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To cite this article: Zahi Nachef MD, Amita Krishnan MD, Terry Mashtare PhD, Tingting Zhuang & M. Jeffery Mador MD (2017): Omalizumab versus Mepolizumab as add-on therapy in asthma patients not well controlled on at least an inhaled corticosteroid: A network meta-analysis, Journal of Asthma, DOI: [10.1080/02770903.2017.1306548](https://doi.org/10.1080/02770903.2017.1306548)

To link to this article: <http://dx.doi.org/10.1080/02770903.2017.1306548>



Published online: 01 May 2017.



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Omalizumab versus Mepolizumab as add-on therapy in asthma patients not well controlled on at least an inhaled corticosteroid: A network meta-analysis

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ABSTRACT

Objective: The purpose of this study is to examine the comparative efficacy of Omalizumab (OMA) and Mepolizumab (Mepo) in the treatment of severe asthma by performing a network meta-analysis. **Method: Data Sources:** A systematic review of the literature was performed through four databases from their inception to February 2016. **Study Selections:** Randomized control trials and cohort studies were considered if they addressed the individual efficacy of OMA and Mepo in the treatment of asthma that was not well controlled on inhaled corticosteroids (ICSs) with or without other agents. **Results:** OMA was significantly better than Mepo in improving the Asthma Quality of Life Questionnaire with a mean difference of 0.38 and a confidence interval of (0.21–0.55), $p < 0.0001$, without reaching the minimal clinically important difference of 0.5. No significant difference was seen in Asthma Control Questionnaire, forced expiratory volume in second 1 (FEV1), and Peak Expiratory Flow Rate (PEFR) improvement from baseline. Both medications were successful in reducing the calculated annualized rates of asthma exacerbations (AEs) vs placebo by approximately 50%. The heterogeneity score for the different comparisons were elevated except for the PEFR. **Conclusion:** When compared indirectly via a network meta-analysis, the efficacy of OMA and Mepo was similar in the treatment of asthma that was not well controlled on at least high-dose ICS. The high heterogeneity observed and the different selection criteria for the use of the two drugs do not permit us to make any definitive recommendations for the preferential use of OMA vs Mepo in the patient populations studied. However, the current data do not suggest any major differences in efficacy.

ARTICLE HISTORY

Received 7 December 2016
Accepted 9 March 2017

KEYWORDS

Asthma; Mepolizumab;
Omalizumab; review;
treatment

Introduction

It is estimated that asthma affects about 7.7% of Americans [1]. Among them, 5–10% have severe asthma [2]. According to the international ERS/ATS guidelines, severe asthma is defined as one that requires high-dose inhaled corticosteroid (ICS) therapy in addition to a second controller and/or systemic glucocorticoids to prevent asthma from becoming “uncontrolled” or which remains “uncontrolled” despite this therapy [3]. It is well known that the mainstay of asthma treatment, besides allergen avoidance, is ICS. However in many instances this cornerstone medication is just not sufficient to control the disease. Add-on therapy to ICS for asthma encompasses a large array of medications, including long-acting beta agonists, mast cell stabilizer medications namely leukotriene receptor antagonist, tiotropium, a long-acting muscarinic antagonist that was recently FDA approved for asthma, and immunization therapy against specific allergens in select patients. Two medications in the form of targeted therapy have been approved by the FDA,

Omalizumab (OMA) in June 2003 and Mepolizumab (Mepo) in November 2015.

Omalizumab is an IgG monoclonal antibody (recombinant DNA derived) which binds to the high-affinity IgE receptor on mast cells and basophils, thereby inhibiting their activation by circulating IgE. This results in a more limited allergic response (early and late phases). Additional effects of OMA are a decrease in serum-free IgE levels and in the number of IgE receptors [4, 5]. According to GINA guidelines OMA can be added to stepwise therapy when patients reach step 5, however it is used less restrictively in current medical practice. More generally, OMA is approved for use in patients above the age of 11 years with moderate-to-severe persistent asthma, or if symptoms are inadequately controlled with inhaled glucocorticoids. Patients should have a total serum IgE level between 30 and 700 international units/mL. Patients should also exhibit allergic sensitization proven by a positive skin test or via in vitro testing for allergen-specific IgE to a perennial allergen. OMA is administered through

a subcutaneous injection every two–four weeks, and the dose is based on body weight and the levels of serum IgE. Studies have shown that OMA results in better control of asthma, less exacerbations, and less emergency department visits. Clinical response can be judged at weeks 12–16 [6].

Mepolizumab is an interleukin-5 antagonist. IL-5 is the principal cytokine responsible for the activation of eosinophils which constitute a major cellular element in the pathogenesis of asthma. By downregulating IL-5 signaling, Mepo decreases the recruitment and survival of eosinophils which translates into an improvement in asthma control in select patients [7]. Eligible asthmatics for the use of Mepo are those with eosinophilic asthma as determined by serum or sputum eosinophil levels. Patients need to have persistently raised eosinophil levels despite appropriate therapy and compliance with ICS [8,9]. Although there is no consensus on the threshold for eosinophilia, most studies with Mepo have included patients with absolute serum eosinophil count above 150 or above 300, or sputum eosinophil levels >3% on more than one occasion [10–13]. In this group of patients, Mepo has been shown to decrease asthma exacerbation (AE) and rates improve asthma control, with a significant systemic glucocorticoid-sparing effect in patients requiring oral corticosteroid maintenance therapy [11, 14].

To date, there has been no direct comparison study to assess the efficacy of OMA versus Mepo as add-on therapy in asthma patients. The purpose of our study is to systematically examine the efficacy of these two agents in patients whose asthma symptoms were not well controlled on at least the ICS therapy with or without other asthma medications. Outcome measures assessed were the magnitude of improvement in forced expiratory volume in second 1 (FEV1), morning Peak Expiratory Flow Rate (PEFR), Asthma Quality of Life Questionnaire (AQLQ) and Asthma Control Questionnaire (ACQ), as well as the rate of AEs. We then compared the efficacy of Mepo and OMA using network meta-analysis.

