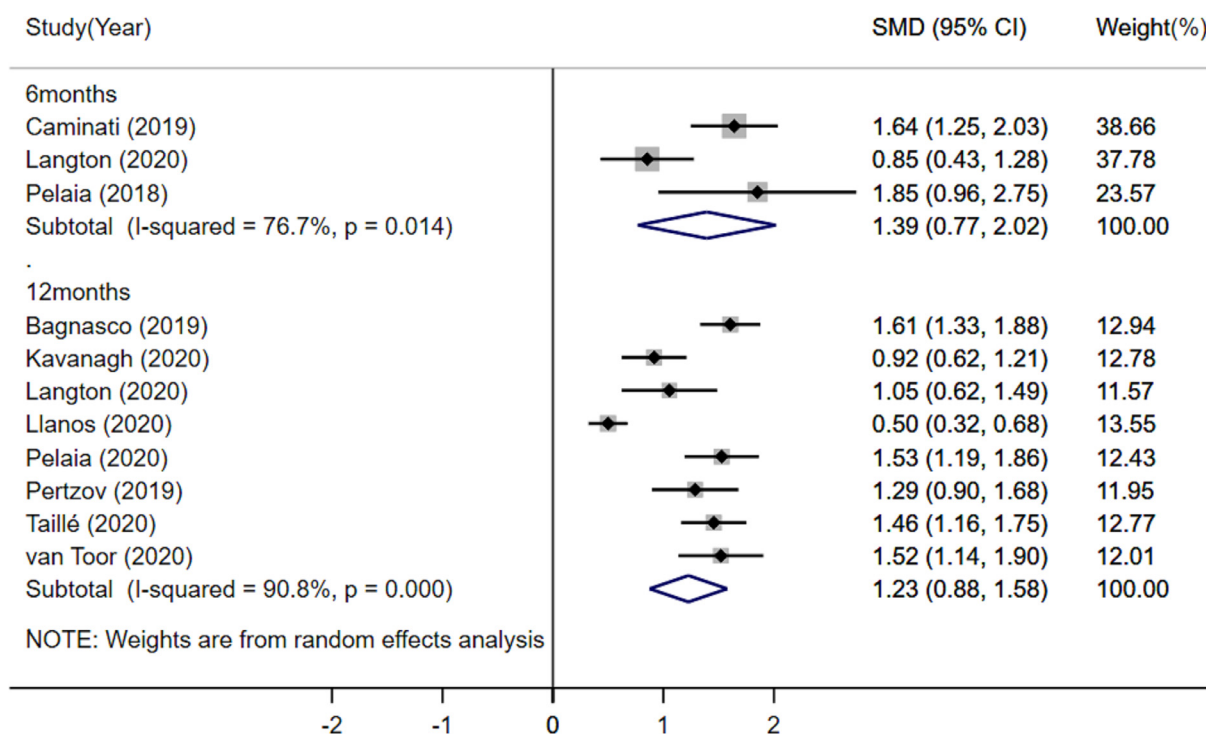


Figure 2. Forest plots for the improvement in asthma exacerbation. There was a significant and considerable reduction in the number of exacerbations after 6 and 12 months of therapy with mepolizumab. SMD = standardized mean difference.

