Characterisation of exacerbations of severe eosinophilic asthma on mepolizumab compared to placebo

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Introduction

Treatment with mepolizumab, a humanised monoclonal antibody that neutralises IL-5, has been shown to reduce exacerbations of severe eosinophilic asthma[1].

The beneficial effect of treatment is most obvious in patients with a raised peripheral blood eosinophil count, a group who are at high risk of exacerbation off treatment. Even in this population exacerbation rates whilst taking mepolizumab are around 1/patient/year. The nature of these remaining exacerbations is unclear.

We test the hypothesis that exacerbations of severe eosinophilic asthma on mepolizumab differ from those off it in inflammatory profile, symptom scores and FEV1.

Methods

We carried out a retrospective analysis of exacerbations occurring during a placebo controlled double blind trial of mepolizumab 750 mg IV given every four weeks for 52 weeks[1]. The study involved 61 patients with severe asthma, an induced sputum eosinophil count of >3% in the previous 12 months and two or more exacerbations of asthma treated with systemic corticosteroids in the last year.

Patients were reviewed at exacerbation, prior to starting rescue treatment or as soon as possible after. Cough, breathlessness and wheeze visual analogue scale (VAS); spirometry; Asthma Control Questionnaire (ACQ5); and induced sputum inflammatory cell counts were measured.

Results

159 exacerbations were treated with oral prednisolone. 105 were in the placebo arm and 54 were in the mepolizumab arm. 83 (28 mepolizumab, 55 placebo) were reviewed prior to prednisolone and 76 (26 mepolizumab, 50 placebo) were seen after starting prednisolone for a mean of 5.4 days in the placebo arm and 5 days in the mepolizumab arm.

Exacerbations on placebo were associated with a higher sputum eosinophil percentage than those on mepolizumab (geometric mean 5.4% vs 2.6%, p=0.03). There was no overall difference in VAS, ACQ5, FEV1, or change in these measures from the baseline study visit between placebo and mepolizumab groups.

However, in subjects seen prior to rescue treatment, symptoms were more severe in the placebo arm when expressed as score at exacerbation (mean exacerbation VAS 65mm vs 55mm, p<0.03), or change from baseline VAS (40mm vs 20mm, mean difference 20mm, 95% CI 9 - 32mm, p<0.001). In contrast in patients seen after starting rescue treatment, mean VAS was similar (mean VAS 66 vs 64mm; p=0.74).

Table. Exacerbation measurements as a change from baseline values

	Pre-treatment			Treated		
	Placebo	Mepolizumab	Mean dif. (p)	Placebo	Mepolizumab	Mean dif. (p)
D Mean VAS (mm)	40 (3)	20 (5)	20 (6) (<0.001)	14 (6)	31 (6)	-17 (9) (0.06)
D ACQ5	0.95 (0.1)	0.82 (0.3)	0.13 (0.3) (0.67)	0.3 (0.2)	0.96 (1.7)	0.66 (0.4) (0.12)
D FEV1 (L)	0.16 (0.1)	0.27 (0.1)	0.11 (0.1) (0.28)	0.14 (0.1)	0.27 (0.1)	0.13 (0.1) (0.34)

Data shown as mean (standard error) D Change from baseline

There was no difference in change between any of the individual components of the VAS score (cough, wheeze and breathlessness) and no significant difference in change from baseline ACQ5 or FEV1 in the placebo and mepolizumab arms either in the pre-treatment or treated group (table 1).

There was a significant difference in change in exacerbation VAS scores compared to baseline between pre-steroid treatment and steroid treated subjects in the placebo arm (40mm vs 14mm, p=0.03). This difference was not seen in the mepolizumab treated arm (20mm vs 31mm, p=0.17) (figure)

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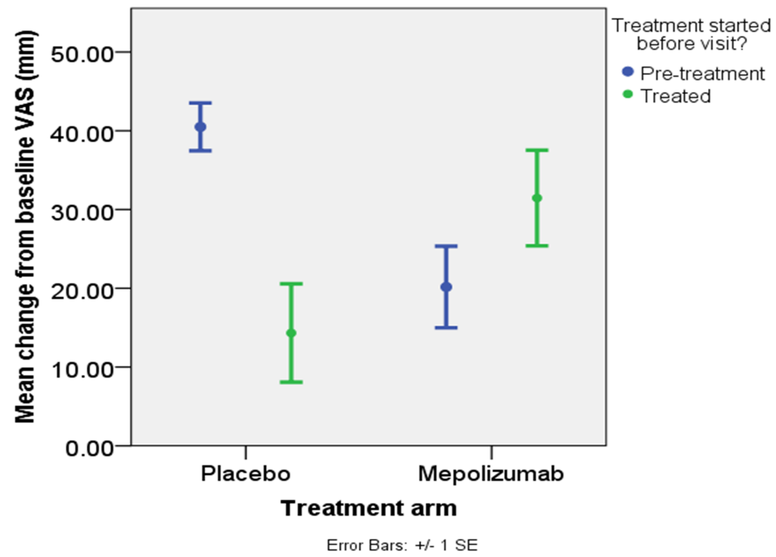
Figure. Changes from baseline VAS at exacerbation



Conclusions

- Exacerbations on mepolizumab are
  - associated with a lower sputum eosinophil count
  - are less severe in terms of VAS symptom scores
- Prednisolone treatment appears to improve exacerbation VAS scores in placebo treated patients but not in mepolizumab treated patients suggesting a different response to prednisolone.
- These preliminary, post-hoc findings suggest that exacerbation events that occur on mepolizumab are different in nature to those that occur on mepolizumab. These exacerbations may require a different treatment approach.

References

1.Haldar, P., et al., *Mepolizumab and exacerbations of refractory eosinophilic asthma.* N Engl J Med, 2009. **360**(10): p. 973-84.
2.Pavord, I.D., et al., *Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial.* Lancet, 2012. **380**(9842): p. 651-9.

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