Materials and methods

Search and selection criteria

Methodology

This review was performed following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [15].

Eligibility criteria

Our search for published studies, revised in February 2016, included the following online databases: Medline, Science Direct, Embase, and CENTRAL (Cochrane

Central Register of Controlled Trials) using the following search terms: “Mepolizumab” OR “anti-interleukin 5” AND “asthma,” “Omalizumab” OR “anti-IgE” AND “asthma.” The search had no language restriction. We have excluded trials that were published in abstract form only as the methods and results could not be precisely analyzed.

Inclusion and exclusion criteria

The following criteria were necessary for study inclusion: (1) adults and/or adolescents above 12 years of age with symptomatic asthma despite being on at least high-dose ICS with or without other asthma medications including maintenance oral steroid therapy. (2) Randomized controlled studies (parallel group or crossover) and cohort studies, whether blinded or open label, with a duration of at least 12 weeks. (3) Comparison of subcutaneously injected OMA with placebo or no treatment, or comparison of intravenously injected Mepo (75, 250, or 750 mg) or subcutaneously injected Mepo (100 mg) with placebo or no treatment. (4) Included studies had to report at least one of the subsequent endpoints: pulmonary function test as determined by pre-bronchodilator FEV1 or AM PEFR, asthma control test score: AQLQ total score, or Asthma Control Questionnaire 7 (ACQ-7) total score, or AE rates.

Exclusion criteria were (1) study addressed the effects of the drug on asthma-related disease, but not asthma per se (i.e. outcomes related to allergic bronchopulmonary aspergillosis, allergic rhinitis, eosinophilic granulomatosis with polyangiitis, or other diseases. (2) study did not directly assess drug (OMA/Mepo) effects, (3) study was not designed as a randomized control trial or cohort study, (4) study included patients less than 12 years of age, (5) study did not use ICS as baseline medication in all subjects in their study population, (6) study did not measure our outcomes of interest, or (7) desired outcomes reported in a fashion that did not allow accurate abstraction of the desired data. Figures 1 and 2 are flowcharts illustrating study selection for OMA (Figure 1) and Mepo (Figure 2).

Data collection and evaluation of risk of bias

Two reviewers independently screened titles, abstracts, and the full text for inclusion and exclusion criteria. Quality and risk of bias of the selected studies were methodologically assessed using the Jadad score also known as the Oxford quality scoring system, which evaluates the following items on multiple levels: (1) Randomization (two points possible), (2) Blinding (two points possible), and (3) Withdrawals and dropouts reporting (one point possible) with a possible total score between

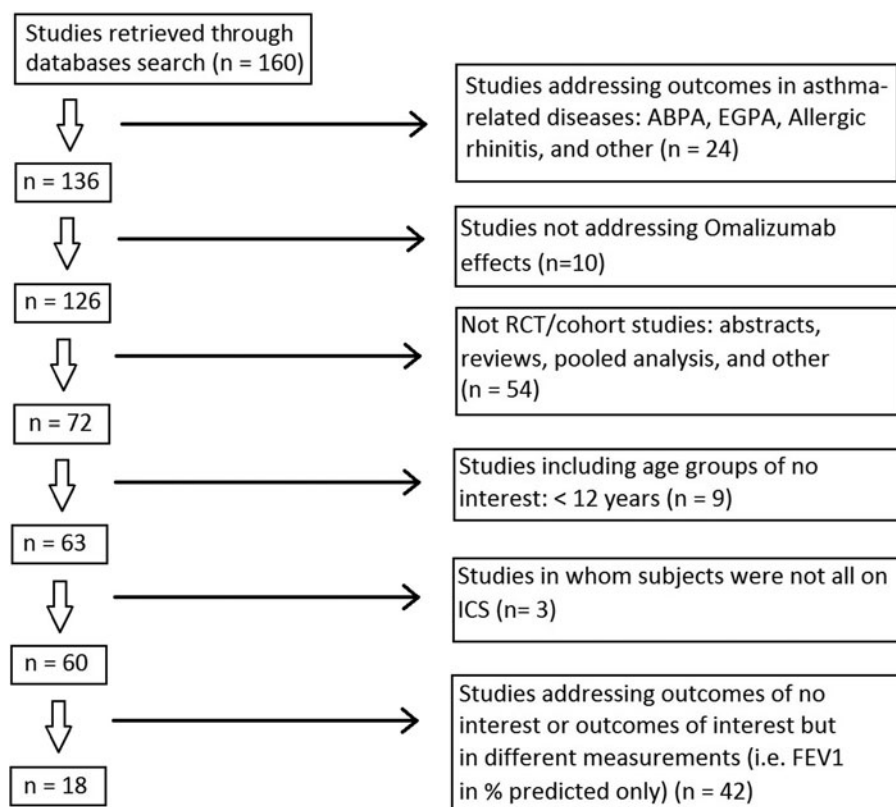


Figure 1. Flowchart illustrating study selection for Omalizumab. Abbreviations: n = number of studies, ABPA = Allergic bronchopulmonary aspergillosis, EGPA = Eosinophilic granulomatosis with polyangiitis, RCT = randomized controlled trial, ICS = inhaled corticosteroid.