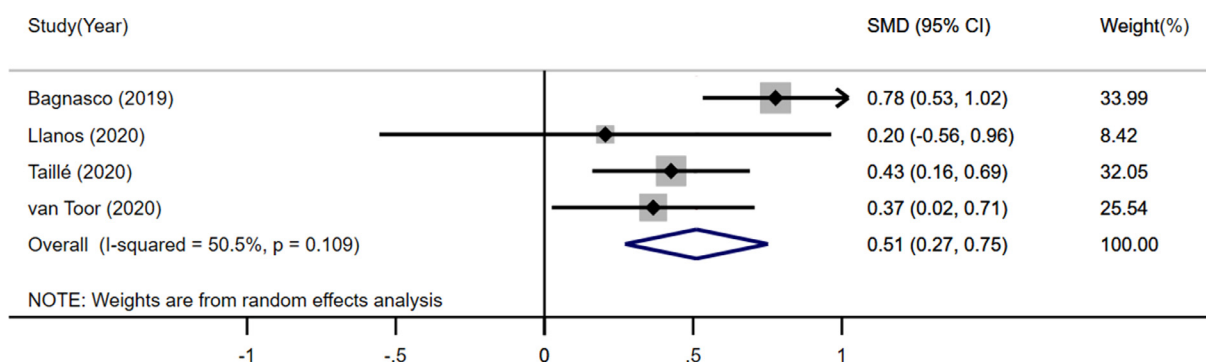


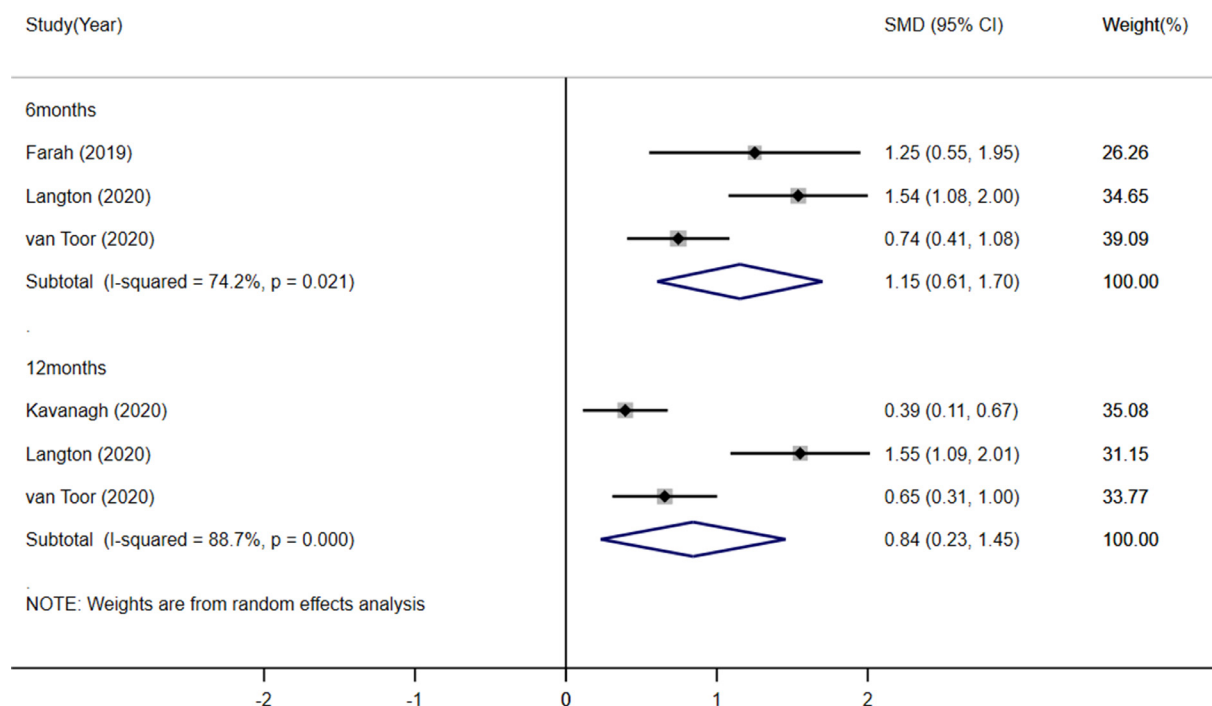
Figure 3. Forest plots for the improvement in asthma-related hospitalizations. Hospitalizations were significantly reduced after 1 year of therapy with mepolizumab. SMD = standardized mean difference.

significant improvements in FeNO after 6 to 12 months of mepolizumab therapy (SMD = 0.34; 95% CI, 0.07–0.62; 13-ppb reduction) (Figure 6B).^{15,16,18,20,24} Removing the study by Bagnasco et al,¹⁵ we found no significant heterogeneity between studies ($I^2 = 0.0\%$),

and the result was still substantially reduced compared with baseline (SMD = 0.22; 95% CI, 0.04–0.40).

Only 3 studies evaluated quality of life. Harvey et al¹⁹ and Pertzov et al²⁵ found the health-related quality of life to be significantly and increasingly improved

