FRESH APPROACHES
A NEW LOOK AT SEVERE ASTHMA

Exacerbations in patients treated with biologics

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Exacerbations in patients treated with mepolizumab

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Disclosures

- Honoraria from Teva UK Limited

Aims

- Impact of biologics on exacerbations of Severe Asthma
- Assessing exacerbation risk with biomarkers
- Comparison of exacerbations on mepolizumab compared to placebo
  - Pathophysiology at time of exacerbation
  - Longitudinal analysis of exacerbations
  - Response to treatments
- Discussion
- Summary

Defining exacerbations

- *"Episodes of progressive increase in shortness of breath, cough, wheezing, or chest tightness, or some combination of these symptoms, accompanied by decreases in expiratory airflow that can be quantified by measurement of lung function"* (GINA 2016)

- *Moderate → Acute severe → Life-threatening* (BTS/SIGN)

Defining exacerbations

- ATS/ERS consensus 2009 – Standardising Endpoints for Clinical Asthma Trials and Clinical Practice
- Severe exacerbations – *"events that require urgent action on the part of the patient and physician to prevent a serious outcome, such as hospitalisation or death from asthma"*
- Moderate exacerbations – *"events that are troublesome to the patient, and that prompt a need for a change in treatment, but that are not severe. These events are clinically identified by being outside the patient's usual range of day-to-day asthma variation"*