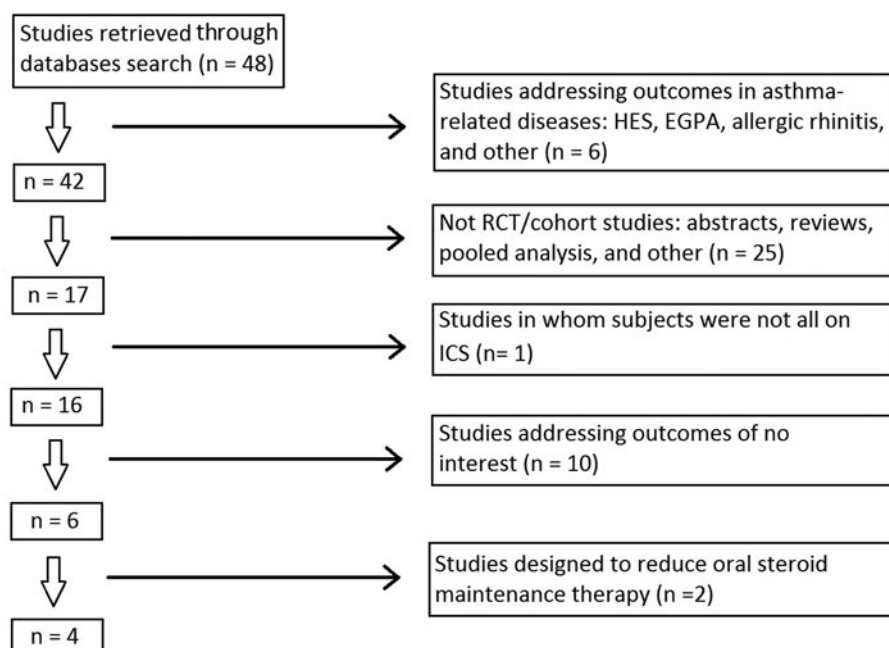


Figure 2. Flowchart illustrating study selection for Mepolizumab. Abbreviations: n = number of studies, HES = hypereosinophilic syndrome, EGPA = Eosinophilic granulomatosis with polyangiitis, RCT = randomized controlled trial, ICS = inhaled corticosteroid.

0 and 5 (highest level of quality). A higher score represented a better quality study (Jadad's score ≥ 4).

Disagreements among the two reviewers were resolved by review by a third reviewer with consensus by the three reviewers.

Statistics and data analysis

Analysis was performed based on the intention to treat study data to minimize bias. Outcomes were pooled using mean differences of change from baseline with corresponding standard deviations. For those studies with no reported standard deviation for the mean difference of change, we used the mean SD of the remaining studies with reported SDs. For studies that reported outcome of interest graphically we determined the value by manual measurement from the graph. We used 95% CI to quantify the precision of the estimates with p equal to 0.05 (two-tailed test) considered significant. We used the i^2 test to measure heterogeneity. The network meta-analysis was performed with SAS 9.4 (Cary, NC, USA). A random-effects model was used to obtain a pooled estimate of FEV1, ACQ, AQLQ, and peak expiratory flow (PEF) means, weighted by the inverse of the standard error obtained in each paper and a pooled estimate for the between-study variance. Using the weighted mean and standard errors, simultaneous 95% confidence intervals were obtained comparing Mepo to OMA, Mepo to Placebo, and OMA to Placebo. The p value for significance was adjusted for the three comparisons using a Bonferroni correction.

Results

All the studies were prospective. Overall, eighteen studies in the OMA group [16–33] and four studies in the Mepo group [11–13, 34] fit the entry criteria and did not meet the exclusion criteria (Figures 1 and 2). Two studies in OMA [20, 22] were 24-week extensions to previous studies [21, 31], respectively. As outlined in the Mepo flowchart two relevant studies were excluded as they were assessing the oral corticosteroid sparing effects of Mepo [10, 14]. Among the included Mepo studies, the dose of Mepo was different, as well as the methods of administration of Mepo (Table 3). If a trial included different doses or route of administration of Mepo, then the different doses/route of administration were analyzed separately.

In the OMA group 12 studies were randomized, double blinded, and placebo controlled [17, 19–25, 27, 29, 31, 32], and 5 studies were randomized but open label and with no placebo given to the control arm [16, 18, 26, 28, 30]. One study was a cohort study with matched controls [33].

Table 1. Simultaneous 95% confidence intervals of the FEV1 change from baseline (ml), of PEF change from baseline (liter/minute), of ACQ score improvement from baseline, and of AQLQ score improvement from baseline.

Comparison	Mean difference	LCLMD	UCLMD	p -value
<i>FEV1 Change from Baseline (ml)</i>				
Mepolizumab vs Placebo	112.034	21.0599	203.0076	0.0096
Omalizumab vs Placebo	102.755	– 3.7982	209.3080	0.0629
Mepolizumab vs Omalizumab	9.279	– 67.7744	86.3320	1.0
<i>PEF Change from Baseline (liter/minute)</i>				
Mepolizumab vs Placebo	19.539	7.0457	32.0327	0.0005
Omalizumab vs Placebo	13.295	5.5404	21.0492	0.0001
Mepolizumab vs Omalizumab	6.244	– 6.4596	18.9484	0.7179
<i>ACQ score improvement from baseline</i>				
Mepolizumab vs Placebo	– 0.411	– 0.7444	– 0.0774	0.0096
Omalizumab vs Placebo	– 0.391	– 0.94	0.1583	0.2651
Mepolizumab vs Omalizumab	– 0.02	– 0.5315	0.4914	1.0
<i>AQLQ score improvement from baseline</i>				
Mepolizumab vs Placebo	0.245	– 0.0796	0.5693	0.2124
Omalizumab vs Placebo	0.627	0.3127	0.9420	<0.0001
Mepolizumab vs Omalizumab	– 0.382	– 0.5515	– 0.2135	<0.0001

FEV1 = forced expiratory volume in second 1.

LCLMD = lower confidence interval limit of the mean difference.

UCLMD = upper confidence interval limit of the mean difference.

PEF = peak expiratory flow.

ACQ = asthma control questionnaire.

AQLQ = asthma quality of life questionnaire.

In the Mepo group all four studies were randomized, double blinded, and placebo controlled [11–13, 34].

The characteristics of the included studies are illustrated in Tables 3 and 4. For each study a Jadad score was calculated.

Table 2. Tests for heterogeneity in Mepolizumab studies, Omalizumab studies, and Combined Placebo for FEV1, PEF, ACQ, and AQLQ.

