Fractional Exhaled Nitric Oxide And The Peripheral Blood Eosinophil Count As Biomarkers Of The Response To Mepolizumab In Patients With Severe Eosinophilic Asthma

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Aims

- Mepolizumab (Nucala) is a monoclonal antibody (IgG1 kappa) against interleukin-5 (IL-5) and the first anti-IL-5 treatment to be approved for use in asthma.
- Mepolizumab has been shown to reduce the rate of severe asthma exacerbations requiring oral corticosteroid treatment in patients with evidence of type-2-high, eosinophilic inflammation.[1]
- Blood eosinophil counts have been shown to be a useful biomarker to predict both the risk of severe asthma exacerbation and the response to mepolizumab treatment. [2]
- Fractional exhaled nitric oxide (FeNO) is another biomarker of type-2 inflammation and has also been shown to predict the risk of severe asthma exacerbations.[3]
- Both peripheral blood eosinophil count and FeNO are easily accessible biomarkers which can be measured in severe asthma.
- We test the hypothesis that the peripheral blood eosinophil count and FeNO have an additive effect in predicting exacerbation risk and the response to treatment with mepolizumab in patients with severe eosinophilic asthma.

Methods

- The DREAM study[1] investigated 3 doses of mepolizumab (75 mg, 250 mg, 750 mg IV) and placebo 4 weekly for 52 weeks in participants with a history of recurrent severe asthma exacerbations, and signs of eosinophilic inflammation (peripheral blood eosinophil count ≥300 cells/µL or sputum eosinophil count ≥3% or FeNO ≥50ppb or prompt deterioration of asthma control after a 25% or less reduction in regular maintenance inhaled or oral corticosteroids).
- We undertook a post-hoc analysis of the DREAM study where participants were divided into subgroups according to their baseline:
  - Peripheral blood eosinophil count (low <150 cells/µL, high ≥150 cells/µL)
  - FeNO (low ≤30ppb, high >30ppb).
- Baseline data and exacerbation rates during the study were compared between placebo and the three mepolizumab doses combined in the biomarker defined subgroups.

Results

Participants

- 606 participants who had baseline peripheral blood eosinophil count and FeNO measurements available were evaluated.

Baseline characteristics

- Baseline peripheral blood eosinophil count and FeNO were increased with the number of exacerbations in the year prior to study enrolment (**Table 1**).

Table 1. Baseline characteristics

	Number of exacerbations in the year prior to study enrolment		
	≤2	3	≥4
n	278	154	174
Baseline blood eosinophil count (cells/µL)	237 (0.92)	266 (1.03)	270 (1.18)
Baseline FeNO (ppb)	28.5 (0.78)	30.5 (0.80)	37.7 (0.78)

Data shown as geometric mean (log SD). ppb, parts per billion.

Analysis

- Participants with a high baseline peripheral blood eosinophil count had a reduced exacerbation rate on mepolizumab compared to placebo regardless of FeNO level (rate ratio [95% CI] compared to placebo 0.64 [0.42-0.99] for FeNO low and 0.38 [0.27-0.53] for FeNO high).
- The FeNO high, blood eosinophil low subgroup did not have reduced exacerbation frequency on mepolizumab treatment whereas those with high blood eosinophil counts, regardless of FeNO, did (**Table 2**).
- Those with both a high blood eosinophil count and high FeNO showed the highest risk of exacerbations on placebo and the most benefit from mepolizumab treatment (**Table 2**).

Table 2. Annualised exacerbation rates by biomarker subgroup

	n (placebo / mepolizumab)	Placebo exacerbation rate/year	Mepolizumab exacerbation rate/year	Rate ratio (95% CI)
PBE low, FeNO low	86 (23 / 63)	1.98	1.71	0.86 (0.47-1.57)
PBE low, FeNO high	60 (9 / 51)	1.78	1.67	0.94 (0.37-2.40)
PBE high, FeNO low	215 (47 / 168)	1.60	1.03	0.64 (0.42-0.99)
PBE high, FeNO high	245 (72 / 173)	3.14	1.20	0.38 (0.27-0.53)

PBE, peripheral blood eosinophil count

Discussion

- In patients with lower blood eosinophils, additional FeNO data does not predict exacerbation risk or response to mepolizumab.
- The combination of a higher peripheral blood eosinophil count and higher FeNO was associated with the highest risk of severe exacerbations and the largest exacerbation rate reduction with mepolizumab treatment.
- The peripheral blood eosinophil count is the best clinically available biomarker for predicting a response to mepolizumab treatment.
- FeNO is more affected by treatment with inhaled corticosteroids (ICS) than the blood eosinophil count, which may limit its utility as a biomarker in ICS treated severe eosinophilic asthma patients.

References

1. Pavord ID, et al. *Lancet* 2012;380(9842):651–9.
2. Ortega HG, et al. *Lancet Respir Med* 2016;4(7):549–56.
3. Powell H, et al. *Lancet* 2011;378(9795):983–90.

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