Type 2 Biomarkers and Eosinophil Activation in Severe Asthma and the Impact of Mepolizumab

Poster No. P663 (A1275)

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Background

- Severe asthma is a heterogeneous disease, with a variety of phenotypes that differ in treatment response.[1]
- Cytokines derived from type 2 (T2) inflammatory cells have been shown to play a role in the eosinophilic and allergic inflammatory responses underlying severe asthma in many patients.[2] As a result, patients with the T2 inflammation phenotype may respond well to T2 cytokine-targeted therapies.
- Mepolizumab binds with high specificity and affinity to human interleukin (IL)-5,[3] the key T2 cytokine responsible for eosinophil regulation.[2]
- In patients with severe eosinophilic asthma (SEA), mepolizumab is well tolerated and has been shown to reduce blood eosinophil count (BEC) and asthma exacerbations as well as improve lung function and health-related quality of life.[4–7]

Objective

- To compare the response to mepolizumab versus placebo in patients with SEA who have differing levels of T2 biomarkers at baseline in the Phase III MENSA trial (MEA115588/NCT01691521).

Methods

- This was a post hoc analysis of data from the MENSA trial.[6]
- Details of the patient inclusion criteria have been published elsewhere.[6] Patients were randomized 1:1:1 to receive mepolizumab 75 mg intravenously (n=191), 100 mg subcutaneously (SC) (n=194), or placebo (n=191) every 4 weeks for 32 weeks.
- The primary endpoint was the annual rate of clinically significant exacerbations (worsening of asthma requiring systemic corticosteroids for ≥3 days and/or hospitalization/emergency room visit).
- Levels of the biomarkers eosinophil-derived neurotoxin (EDN), eosinophil cationic protein (ECP), IL-13, chemokines (CCL-13, CCL-17, and CCL-22), eotaxin-1, and periostin were quantified using serum samples taken at randomization (Week 0) and the exit visit (Week 32).
- The impact of mepolizumab 100 mg SC versus placebo on BEC and the annual rate of clinically significant exacerbations was assessed in subgroups of patients with high (>median value) and low (≤median value) EDN at baseline.

Results

Baseline biomarker correlations

- At baseline, serum levels of EDN, ECP, and IL-13 showed a moderately positive correlation with baseline BEC; CCL-13 (MCP-4), CCL-17 (TARC), and CCL-22 (MDC) were also positively correlated with baseline BEC, although the correlation was weaker (**Table 1**).
- No correlation was found between baseline BEC and serum eotaxin-1 or serum periostin.

Table 1. Correlation between BEC and biomarker levels at baseline

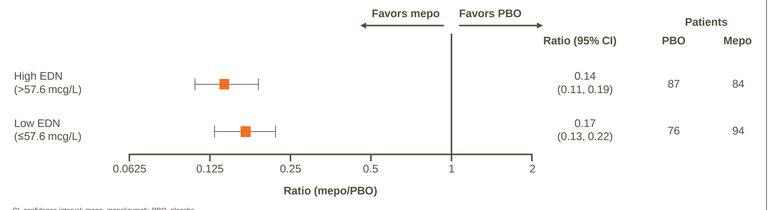
	EDN n=347	ECP n=356	CCL-13 (MCP-4) n=345	CCL-17 (TARC) n=346	CCL-22 (MDC) n=346	Eotaxin-1 n=345	Periostin n=165	IL-13 n=161
Correlation coefficient	0.649	0.568	0.257	0.267	0.307	−0.084	0.119	0.608
***P*-value**	<0.001	<0.001	<0.001	<0.001	<0.001	0.119	0.127	<0.001

n, number of patients included in the analysis.

Mepolizumab response according to baseline EDN levels

- The placebo-adjusted ratios of BEC at Week 32 versus baseline were similar for mepolizumab-treated patients with high versus low baseline EDN levels (**Figure 1**).

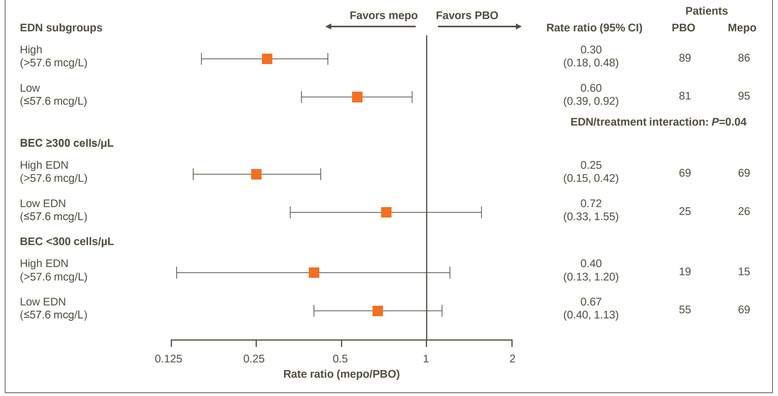
Figure 1. Ratio to baseline of BEC at Week 32 by baseline EDN subgroup



CI, confidence interval; mepo, mepolizumab; PBO, placebo

- Greater improvements in the placebo-adjusted annual rates of clinically significant exacerbations were observed in patients with high versus low baseline EDN (**Figure 2**).