Treatment	Tau ²	Chi ²	df	p -value	I^2
<i>Tests for heterogeneity for FEV1</i>					
Mepolizumab	199.92	6.768	6	0.3428	11.3474
Omalizumab	4396.08	113.270	6	0.0	94.7029
Combined Placebo	10669.54	222.801	9	0.0	95.9605
<i>Tests for heterogeneity for PEF</i>					
Mepolizumab	0	1.48267	3	0.6863	0
Omalizumab	0	0.63787	4	0.9588	0
Combined Placebo	0	2.52381	6	0.8658	0
<i>Tests for heterogeneity for ACQ score</i>					
Mepolizumab	0.028615	24.0131	5	0.0002	79.1780
Omalizumab	0.056933	3.0996	1	0.0783	67.7375
Combined Placebo	0.046255	18.6191	4	0.0009	78.5167
<i>Tests for heterogeneity for AQLQ</i>					
Mepolizumab	0.00167	3.459	3	0.3261	13.28
Omalizumab	0.00588	11.747	7	0.1092	40.4099
Combined Placebo	0.13278	127.723	9	0.0	92.9535

FEV1 = forced expiratory volume in second 1.

Tau² = estimate of the between-study variance in a random-effects model.

Chi² = chi-squared statistic.

df = degree of freedom.

I^2 = heterogeneity.

PEF = peak expiratory flow.

ACQ = asthma control questionnaire.

AQLQ = asthma quality of life questionnaire.

Table 3. The characteristics of the included Mepolizumab studies.

Study	Design	Jadad Score (0–5)	Study duration (weeks)	Number of subjects (n)	Mean Age (Years) (PB and Mepo, respectively)	Mean Baseline FEV1 in Liters (L) (PB and Mepo, respectively)	Use of OCS (PB and Mepo, respectively)	Mean IgE serum levels with SD PB and Mepo, respectively)	Primary outcome	Other outcomes	Comparisons of interest
Ortega 2014	R, DB, PC	5	32	Total of 576 (191 in PB) (191 IV mepo 75 mg) (194 SC mepo 100 mg)	49 in PB 50 in IV Mepo 75 mg 51 in SC Mepo 100 mg	1.86 L in PB 1.86 L in IV Mepo 75 mg 1.73 L in SC Mepo 100 mg	23% in PB 25% in IV Mepo 75 mg 27% in SC Mepo 100 mg	150 (1.5) in PB 180 (1.5) in IV Mepo 75 mg 150 (1.5) in SC Mepo 100 mg	Exacerbations	FEV1, PEF change ACQ change	Mepolizumab IV 75 mg vs Mepolizumab SC 100 mg vs Placebo Every 4 weeks for 32 weeks
Flood Page 2007	R, DB, PC	4	20	Total of 362 (126 in PB) (120 in Mepo IV 250 mg) (116 in Mepo IV 750 mg)	36.8 in PB 35.8 in IV Mepo 250 mg 36.3 in IV Mepo 750 mg	2.39 L in PB 2.46 L in Mepo IV 250 mg 2.51 L in Mepo IV 750 mg	none	Median and range: 178 (4–9237) in PB 203 (4–3068) in IV Mepo 250 mg 161 (1.9–5124) in IV Mepo 750 mg	PEF change	FEV1 change Asthma symptoms score Use of rescue inhaler	3 IV doses of Mepolizumab (750 mg), Mepolizumab (250 mg) or placebo at weeks 0, 4 and 8
Halder 2009	R, DB, PC	4	50	Total of 61 (32 PB) (29 in Mepo IV 750 mg)	50 in PB 48 in Mepo IV 750 mg	2.39 L in PB (post BD) 2.31 L in Mepo IV 750 mg (post BD)	53% in PB 57% in Mepo IV 750 mg	195 (2.64) in PB 177.8 (2.47) in IV Mepo 750 mg	Exacerbations Eosinophils counts change AQLQ change ACQ change FEV1 change	Exacerbations	750 mg versus matched placebo (150 mL of 0.9% saline) at monthly intervals for 1 year
Pavord 2012	R, DB, PC	5	52	Total of 621 (159 in PB) (154 in Mepo IV 75 mg) (152 in Mepo IV 250 mg) (156 in Mepo IV 750 mg)	46 in PB 50 in Mepo IV 75 mg 49.4 in Mepo IV 250 mg 48.6 in Mepo IV 750 mg	1.9 L in PB 1.81 L in Mepo IV 75 mg 1.85 L in Mepo IV 250 mg 1.95 L in Mepo IV 750 mg	29% in PB 30% in Mepo IV 75 mg 33% in Mepo IV 250 mg 30% in Mepo IV 750 mg	Not reported	FEV1 change ACQ change AQLQ Change Exacerbations	13 infusions in total given every 4 weeks of 750 mg, 250 mg, 75 mg or placebo	

R = randomized, DB = double blinded, PC = placebo controlled, PB = placebo, Mepo = Mepolizumab, IV = intravenous, SC = subcutaneous, ACQ = Asthma Control Questionnaire, BD = bronchodilation, AQLQ = asthma quality of life questionnaire, OCS = oral corticosteroid.

Table 4. The characteristics of the included Omalizumab studies.

