Characterisation of Exacerbations of Severe Eosinophilic Asthma on Mepolizumab Compared to Placebo

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Aims

- Mepolizumab, a humanised monoclonal antibody, targets IL-5 and has been shown to reduce exacerbations of severe eosinophilic asthma.[1]
- We have previously shown, in an analysis of exacerbations occurring in 60 patients receiving mepolizumab or placebo, that exacerbations occurring on mepolizumab are associated with lower sputum eosinophil counts and lower decrements in symptom scores measured by the visual analogue scale (VAS) compared to placebo.[2]
- We suggest that this might reflect a different, less corticosteroid responsive mechanism of exacerbation in patients treated with mepolizumab.
- We investigated whether exacerbations differ between those receiving mepolizumab and placebo with respect to change from baseline in lung function and symptom scores, and the rate of recovery following oral prednisolone treatment.

Methods

- We carried out a post-hoc comparison of exacerbations occurring during treatment with mepolizumab or placebo in three previously reported placebo-controlled trials.[1, 3, 4]
- Diary card data was reviewed from the 3 studies involving 1743 patients with severe eosinophilic asthma; DREAM[1], a 52-week study of 3 doses of mepolizumab (75, 250 or 750mg IV 4 weekly) versus placebo; MENSA[3], an 32-week study of 2 doses of mepolizumab (75mg IV or 100mg s/c 4 weekly) versus placebo; and MUSCA[4], a 24-week study of mepolizumab 100mg s/c 4 weekly versus placebo.
- All studies recruited patients with a history of 2 or more exacerbations in the previous year and evidence of eosinophilic airway inflammation.
- Patients completed a daily diary card including a 6 point symptom score assessing asthma symptoms in the previous 24 hours (0 – no symptoms, 6 – worst symptoms) and a best-of-three morning peak expiratory flow (PEF) recorded in L/min. Patient medication usage was recorded
- Exacerbations were defined as worsening symptoms and/or rescue inhaler use that required rescue oral corticosteroids (OCS) for 3 or more days. Events with at least 20 days of diary data in the period from 14 days prior to starting OCS (Day -14) to 14 days (Day 14) after starting OCS were included in the analysis.
- PEF and symptom score at each day was averaged across all included exacerbations. Unpaired t-tests were used to compare mean change from Day -14 at day of OCS start (Day 0) between treatment groups with no adjustment for within subject correlation of events. The latest value recorded prior to OCS start was used for patients with missing assessment at Day 0.

Results

- 741 study participants across the 3 studies had at least one exacerbation. Their demographics are shown in **Table 1**.

Table 1. Participant demographics – participants who experienced one or more exacerbation during the study

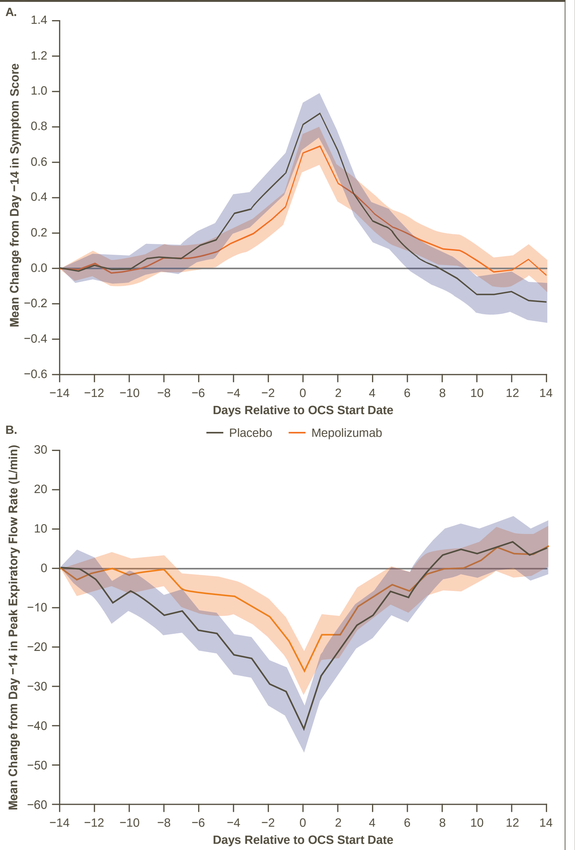
	Placebo (N=623)	Mepolizumab All Doses (N=1120)
n	322	419
Age (years)	49.9 (13.1)	49.9 (12.0)
Sex (% female)	211 (66%)	265 (63%)
BMI (kg/m^2)	28.4 (6.5)	28.9 (6.1)
Baseline Maintenance OCS Therapy	106 (33%)	148 (35%)
Baseline Prednisolone-Equivalent Dose (mg)	14.4 (11.4)	16.3 (12.7)
Exacerbations in previous year		
≤2	134 (42%)	169 (40%)
3	87 (27%)	96 (23%)
4+	101 (31%)	154 (37%)
Baseline Blood Eosinophil Count (GI/L) **	0.34 (1.0)	0.23 (1.1)

Data shown as mean (SD) unless otherwise specified.

** Geometric mean (log SD)

- 1026 exacerbations were included in the analysis. 476 occurred in 248 subjects on placebo treatment and 550 occurred in 338 subjects on mepolizumab treatment. 717 exacerbations were not analysed due to insufficient diary card data.
- The baseline participant age, sex, BMI, maintenance OCS use or maintenance OCS dose, and lung function measures were similar between placebo and mepolizumab treated groups. The blood eosinophil count tended to be higher in the placebo treated group.
- Exacerbations on placebo had a larger increase in daily symptom score compared to mepolizumab (0.8 points vs 0.6 points respectively; mean difference 0.2; 95% CI 0.0, 0.4; Figure 1a) at the time of starting OCS. Placebo treated exacerbations tended to return to their baseline more quickly than mepolizumab groups following OCS (**Figure 1a**).
- Exacerbations on placebo were associated with a larger drop in PEF compared to mepolizumab at the time of starting OCS (-41 vs -26 L/min; mean difference -15 L/min; 95% CI -23, -6; Figure 1b). The rate of decline prior to OCS initiation was greater in the placebo group compared to the mepolizumab group. Both mepolizumab and placebo groups returned to their baseline in a similar time and rate (**Figure 1b**).

Figure 1. Changes in symptoms and PEF during an exacerbation



Shaded areas shows 95% confidence intervals

Conclusions

- Our results add further evidence that exacerbations occurring on mepolizumab are different to those that occur on placebo.
- Exacerbations on mepolizumab are less severe in terms of falls in lung function as measured by PEF and a similar trend was seen for symptoms.
- Our results also support the suggestion that there may be a difference in recovery from these different episodes with a trend towards longer symptom recovery to baseline in the mepolizumab group. This may be explained by a differential response to oral corticosteroid treatment in mepolizumab treated patients compared to placebo.

References

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