A



B

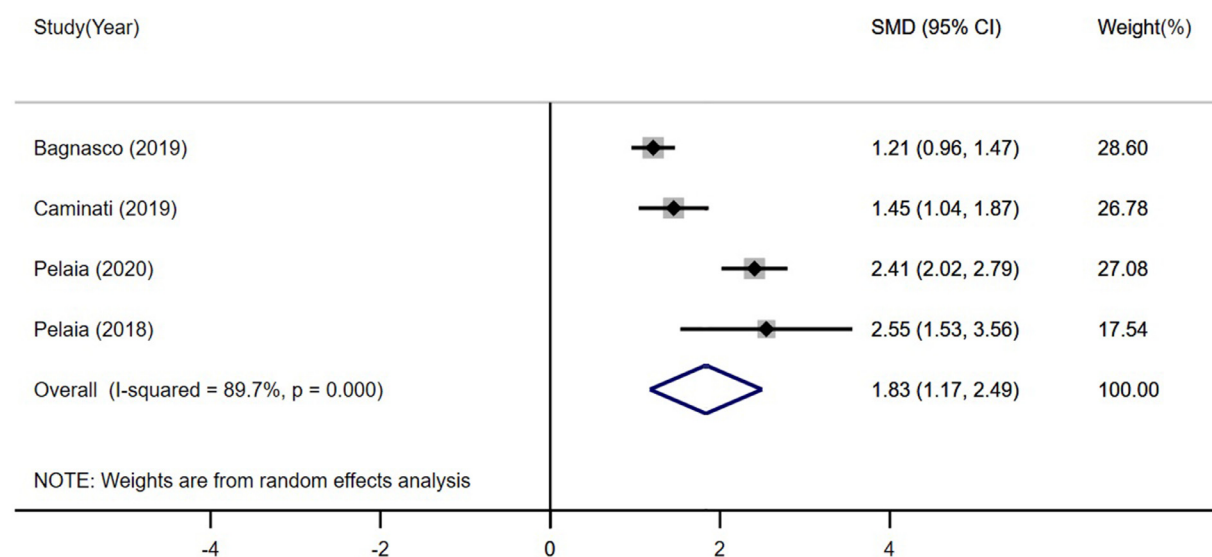


Figure 4. Forest plots for asthma control. A, Improvements in Asthma Control Questionnaire (ACQ) scores. ACQ scores were significantly and largely improved after 6 and 12 months of mepolizumab treatment. B, Improvements in Asthma Control Test (ACT) score. ACT scores were significantly and largely improved after 6 to 12 months of mepolizumab treatment. SMD = standardized mean difference.