Study	Design	Jadad Score (0–5)	Study duration (weeks)	Number of subjects (n) (Total, in PB and in OMA, respectively)	Mean Age (Years) (PB and OMA, respectively)	Mean Baseline FEV1 in Liters (L) (PB and OMA, respectively)	Use of OCS (PB and OMA, respectively)	Primary outcome	Other outcomes
Hanania 2011	R, DB, PC	5	48	850, 423, and 427	45.3 and 43.7	64.4–65.4% predicted	16.9–17.1%	Exacerbations	Change in mean daily number of puffs of albuterol Asthma
Otha 2009	R, DB, PC	3	16	315, 164, and 151	49.2 and 48.8	2.1 L	6.7–12.6%	PEF change	FEV1, PEF change Rate of exacerbations Change in rescue inhaler use
Bardelas 2012	R, DB, PC	3	24	271, 135, and 136	40.7 and 41.9	2.5–2.4	none	ACT score change	FEV1 change IGETE change WPAIA change
Garcia 2013	R, DB, PC	3	16	41, 21, and 20	54.6–55	2.07–1.67	33.3% and 40%	Serum change of Fc RI expression on basophils and pDC2s	FEV1 change ACQ change GETE change Rate of exacerbations Fraction of exhaled nitric oxide
Humbert 2005	R, DB, PC	5	28	419, 210, and 209	43.3 and 43.4	61–61.6%	20% and 23.9%	Exacerbation	FEV1, PEF change AQLQ change Use of rescue inhaler
Makoto Hoshino 2001	R, Not DB, not PC	1	16	30, 16, and 14	51.2 and 59.2	1.43–1.32	31% and 29%	Airway dimensions by CT technique	FEV1 change AQLQ change Percentage of eosinophils in induced sputum
Niven 2008	R, Not DB No PC	2	52	164, 49, and 115	39.3 and 38.7	2.08–2.09	17.9% and 22.8%	asthma deterioration-related incidents	Exacerbation rates FEV1 change AQLQ
Rubin 2012	R, not DB, not PB	2	20	116, 38, and 78	45.2 and 43.8	Not provided	none	AQLQ score	FEV1 change GETE score, AQLQ increase by > 1.5
Bousquet 2011	R, not DB, not PC	3	32	404, 133, and 271	45.7 and 45.6	61.1–63% of predicted	21.1% and 22.4%	GETE score	FEV1 change Exacerbations rates ACQ score
Busse 2001	R, DB, PC	3	28	525, 257, and 268	39–39.3	2.3–2.4 L	None	Exacerbation	FEV1, PEF change GETE Patients with at least 1 exacerbation Daily asthma symptoms rescue medication use
Bul Hanf 2002	R, DB, PC	3	52	98, 47, and 51	39–40	70% predicted in both grip	None	AQLQ	
Finn 2003 (24 weeks extension of Busse 2001)	R, DB, PC	3	52	525, 257, and 268	39–39.3	2.3 and 2.4	None	AQLQ	

Vignola 2004	R, DB, PC	3	28	405, 196, and 209	38.5 and 38.3	2.7–2.9 L	None	Exacerbations Combined AQLQ and RQLQ	Rescue-medication use AQLQ RQLQ Wasserfallen asthma and rhinitis clinical symptom scores, GETE FEV1, FVC, PEF ICS use
Soler 2001	R, DB, PC	3	28	546, 272, and 274	39–40	2.5 L for both	None	Exacerbations	Patients with at least one exacerbation Reduction in the BDP dose Rescue inhaler use Asthma symptom scores PEF change
Buhl-Soler 2002 (a 24 weeks extension to Soler 2001)	R, DB, PC	3	52	546, 272, and 274	39–40	2.5 L for both	None	asthma exacerbations	Patients with at least one exacerbation Reduction in the BDP dose Rescue inhaler use Asthma symptom scores PEF change
Holgate 2004	R, DB, PC	3	32	246, 120, and 126	40.5–41	63–66% of predicted	none	Relative Reduction In ICS	Absolute Reduction in ICS Exacerbations Use of rescue inhaler Asthma symptom score PEF change
Wittchen 2012	Cohort study with matched controls	1	24	112, 56, and 56	52 and 48	62–67% of predicted	40% and 66%	Exacerbations ACT	Euro-Qol 5D Number of medications
Ayres 2004	R, not DB, not PC	2	1 year	312, 106, and 206	39 and 37	70–72% predicted	18–23%	asthma deterioration- related incidents (ADRs)	Exacerbation FEV1 change Use of rescue inhaler Wasserfallen asthma symptom score

R = randomized, DB = double blinded, PC = placebo controlled, PB = placebo, OMA = Omalizumab, OCS = oral corticosteroid, AQLQ = asthma quality of life questionnaire, IGETE = Investigator's Global Evaluation of Treatment Effectiveness, WPAIA = Work Productivity and Activity Impairment Questionnaire—Asthma, Fc RI = high-affinity IgE receptor, pDC2 = plasmacytoid dendritic cells, GETE = Global Evaluation of Treatment Effectiveness, ICS = inhaled corticosteroid, BDP = beclomethasone dipropionate, Euro-Qol 5D = European quality of life-5 dimensions, ACT = asthma control test, ACQ = Asthma Control Questionnaire, Omalizumab was administered subcutaneously every two or four weeks according to the patient's pretreatment bodyweight and baseline IgE levels, using a dosing table to provide a dose of at least 0.016 mg/kg per IU/mL for every IU/mL of total IgE.

In the OMA studies a total of 4854 subjects were included, of whom 2243 received placebo or no additional therapy, and 2611 received OMA. In the Mepo studies a total of 1620 subjects were included, of whom 508 received placebo and 1112 received Mepo (194 subjects received subcutaneous Mepo at 100 mg, and the rest received intravenous Mepo in the following distribution: 345 subjects received IV Mepo at 75 mg, 272 subjects received IV Mepo at 250 mg, and 301 subjects received IV Mepo at 750 mg).

In the Mepo studies, inclusion criteria were having eosinophilic asthma and being not well controlled on at least ICS as a chronic maintenance therapy. The threshold for defining eosinophilia was variable among studies: In Haldar 2009 [11] subjects had to have a sputum eosinophil count $>3\%$. In Ortega 2014 [12] subjects had to have a serum eosinophil count of at least 150 cells per microliter in the peripheral blood at screening or at least 300 cells per microliter at some time during the previous year. In Pavord 2012 [13], subjects had to have either a sputum eosinophil count of 3% or more, or peripheral blood eosinophil count of 0.3×10^9 per L or more. In Flood-Page 2007 [34], the threshold for eosinophilia was not defined. Duration of the studies ranged from 20 to 52 weeks.

