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

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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 cytokine 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.3

In patients with severe eosinophilic asthma (SEA), mepolizumab is well tolerated and has been shown to reduce blood eosinophil count (BEC) and eosinophil exacerbations as well as improve lung function and health-related quality of life.4

Methods

To compare the response to mepolizumab versus placebo in patients with SEA who have differing levels of T2 biomarkers at baseline in the Phase II MENSA trial (NCT01516686; NCT01915321).

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 (RANTES) were also positively correlated with baseline BEC, although the correlation was weaker (Table 1). No correlation was found between baseline BEC and serum eosinophil-1 or serum perils.

Conclusions

At baseline, BEC was positively correlated with the assessed T2 biomarkers, except for eotaxin-1 and perils.

High versus low baseline BEC levels 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 market, and is likely to be more practical for use in the clinic.

The rate 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.

References

4. Goodness of fit*: 871.5

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

Table 1. Correlation between BEC and biomarker levels at baseline

Table 2. Mepolizumab response according to baseline EDN levels

- 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 29%, 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 baseline EDN groups (60% vs 33%, respectively) (Figure 2).

Modeling of the predicted rate ratio of clinically significant exacerbations demonstrated that the predicted model based on baseline BEC was marginally better than that based on baseline EDN in terms of precision and model fit (Figure 3).

Figure 3. Predicted ratio rate (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

Figure 4. Rate ratio of the annual rate of clinically significant exacerbations by baseline EDN subgroup and baseline BEC category

Figure 5. Ratio to baseline (mean (

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