Efficacy of Mepolizumab in Patients With Severe Eosinophilic Asthma by Age of Asthma Onset: Meta-analysis of Two Phase III Trials

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Background

- Late-onset asthma is a distinct phenotype associated with difficult-to-treat symptoms and poor disease management. Compared with early-onset asthma, patients with late-onset asthma are less atopic and have lower immunoglobulin E levels.[1,2]
- A subset of patients with asthma also have severe eosinophilic asthma (SEA), characterized by persistent eosinophilic airway inflammation and frequent exacerbations, despite the use of high-dose inhaled corticosteroids and other controllers.[1,3]
- Mepolizumab has been shown to reduce exacerbations and improve health-related quality of life (HRQoL) and asthma control, compared with placebo, in patients with SEA.[4–8]
- Owing to the distinct allergic characteristics and symptom profiles associated with early- and late-onset asthma,[1,2] it is possible that age of asthma onset may affect treatment responses to biologic therapies. As such, the efficacy of mepolizumab in patients with late- and early-onset SEA is of clinical interest.

Objective

- To assess the effects of the licensed dose of mepolizumab (100 mg subcutaneously [SC] every 4 weeks) on exacerbation rate, HRQoL, and asthma control in patients with SEA stratified by age of asthma onset.

Methods

- This was a post hoc meta-analysis (GSK ID: 208115) of data from the Phase III MENSA (MEA115588/NCT01691521)[7] and MUSCA (200862/NCT02281318)[8] trials.
- This meta-analysis presents data from patients who received ≥1 dose of mepolizumab 100 mg SC or placebo. Eligible patients were ≥12 years of age with SEA and a history of ≥2 exacerbations in the previous 12 months despite using high-dose inhaled corticosteroids and ≥1 additional controller.
- The primary endpoint was the annual rate of clinically significant exacerbations (asthma worsening requiring systemic corticosteroids and/or hospitalization and/or an emergency room [ER] visit).
- Secondary endpoints included: annual rates of exacerbations requiring ER visits/ hospitalization; the proportion of patients with no clinically significant exacerbations during the treatment period; changes from baseline in pre-bronchodilator forced expiratory volume in 1 second (FEV_1); the proportion of patients achieving a minimal clinically important difference (MCID) from baseline in St George's Respiratory Questionnaire (SGRQ) total score, and Asthma Control Questionnaire (ACQ)-5 score at study end.
- Analyses were stratified by age of asthma onset (age at study entry minus disease duration): <18 years, 18-<40 years, and ≥40 years.
- Exacerbation rates and FEV_1 were analyzed using negative binomial regression and mixed model repeated measures, respectively; SGRQ/ACQ-5 responses and proportions of patients with no clinically significant exacerbations were analyzed using logistic regression. The estimated end-of-study treatment differences for each study were combined using an inverse variance weighted fixed-effects meta-analysis.

Results

- Of the 936 patients included, 468 received mepolizumab (132 <18 years, 173 18-<40 years, and 162 ≥40 years at asthma onset; one patient was missing asthma duration data) and 468 received placebo (122 <18 years, 172 18-<40 years, and 174 ≥40 years at asthma onset).
- Patient baseline demographics and clinical characteristics are shown in **Table 1**.

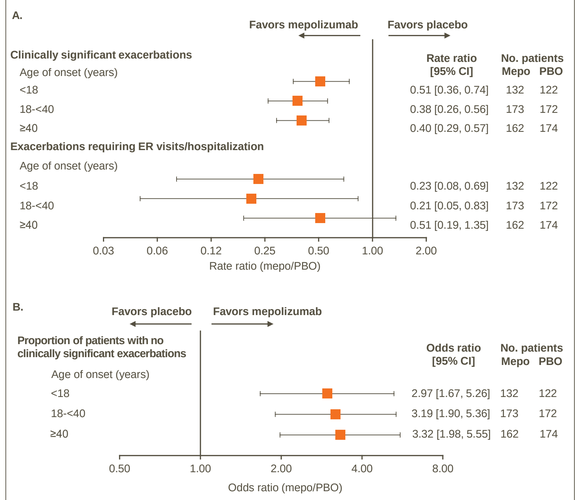
Table 1. Baseline demographics and clinical characteristics by age of onset