In the OMA studies, inclusion criteria were having allergic asthma and being not well controlled with at least one ICS. Patients also had to have a positive skin-prick test to at least one perennial allergen, with total serum IgE level between 30 and 700 IU. Duration of the studies ranged from 16 to 52 weeks. OMA was administered subcutaneously every two or four weeks according to the patient's pretreatment bodyweight and baseline IgE levels, using a dosing table to provide a dose of at least 0.016 mg/kg for every IU/ml of total IgE.

The weighted mean baseline FEV1 in patients who received OMA and Mepo were similar: 2.4 and 2.2 L respectively. The weighted mean age among the subjects who received OMA and Mepo were also similar: 42.4 and 47.3 years respectively. The use of oral corticosteroid as a maintenance therapy in patients who received OMA and Mepo was also not statistically significant: 12.4% (325/2611) and 23% (260/1112) respectively, $p = 0.08$ although there was a trend for greater oral steroid usage in the Mepo patients.

In regard to FEV1 improvement from baseline, we included studies that measured pre-bronchodilator FEV1 in ml or provided the improvement from baseline in ml, and we excluded studies that did not do so or did not provide sufficient information for us to derive this value. The remaining trials for FEV1 were seven in OMA [17, 23, 26–30], and seven in Mepo if different dosages within a

trial were analyzed separately [12, 13, 34]. Haldar 2009 was not included in the FEV1 study as it addressed the post-bronchodilator FEV1 [11].

Results of the network meta-analysis for FEV1 improvement from baseline did not show a significant difference between OMA and Mepo. The mean difference was 9.3 ml in favor of Mepo, CI (−67.7–86.3) with $p = 1$. Heterogeneity between the placebo arms of the two drugs was high; $i^2 = 96\%$. See Figure 3, Tables 1 and 2.

Likewise, the two drugs were not significantly different in terms of morning PEF improvement when indirectly compared to each other. The mean difference was 6.24 L/min in favor of Mepo, CI (−6.46; 18.9), with $p = 0.72$. Heterogeneity between the placebo arms of the two drugs was zero. Five trials in OMA [21, 25, 26, 29, 31] and four trials in Mepo [12, 34] evaluated morning PEF (Figure 4 and Tables 1 and 2).

In regard to ACQ score improvement, two trials in OMA [18, 23] and six trials in Mepo [11–13] addressed this variable.

The results of the network meta-analysis showed no significant difference between OMA and Mepo, with a difference favoring Mepo by a mean decrease in the ACQ score of −0.02, CI (−0.53; 0.5) with $p = 1$. Heterogeneity between the placebo arms of the two drugs was high at 78% (Figure 5 and Tables 1 and 2).

On the other hand, when studying the other asthma control tool AQLQ, which was assessed by eight trials in OMA [19, 22, 24, 26–28, 30, 32] and four trials in Mepo [11, 13], the difference in improvement was statistically significant favoring OMA although the magnitude of the difference did not reach the minimal clinically important threshold of 0.5. The mean difference was 0.38, CI (0.21; 0.55) with $p < 0.0001$. Heterogeneity between the placebo arms of the two drugs was high at 93% (Figure 6 and Tables 1 and 2).

As for AEs, we converted the reported total number of exacerbations per patient in each study to an annual rate (studies that reported exacerbation in a different fashion could not be included). Thirteen OMA studies [16–18, 20, 21, 23–25, 27, 28, 31–33] evaluated the AE rates per patient. With OMA, the mean annualized AE rate among the 13 studies was 1.22 ± 0.75 , 95% CI = 0.76–1.67. For those receiving placebo or baseline therapy only, the mean of the annualized AE rate was 2.29 ± 1.43 , 95% CI = 1.43–3.15. The annualized AE rates between OMA and placebo/baseline therapy were significantly different in favor of OMA with a $p = 0.0001$ and the mean reduction in AE rate was 47%.

Three Mepo trials [11–13] evaluated the AE rates per patient. With the drug Mepo, the mean annualized AE for

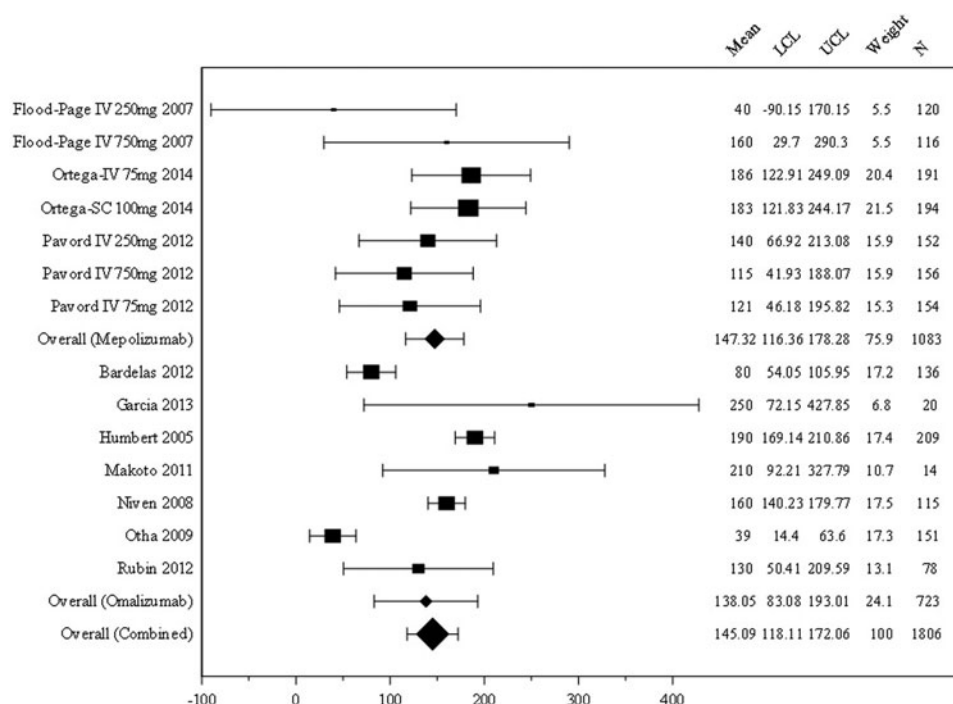


Figure 3. Network meta-analysis forest plots for FEV1 change from baseline (ml) with 95% confidence intervals. Abbreviations: LCL = lower confidence interval limit, UCL = upper confidence interval limit, N = number of patients.

different types of Mepo was 1.28 ± 0.45 , 95% CI = 0.8–1.75. For those receiving placebo, the mean annualized AE was 2.56 ± 0.9 , with 95% CI = 0.3–4.8. The annualized AE rates between Mepo and placebo were significantly different in favor of Mepo with a $p = 0.0001$ and the mean reduction in AE rate was 50%. Both medications

(OMA and Mepo) reduced the rates of AE by a similar magnitude.