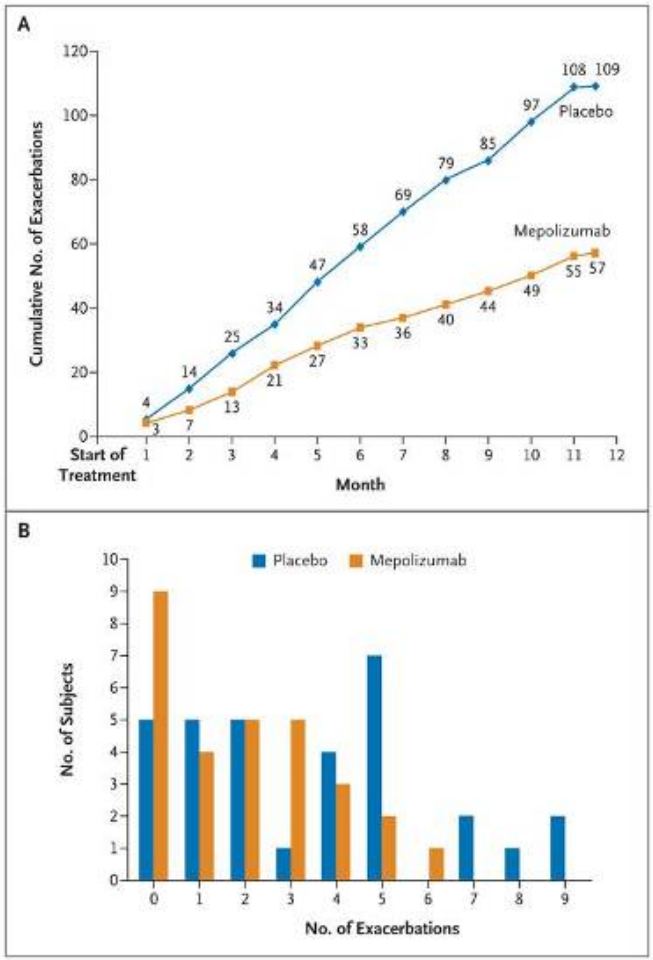
AJRCCM 2009;180

Mepolizumab

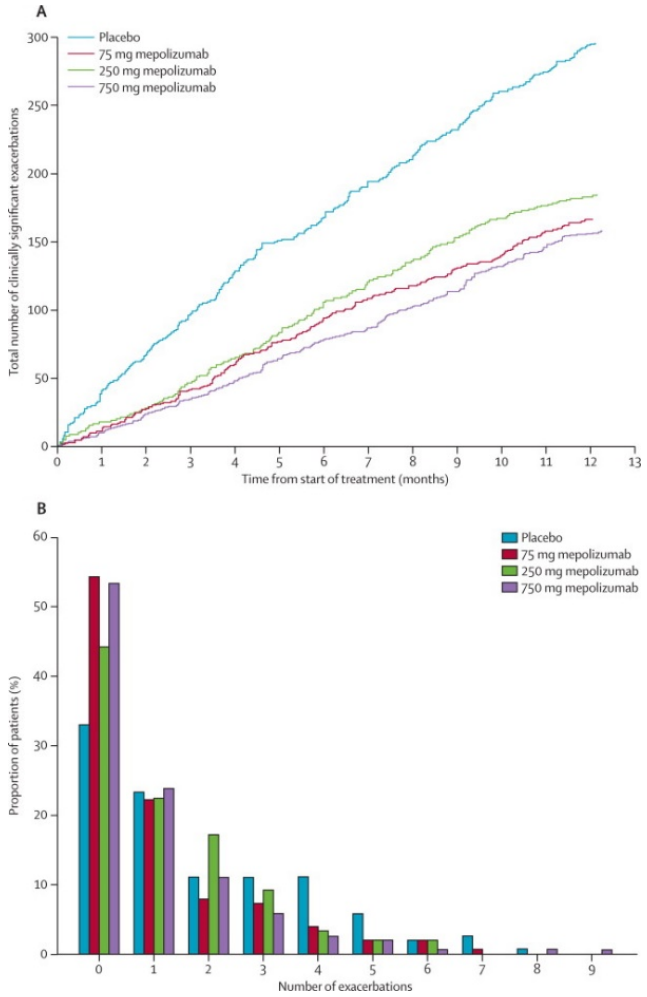
- ≥300 eosinophils/µL (peripheral blood) last 12 months
- On maintenance oral prednisolone and/or 4 or more courses of prednisolone in the last year
- On optimised inhaled therapy
- Adherence formally measured

- SC injection
- 100mg monthly for 12 years+ and 40mg monthly for 6-11 year olds
- Assess response at 1 year

Mepolizumab – effect on exacerbation rate



Haldar P *et al*. N Engl J Med 2009;360(10):973-84



Pavord I *et al*. Lancet 2012; 380(9842):651-9

Predicting exacerbation risk and response to treatment

- Easily accessible biomarkers of type-2 inflammation
  - Blood eosinophil count
  - FeNO
- Both have been shown to be associated with an increased risk of exacerbation

Methods

- Post-hoc analysis of DREAM study
  - Investigated 3 doses of mepolizumab (75mg, 250mg, 750mg IV) and placebo 4 weekly for 52 weeks in participants with a history of recurrent Severe Asthma exacerbations, and signs of eosinophilic inflammation
  - 606 participant evaluated
- 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