Age of asthma onset	<18 years n=254	18-<40 years n=345	≥40 years n=336
Age at enrollment, years, mean (SD)	40.5 (15.3)	48.9 (10.8)	60.1 (8.4)
Asthma duration, years, mean (SD)	32.8 (15.2)	19.7 (11.1)	9.8 (6.9)
Female, n (%)	149 (59)	208 (60)	191 (57)
Number of exacerbations in last year, n (%) 2 3 ≥4	 148 (58) 47 (19) 59 (23)	 196 (57) 74 (21) 75 (22)	 177 (53) 68 (20) 91 (27)
Maintenance OCS use, n (%)	51 (20)	81 (23)	95 (28)
Pre-bronchodilator FEV_1, mL, mean (SD)	1944 (715)	1844 (657)	1717 (632)
Pre-bronchodilator FEV_1, % predicted, mean (SD)	60.0 (18.5)	59.0 (16.9)	59.8 (15.5)
SGRQ total score, mean (SD)	44.4 (18.2)	47.7 (19.5)	48.3 (18.7)
ACQ-5 score, mean (SD)	2.31 (1.14)	2.23 (1.21)	2.17 (1.15)
Blood eosinophil count, cells/μL, geometric mean (SD*)	300 (0.95)	300 (1.01)	340 (1.06)

*SD of log-transformed eosinophil count. OCS, oral corticosteroid; SD, standard deviation

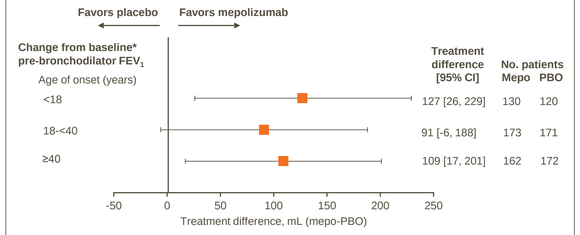
- Compared with placebo, mepolizumab reduced the rate of clinically significant asthma exacerbations and exacerbations requiring ER visits/hospitalization in all age of onset categories (**Figure 1A**).
- A greater proportion of patients receiving mepolizumab treatment reported no asthma exacerbations on-treatment compared with those receiving placebo (**Figure 1B**).
- Improvements in pre-bronchodilator FEV_1 were greater for patients receiving mepolizumab compared with those receiving placebo in all age of onset categories (**Figure 2**).
- Compared with placebo, a greater proportion of patients receiving mepolizumab in all age of onset categories achieved MCIDs in SGRQ total score and ACQ-5 score at study end (**Figure 3**). Treatment differences were greatest in those patients ≥40 years of age at asthma onset.

Figure 1. Rate ratio of clinically significant exacerbations and exacerbations requiring ER visits/ hospitalization (A) and Odds ratio of patients with no clinically significant exacerbations (B) by age of onset



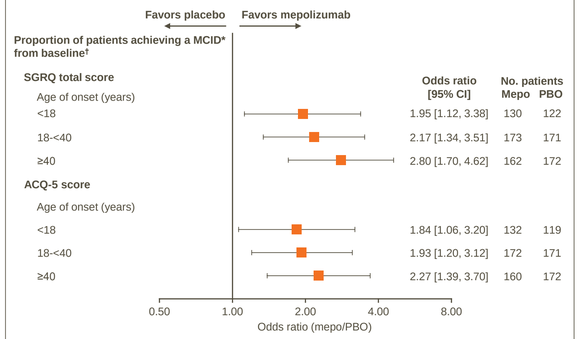
CI, confidence interval; Mepo, mepolizumab; PBO, placebo.

Figure 2. Treatment difference in change from baseline pre-bronchodilator FEV_1 by age of onset



*Baseline defined as the latest value recorded prior to the first dose of study treatment.

Figure 3. Odds ratio of HRQoL and asthma control by age of onset



*MCID for SGRQ is a reduction from baseline of ≥4 points and MCID for ACQ-5 is a reduction from baseline of ≥0.5 points; †baseline defined as the latest value recorded prior to the first dose of study treatment.

Conclusions

- Consistent improvements in exacerbation rates, HRQoL, and asthma control were seen with mepolizumab versus placebo in both patients with late- (18-<40 and ≥40 years) and early- (<18 years) onset SEA.
- Overall, these findings suggest that mepolizumab has consistent benefits in patients with SEA, irrespective of the age of asthma onset.

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