We did not study the magnitude of improvement in the use of rescue inhalers as part of the network meta-analysis, as only one study in Mepo evaluated that variable (Flood-Page 2007) [34].

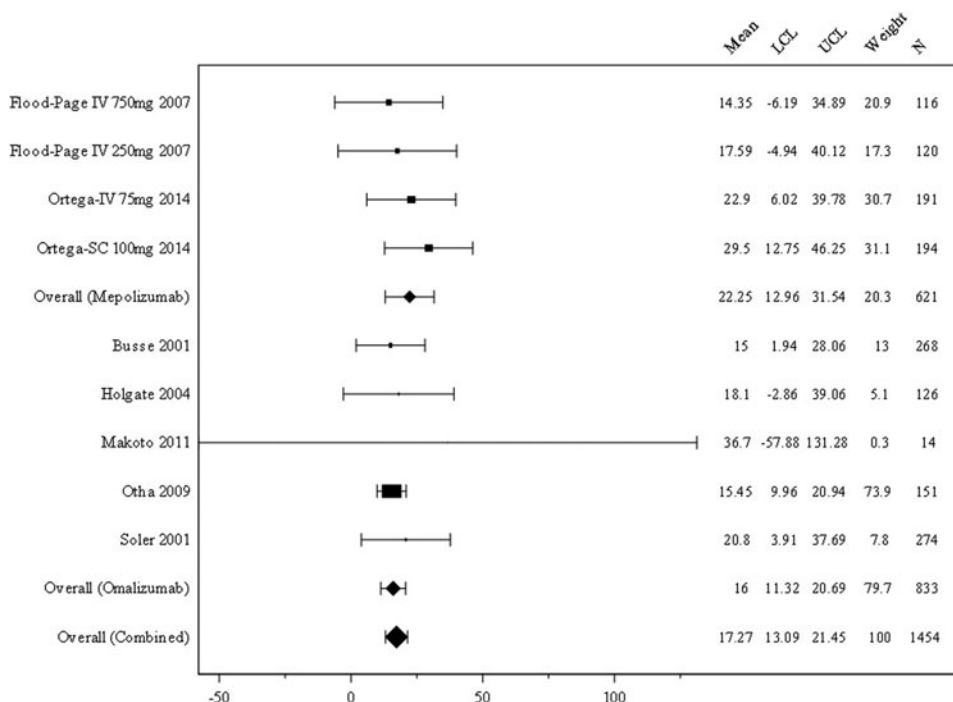


Figure 4. Network meta-analysis forest plots for PEF change from baseline (liter/minute) with 95% confidence intervals. Abbreviations: LCL = lower confidence interval limit, UCL = upper confidence interval limit, N = number of patients.

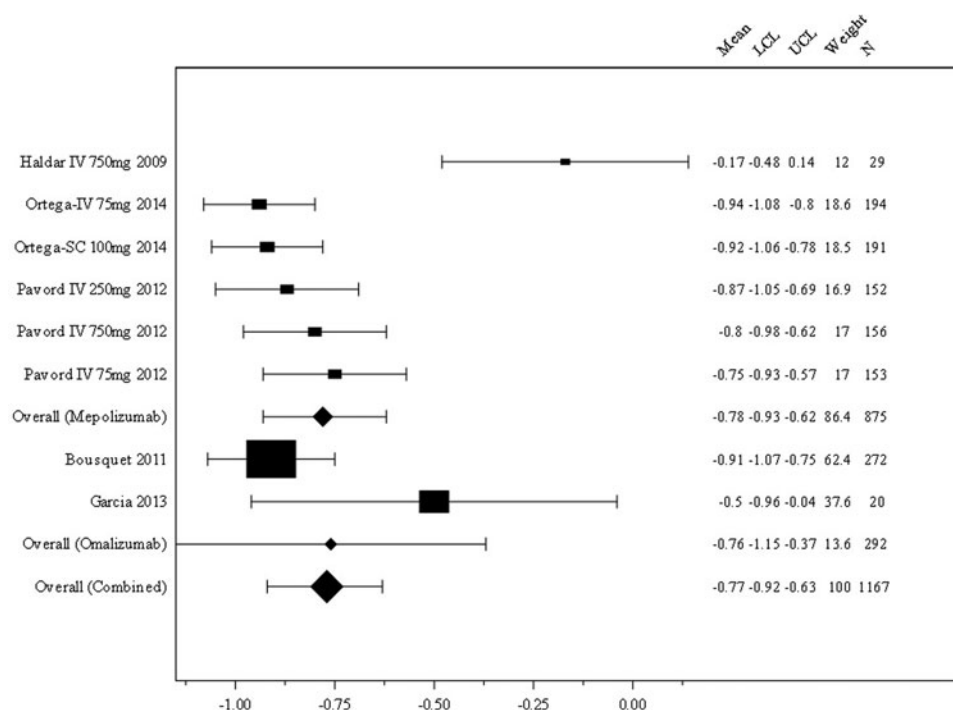


Figure 5. Network meta-analysis forest plots for ACQ score improvement from baseline. Abbreviations: LCL = lower confidence interval limit, UCL = upper confidence interval limit, N = number of patients.