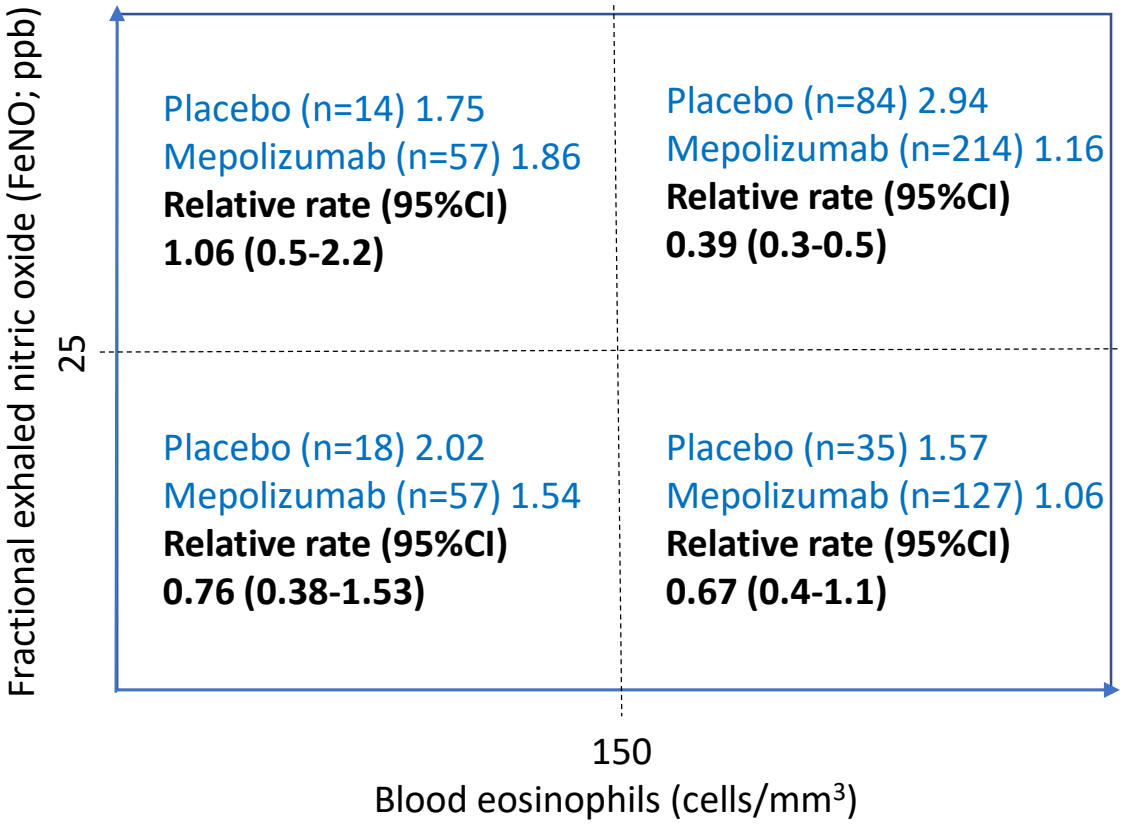
At baseline

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

Annualised exacerbation rates compared to placebo by biomarker subgroups



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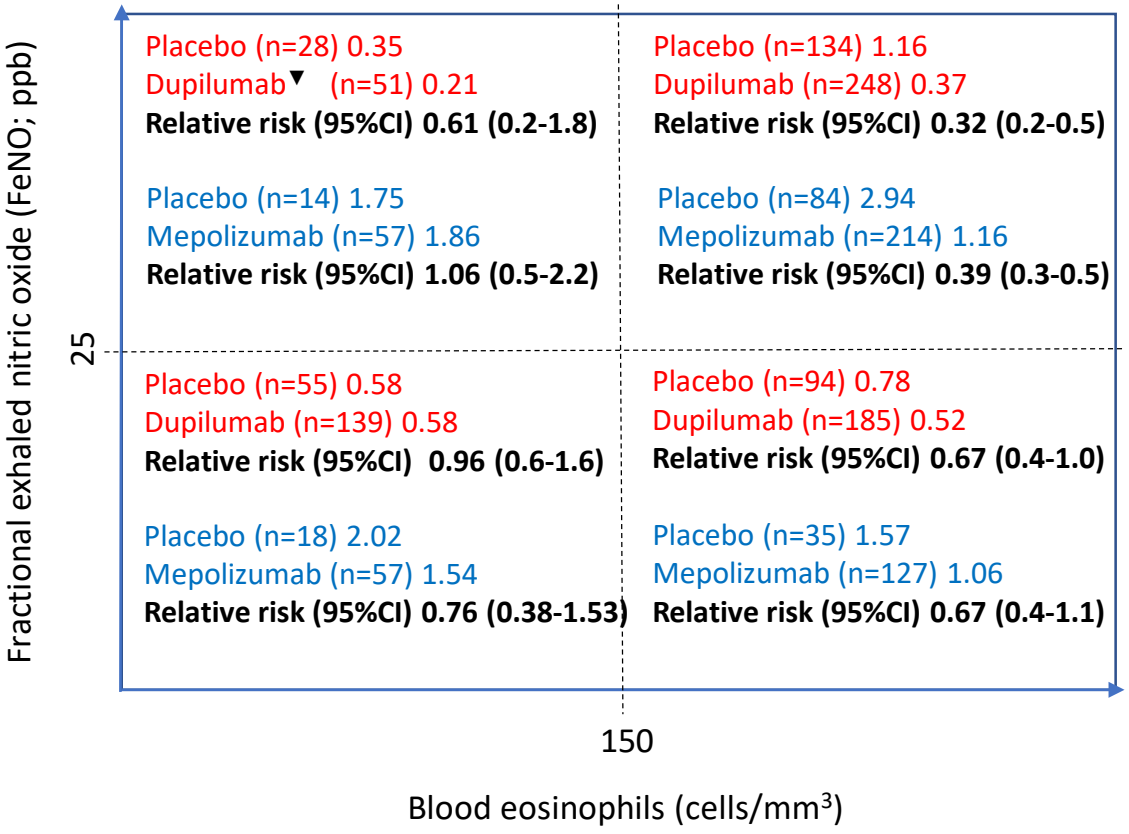