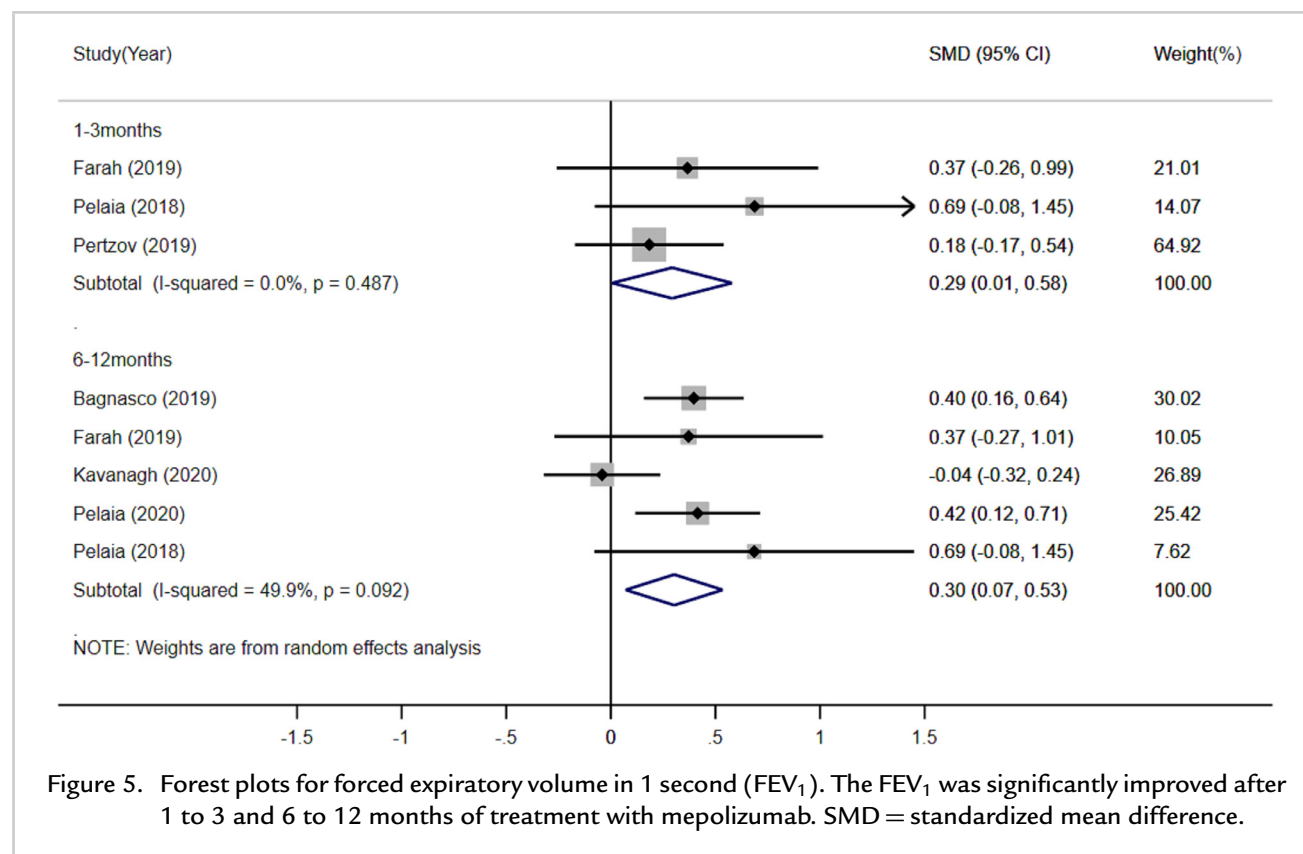


Figure 5. Forest plots for forced expiratory volume in 1 second (FEV₁). The FEV₁ was significantly improved after 1 to 3 and 6 to 12 months of treatment with mepolizumab. SMD = standardized mean difference.

(data not given). In the study by Kavanagh et al,²⁰ the quality-of-life score as measured by the mini Asthma Quality of Life Questionnaire increased by 0.86 from 4.05 (1.34) to 4.91 (1.54).

Oral Corticosteroids

Patients were much less likely to require OCSs after 6 (OR = 0.29; 95% CI, 0.17–0.50)^{16,19,26,27} and 12 (OR = 0.19; 95% CI, 0.10–0.37) months mepolizumab of therapy (Figure 7A).^{15,17,20–22,24–27} The OCS dosages were also significantly decreased after 6 (SMD = 0.90; 95% CI, 0.38–1.42; 9.02-mg reduction)^{16,19,23,26} and 12 (SMD = 0.77; 95% CI, 0.39–1.15; 7.68-mg reduction) months of therapy (Figure 7B).^{15,17,20,21,25,26} For OCS dosages, publication bias was found among the 6-month subgroup (Egger test $P = 0.036$), and OCS dosages had a significant impact on the final results (trim-and-fill test: SMD = 0.554, $P = 0.066$).

Publication Bias

Except for the 12-month subgroup of asthma exacerbation and the 6-month subgroup of OCS dosages, no significant publication bias was found in

the meta-analysis results of random effects for other outcomes. The results of the meta-analysis statistical analysis are summarized in Table IV

Adverse Events

The adverse events of observational study depend on voluntary reporting under local laws and regulations. The extent and scope of data on tolerability generated by different regions and research centers are different. Table V summarizes the incidence of adverse events associated with mepolizumab treatment in each study. A total of 6 studies reported adverse events, the most common of which were headache, local injection reaction, and arthralgia.^{15,17,19,21,26,27}

DISCUSSION

Currently, a large number of RCTs have confirmed the pharmacotherapeutic efficacy of mepolizumab and have been extensively reviewed.^{37,38} Several studies have evaluated the effectiveness of mepolizumab in the real world,^{15–27} but to the best of our knowledge, this is the first review of those real-world studies. In summary, despite considerable heterogeneity among patients, clinicians, and treatment regimens, mepolizumab is still