Discussion

Medical asthma therapy has seen marked advancements in the last 15 years, which culminated with the advent of the anti-IgE OMA and the anti-IL5 Mepo. These two

medications can be classified under the title of personalized therapy since each one addresses a specific phenotype of asthma; OMA for those with allergic asthma with high serum IgE levels, and Mepo for those with eosinophilic asthma. However, these 2 phenotypes often

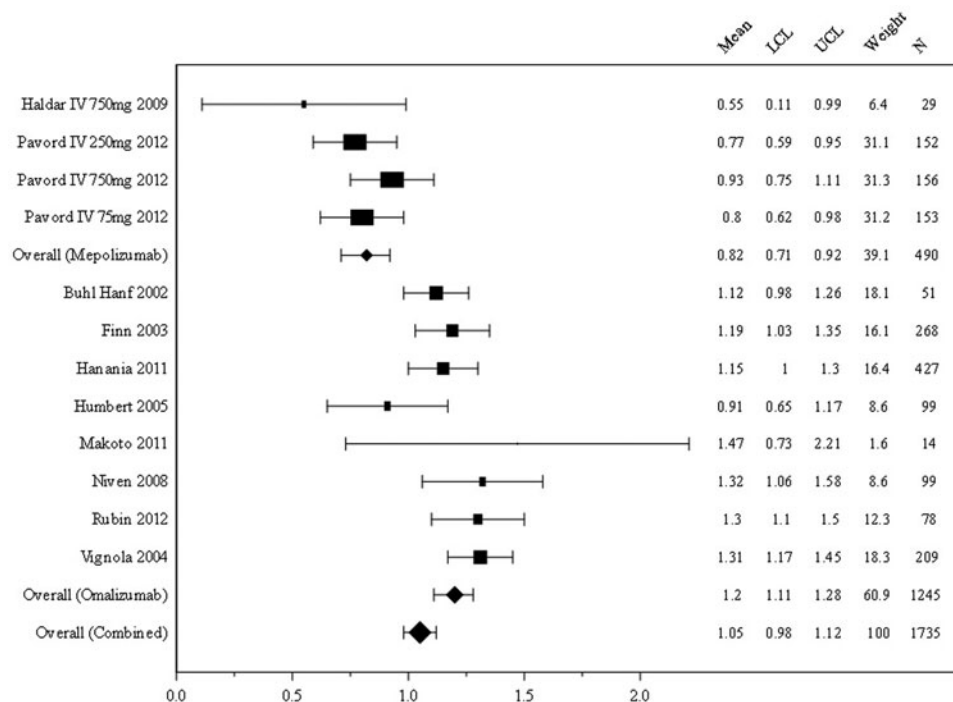


Figure 6. Network meta-analysis forest plots for AQLQ score improvement from baseline. Abbreviations: LCL = lower confidence interval limit, UCL = upper confidence interval limit, N = number of patients.

overlap as both have th2-related asthma and thus many patients will have both eosinophilia and high IgE levels. In fact, the comparison of these two medications would be most interesting in this overlap population. Whether a combination of the two drugs in this overlap group is beneficial or not is yet to be determined. In this analysis we attempted to compare the two medications indirectly using a network meta-analysis model, which assumes that the placebo arms in both medication trials were similar enough to be used as a common intersection to compare Mepo and OMA. Although this is not the optimal way to compare two medications, it is still the best available, as no clinical trial has been conducted to directly compare them in a head-to-head fashion. To our knowledge this is the first network meta-analysis to compare Mepo to OMA in asthmatic patients.

There are limitations to our study. First, the criteria used to determine eligibility for the two drugs is not identical, meaning that there will be some differences in the characteristics of the study populations, which may have implications in comparing the efficacy of the two drugs. While the Mepo studies (except Pavord 2012) had reported their mean IgE serum levels which in many patients were high enough to be eligible for treatment with OMA (see Table 3), the OMA studies did not study baseline eosinophilia in their patients. The underpinning of a network analysis is that the study populations are reasonably similar since it relies on the comparison of study drug to placebo, and in order for this comparison to be reliable the response in the placebo groups should be similar. In this regard the fact that the baseline FEV1 and age were similar in the Mepo and OMA groups is helpful while the trend for greater oral corticosteroid usage in the Mepo group and different inclusion criteria for the two drugs could introduce bias to the results.

In our analysis, we elected to include studies in which patients were on at least ICS because the inclusion criteria used in both OMA and Mepo trials were highly variable in regard to additional asthma medications. Some of the studies permitted the use of long-acting beta agonist, leukotriene receptor antagonists, a combination of the two, while other studies allowed only ICSs. These differences in permitted additional medications could clearly influence the magnitude of improvement that OMA or Mepo can produce. This may be responsible for the high heterogeneity levels we have obtained in our network meta-analysis, except when we studied PEFr where the heterogeneity was low. We have no clear-cut explanation why PEF results were so homogenous. However, the lack of heterogeneity between the two placebo groups makes the lack of any difference in improvement in PEF between Mepo and OMA more meaningful. It is difficult to directly compare the improvement in FEV1 and AQLQ between

the two drugs as the heterogeneity levels in the placebo arm were above 90%. In regard to AE both drugs have shown a marked annualized AE reduction with similar ranges as compared to placebo, 47 and 50% for OMA and Mepo respectively.

Finally the studies used for Mepo were of higher quality (Jadad score 4 or 5) than some of the OMA studies. Many OMA studies, despite being randomized, were not double blinded or their control group did not receive placebo (see Table 4).

In conclusion, a definitive recommendation for preferential use of OMA vs Mepo in patients eligible for both cannot be made from the existing studies published in the literature although the data available show similar efficacy for the two drugs. A prospective randomized double-blinded study would be required to accurately evaluate the efficacy of Mepo against OMA preferably in a select group of patients with both high serum IgE and eosinophilia, and with similar baseline asthma severity and controller medications.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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