Figure 2. Rate ratio of the annual rate of clinically significant exacerbations by baseline EDN group and baseline BEC subgroup

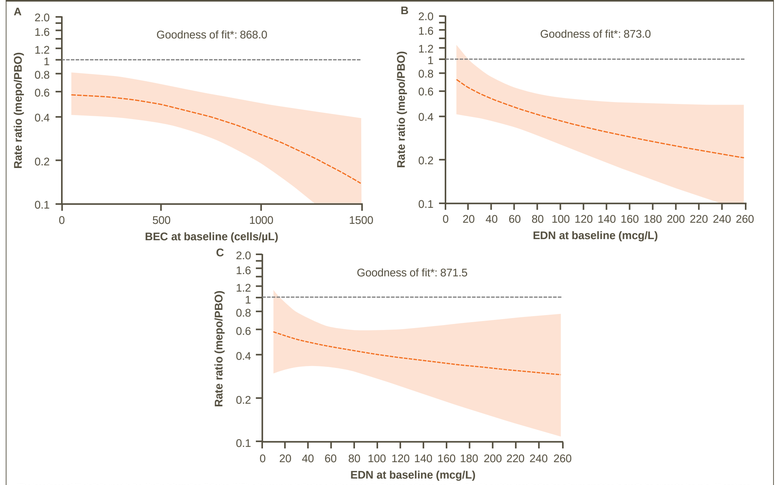


  - In patients with baseline BEC ≥300 cells/µL, mepolizumab was associated with a larger reduction in exacerbations in the high versus low baseline EDN groups (75% vs 28%, respectively) (**Figure 2**).
  - In patients with baseline BEC <300 cells/µL, mepolizumab was similarly associated with a larger reduction in exacerbations in the high versus low EDN groups (60% vs 33%, respectively) (**Figure 2**).

EDN versus baseline BEC as a predictor of treatment response

- Modeling of the predicted rate ratio of clinically significant exacerbations demonstrated that the predictive model based on baseline BEC was marginally better than that based on baseline EDN in terms of precision and model fit (**Figure 3**).
  - Comparing the model of the rate ratio by EDN (unadjusted) (**Figure 3B**) with the model of EDN with an adjustment for baseline BEC and treatment interaction (**Figure 3C**), the precision of the latter was greatly reduced.

Figure 3. Predicted rate ratio (95% CI) for clinically significant exacerbations per year versus A) baseline BEC, B) baseline EDN concentration, and C) baseline EDN concentration adjusted for baseline BEC and treatment interaction



*The 'goodness of fit' statistic used is the Akaike Information Criterion (AIC); a lower value indicates a better model fit. Shading indicates the 95% CI, with a wider band indicating a lower precision in predicting exacerbation rate. All analyses were performed using a negative binomial regression model with the following covariates: treatment, use of maintenance corticosteroids, and number of exacerbations in the previous year. The following additional covariates were used: (A) BEC at baseline (square transformation) including additional term for treatment interaction; (B) EDN concentration at baseline (square root transformation) including additional term for treatment interaction; and C) EDN concentration at baseline (square root transformation) including additional term for treatment interaction and baseline BEC (log transformation) with treatment interaction.

Conclusions

- At baseline, BEC was positively correlated with the assessed T2 biomarkers, except for eotaxin-1 and periostin.
- High versus low baseline EDN level was associated with a greater reduction in exacerbations with mepolizumab, even when taking into consideration the baseline BEC.
- Although EDN showed potential as an additional predictive marker of mepolizumab treatment response, BEC was found to have greater precision as a sole predictive marker, and is likely to be more practical for use in the clinic.
- The role of EDN in identifying patients who might respond to mepolizumab should be investigated further especially in patients with higher levels of activated eosinophils and a low BEC.

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Acknowledgments

- This post hoc analysis and the parent study (MEA115588/NCT01691521) was funded by GlaxoSmithKline (GSK).
- PH, SM, SB, FCA, and NK are employees of GSK and hold stocks/shares. SQ has served as a consultant to AstraZeneca, Novartis, Sanofi, Genentech, Teva, ALK, Mundipharma, and GSK, and has received lecture fees from Chiesi, Novartis, GSK, Leti, AstraZeneca, and Mundipharma. AP reports grants, personal fees, non-financial support and other from Chiesi, AstraZeneca, GSK, Boehringer Ingelheim, Mundipharma, and Teva, personal fees and non-financial support from Menarini, Novartis, and Zambon, and grants from Sanofi, all outside the submitted work. EI has served as a consultant to and received personal fees from AstraZeneca, Equillium, GSK, Novartis, 4D Pharma, Pneuma Respiratory, Regeneron Pharmaceuticals, Sanofi, Sienna Biopharmaceuticals, and Teva, reports non-financial support from Teva, and other from Vorso Corp, and has received clinical research grants from AstraZeneca, Genentech, Novartis, and Sanofi.
- Editorial support (in the form of writing assistance, including development of the initial draft, assembling tables and figures, collating authors comments, grammatical editing, and referencing) was provided by Roisin McCorkell, MSc, and Laura Pearce, PhD, of Fishawack Indicia Ltd, UK, and was funded by GSK.