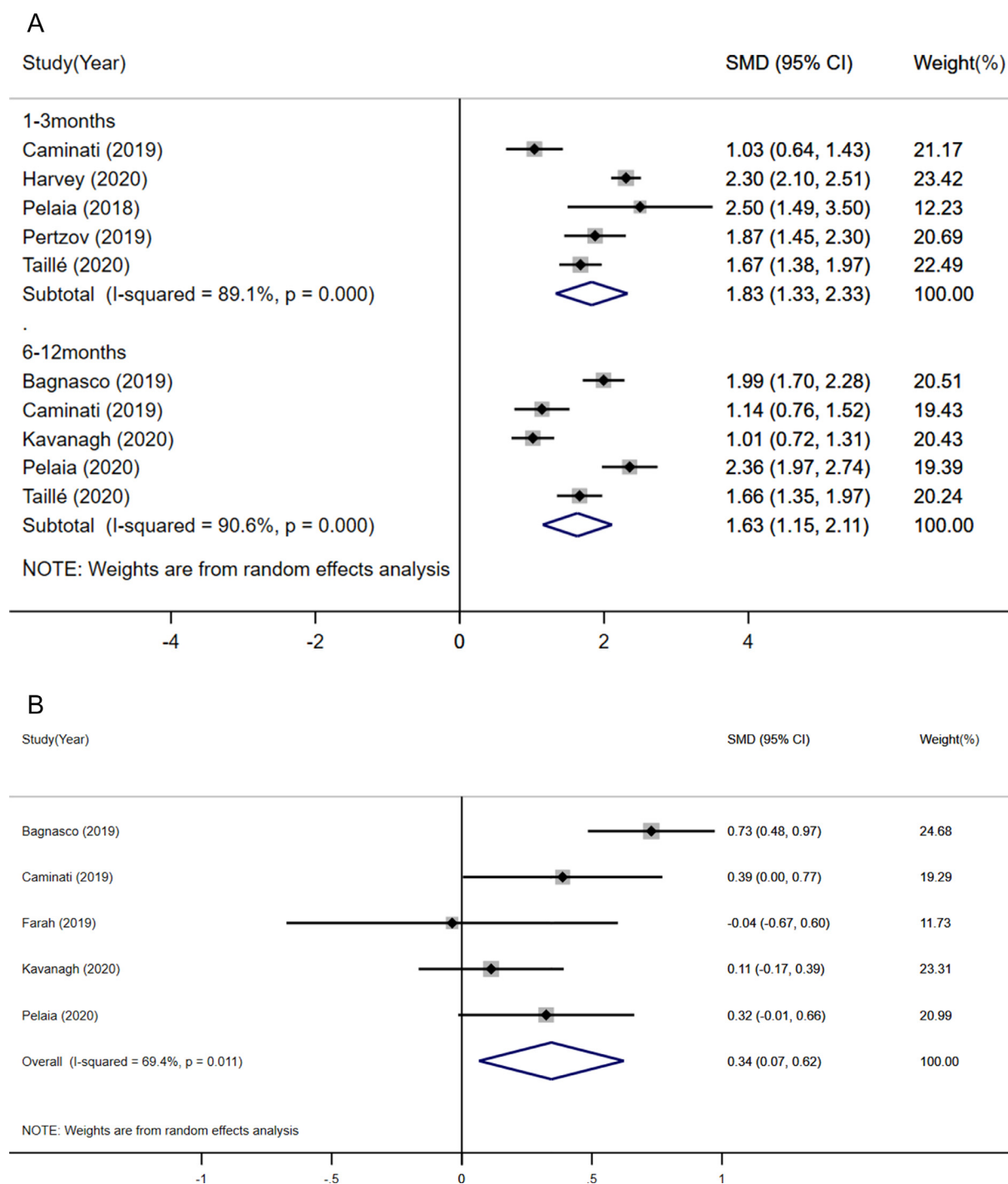


Figure 6. Forest plots for biomarkers of eosinophilic asthma. A, Improvement in peripheral blood eosinophil (PBE) counts. There were large and significant reductions in PBE counts after 1 to 3 and 6 to 12 months of treatment with mepolizumab. B, Improvement in fraction of exhaled nitric oxide (FeNO). There were substantial reductions in FeNO after 6 to 12 months of mepolizumab therapy. SMD = standardized mean difference.

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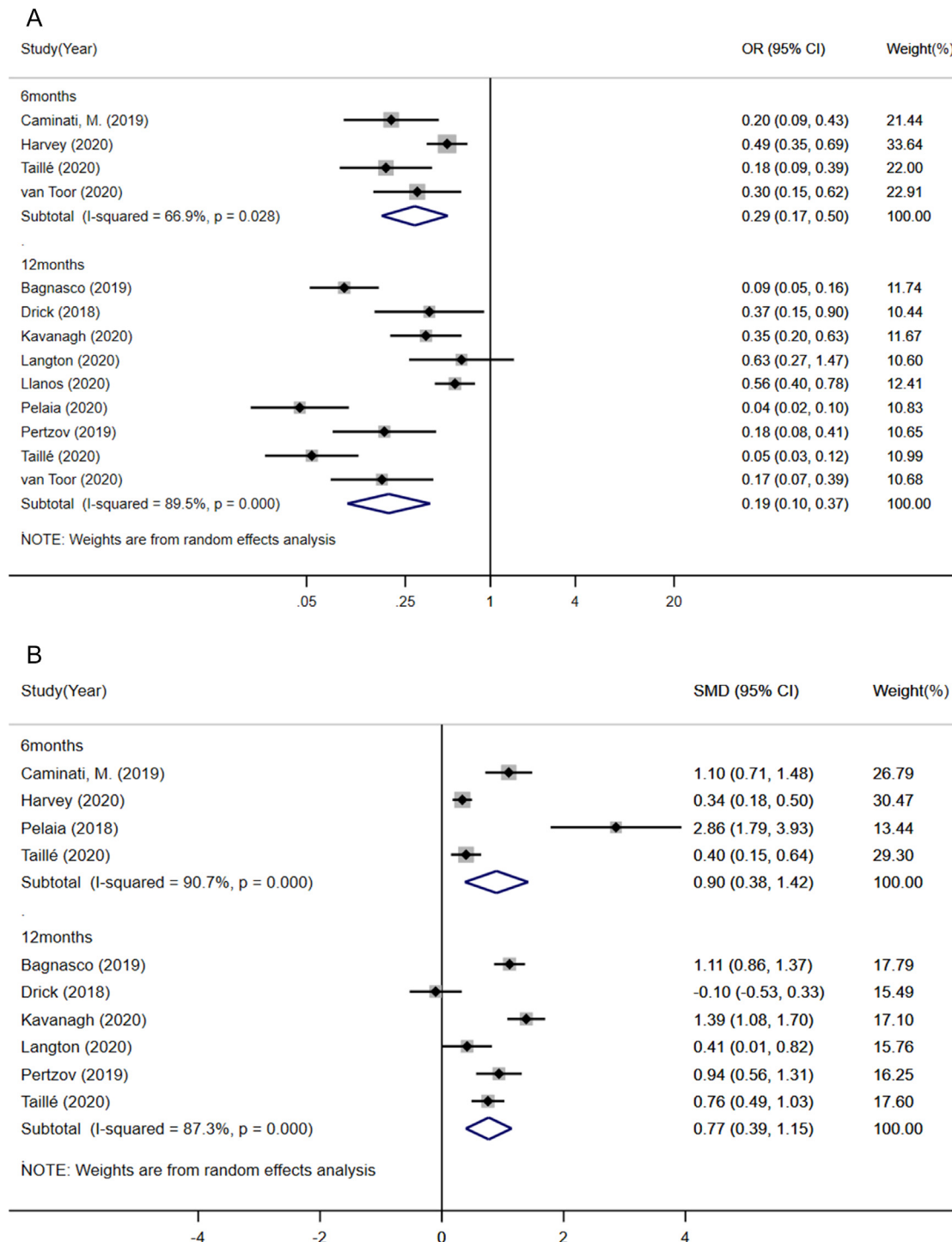


Figure 7. Forest plots for oral corticosteroids. A, Reduction in the proportion of patients requiring oral corticosteroids (OCSs). Patients were much less likely to require OCSs after 6 and 12 months of mepolizumab of therapy. After 6 months, the proportion of patients requiring OCSs decreased from 61% to 38%, and after 12 months, the proportion decreased from 59% to 26%. B, Reduction in OCS dosages. The OCS dosages were also significantly decreased after 6 and 12 months of therapy. SMD = standardized mean difference.

Table IV. Summary of meta-analysis statistics.

	3 mo						6 mo						12 mo					
	n	Effect Size (95% CI)	Q	I ² , %	z	P	n	Effect Size (95% CI)	Q	I ² , %	z	P	n	effect size (95% CI)	Q	I ² , %	z	P
Exacerbations / per patient per year, MD							126	2.92 (1.39–4.45)	16.41	87.8	3.74	<0.001	811	2.73 (1.88–3.59)	124.8	94.4	6.24	<0.001
Exacerbations, SMD								1.39 (0.77–2.02)	8.58	76.7	4.37	<0.001		1.23 (0.88–1.58)	76.17	90.8	6.86	<0.001
Hospitalizations per patient per year, MD													302	0.36 (0.15–0.56)	8.48	64.6	3.46	0.001
Hospitalizations, SMD														0.51 (0.27–0.75)	6.06 [†]	50.5	4.16	<0.001
ACT score, MD*							292	6.52 (4.73–8.32)	23.84	87.4	7.12	<0.001						
ACT, SMD*								1.83 (1.17–2.49)	29.02	89.7	5.45	<0.001						
ACQ score, MD							145	1.32 (0.71–1.93)	8.79	77.2	4.23	<0.001	224	1.03 (0.30–1.77)	17.88	88.8	2.75	0.006
ACQ, SMD								1.15 (0.61–1.70)	7.76	74.2	4.13	<0.001		0.84 (0.23–1.46)	17.66	88.7	2.7	0.007
FEV ₁ , MD, L* [‡]	95	0.23 (0.03–0.42)	0.57 [†]	0	2.26	0.024	357	0.23 (0.06–0.41)	8.58	53.4	2.62	0.009						
FEV ₁ , SMD* [‡]		0.29 (0.01–0.58)	1.44 [†]	0	2	0.045		0.30 (0.07–0.54)	7.98	49.9	2.56	0.01						
Proportion of patients requiring OCSs, OR (95% CI)							547	0.29 (0.17–0.50)	9.07	66.9	4.48	<0.001	975	0.19 (0.10–0.38)	76.41	89.5	4.82	<0.001
OCS, MD, mg							495	9.02 (2.83–15.20)	70.56	95.7	2.86	0.004	482	7.68 (3.84–11.53)	62.86	92	3.92	<0.001
OCS, SMD								0.90 (0.38–1.42)	32.33	90.7	3.38	0.001		0.77 (0.39–1.15)	39.46	87.3	4.01	<0.001
PBE, mean difference, cells/ μ L* [‡]	536	559.11 (497.46–620.77)	8.12	50.7	17.77	<0.001	471	599.17 (321.23–877.11)	223.27	98.2	4.23	<0.001						
PBE, SMD* [‡]		1.83 (1.33–2.33)	36.67	89.1	7.2	<0.001		1.63 (1.15–2.11)	6.65	90.6	6.65	<0.001						
FeNO, MD, ppb*							380	13.17 (0.64–25.69)	20.26	80.3	2.06	0.039						
FeNO, SMD*								0.35 (0.07–0.62)	13.05	69.4	2.43	0.015						

ACQ = Asthma Control Questionnaire; ACT = Asthma Control Test; FeNO = fraction of exhaled nitric oxide; FEV₁ = forced expiratory volume in 1 second; MD = mean difference; OCS = oral corticosteroids; OR = odds ratio; PBE = peripheral blood eosinophil; SMD = standard mean difference.

* Six- to 12-month meta-analysis.

[†] Nonsignificant between-study heterogeneity.

[‡] One- to 3-month meta-analysis.

Table V. Adverse drug-related reactions in patients treated with mepolizumab.

Reaction	No. (%) of adverse drug-related reactions					
	Bagnasco et al, ¹⁵ 2019	Drick et al, ¹⁷ 2018	Harvey et al, ¹⁹ 2020	Langton et al, ²¹ 2020	Taillé et al, ²⁶ 2020	van Toor et al, ²⁷ 2020
Headache	1 (0.7)	3 (7.1)	2 (0.6)	2 (4.3)	14 (9.6)	7 (9.0)
Myalgia/arthralgia	2 (0.7)	2 (4.8)	1 (0.3)	2 (4.3)		
Local site injection reaction	6 (4.3)	2 (4.8)			1 (0.7)	
Back pain			1 (0.3)			6 (7.7)
Urinary tract infection	1 (0.7)					5 (6.4)
Nausea		1 (2.3)				3 (3.9)
Dizziness	1 (0.7)					2 (2.6)
Asthenia					12 (8.2)	3 (3.9)
allergic symptoms						2 (2.6)
Urticaria	1 (0.7)					
Rash				1 (2.1)	2 (1.4)	
eczematous			1 (0.3)			
Asthma					3 (2.1)	
Pruritus			1 (0.3)			
Infections*					5 (3.4)	
Insomnia						2 (2.6)
Cardiac and vascular disorders [†]					6 (4.1)	
PSVT	1 (0.7)					
Diarrhea	1 (0.7)					
Spinal disk herniation						3 (3.9)

PSVT = paroxysmal supraventricular tachycardia.
 * Herpes or respiratory infection.
 † Hot flush, capillary fragility, hypertension, and palpitations.

associated with reductions in exacerbations, asthma-related hospitalizations, OCS use, and improvements in pulmonary function (FEV₁), asthma control (ACT and ACQ), FeNO, and PBE counts.

Currently, most guidelines point out that the long-term goals of asthma are to achieve well symptom control and minimize the risk of future acute exacerbations, irreversible airflow restriction, and treatment adverse effects. According to our analysis, these goals are basically achieved in the real-world application of mepolizumab, and the airway and body inflammation levels are also improved. After a short period of treatment (1–3 months) with mepolizumab, FEV₁ improved slightly (small effect), and PBE counts decreased significantly (large effect). After 6 months of treatment, the exacerbations and asthma control (ACQ score) improved significantly, and at the same time, the number of people who use OCSs decreased significantly. At 6 to 12 months, ACT scores and PBE counts were considerably improved, whereas FEV₁ and FeNO were only moderately ameliorated (medium effect). After 1 year of treatment, we also found that the acute exacerbations, asthma-related hospitalizations, and OCS use were reduced, and asthma control was remarkably improved. Our findings are consistent with the conclusions of clinical studies.^{9–12,14}

In general, after a period of treatment with mepolizumab, except for the apparent improvement of PBE counts, the objective monitoring indicators of pulmonary function and FeNO were only slightly improved (low to medium effect) compared with baseline values. Similar results have been found in previous clinical studies.^{9,10,13,14} FEV₁ was not significantly improved^{10,13,14} or was only slightly improved (<200 mL)⁹ after treatment with mepolizumab. This finding may be attributable to the high remodeling of the airway in these patients. FeNO has an inadequate response to IL-5 therapy, which may be related to different aspects of T2 inflammatory response (eg, IL-4/IL-13).⁸

There is publication bias in the 6-month subgroup of OCS dosages, and the results were not robust after the trim-and-fill test. However, because of the small number of studies included, the Egger test and trim-and-fill test were not reliable; therefore, it is expected that more studies in this area will be performed in the future to solve this problem. According to our statistical analysis, despite publication bias, acute asthma exacerbations were still significantly improved after the trim-and-fill test in the 12-month subgroup,

so publication bias likely had little effect on the final results.

In addition to mepolizumab, several biologics have been approved for the treatment of SEA (benralizumab, dupilumab, omalizumab, and reslizumab), and all are effective in reducing exacerbation rates and have modest certainty in improving asthma control, quality of life, and FEV₁.³⁹ The commonly used IL-5/IL-5 α monoclonal antibodies mepolizumab, benralizumab, and reslizumab can reduce PBE counts and reduce OCS use significantly.^{3,39–42} In indirect comparisons of appropriate doses, no difference was found in efficacy or tolerability among the above anti-IL-5 drugs.^{3,42} However, indirect comparisons have also found that mepolizumab is superior to reslizumab and benralizumab in improving exacerbations and asthma control at the same eosinophilic levels.⁴¹ Because of the lack of head-to-head studies of anti-IL-5 agents, the above comparative findings still require further validation by clinical studies, but anti-IL-5 agents certainly have positive implications in the treatment of SEA.

On the whole, our meta-analysis is highly heterogeneous. Despite the use of statistical methods such as random-effect models, trim-and-fill test, and removal of single studies, the effect remains limited, and heterogeneity in some end points still existed, which may be related to the characteristics of the meta-analysis of observational studies. First, the age, disease severity, and comorbidities of the patients in the observational study meta-analysis could not be unified. Second, because of the lack of rigorous evaluation as RCT studies, the end point evaluation of observational studies is greatly affected by subjective factors. Different research centers, methods (prospective or retrospective), definitions of severe asthma, and acute exacerbations also cause heterogeneity. There are only 3 prospective studies in this meta-analysis. Because the study's end points are not consistent, only 1 or 2 studies mentioned each result, so we did not conduct a subgroup analysis. Although the definition of acute exacerbation in each study is mainly based on additional systemic glucocorticoids, there are slight differences in dose and days, increasing the heterogeneity in this meta-analysis. Currently, our meta-analysis has not been able to explain or eliminate heterogeneity from the perspective of subgroup analysis because patient-level data are not available. As a meta-analysis of observational studies, our study's focus is to observe whether mepolizumab is equally effective in the

other 80% of patients not included in RCT studies⁵ in the real world, where patients, physicians, and treatment strategies are different. Therefore, despite the heterogeneity, we can still draw a relatively positive conclusion from this overall level meta-analysis on the treatment of SEA with mepolizumab. The relative heterogeneity of patients' prognosis suggests that some patients may have a better response to mepolizumab. Considering that these data complement and extend the effectiveness of mepolizumab in a broader range of patients with severe asthma, real-world studies should acquire considerable recognition.

In conclusion, our study is the first meta-analysis of mepolizumab's effectiveness under heterogeneous, nonrestricted conditions, indicating that mepolizumab is still useful in the real world under non-RCT conditions.

CONFLICTS OF INTEREST

All authors declare that: (i) no support, financial or otherwise, has been received from any organization that may have an interest in the submitted work; and (ii) there are no other relationships or activities that could appear to have influenced the submitted work.

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