Exacerbations that occur on mepolizumab

- Are they different to those on placebo?
- Does reducing blood eosinophils change the exacerbation phenotype?

Exacerbations that occur on mepolizumab

- Only one study of mepolizumab that has seen patients at the time of exacerbation – Haldar *et al*. 2009
- Analysis of exacerbation events on mepolizumab compared to placebo

Exacerbations that occur on mepolizumab

	Exacerbation – seen pre-treatment			Exacerbation – seen during treatment		
	Placebo (n=55)	Mepolizumab (n=28)	*p*	Placebo (n=26)	Mepolizumab (n=50)	*p*
Δ Mean VAS (mm)	40 (3)	16 (4)	<0.001	14 (6)	28 (8)	0.1
Δ ACQ5	1.0 (0.1)	0.6 (0.2)	0.1	0.3 (0.2)	0.8 (0.3)	0.2
Δ FEV1 (L)	-0.11 (0.1)	-0.16 (0.1)	0.65	-0.12 (0.1)	-0.20 (0.1)	0.55
Sputum total cell count (cells x10^6/ml)	5.7 (1.2)	4.7 (1.9)	0.66	6.0 (2.7)	4.9 (1.8)	0.74
Sputum eosinophils (%) *	6.7% (0.1)	2.6% (0.2)	0.046	2.7% (0.1)	1.1% (0.1)	0.1
Sputum neutrophils (%)	57.5% (4.6)	57.2% (6.1)	0.96	54.8 (5.8)	59 (5.8)	0.62

Data shown as mean (standard error). Δ - Change from baseline. * Geometric mean (log standard error)

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Shrimanker R *et al.* ERJ 2018

Limitations

- Small numbers – 30 patients *per* group
- No longitudinal data

Further analysis

Diary card data was reviewed from the 3 studies

- DREAM(1), a 52-week study of 3 doses of mepolizumab (75, 250 or 750mg IV 4 weekly) *vs* placebo;
- MENSA(2), an 32-week study of 2 doses of mepolizumab (75mg IV or 100mg s/c 4 weekly) *vs* placebo;
- MUSCA(3), a 24-week study of mepolizumab 100mg s/c 4 weekly *vs* placebo. All studies recruited patients with severe eosinophilic asthma and a history of 2 or more exacerbations in the previous year. Mepolizumab dose groups were combined for analysis

1. Pavord I *et al*. Lancet 2012;**380**(9842):651-9
2. Ortega H et al. N Engl J Med 2014;**371**(13):1198-207
3. Chupp G *et al*. Lancet Respir Med 2017;**5**(5):390-400

Methods

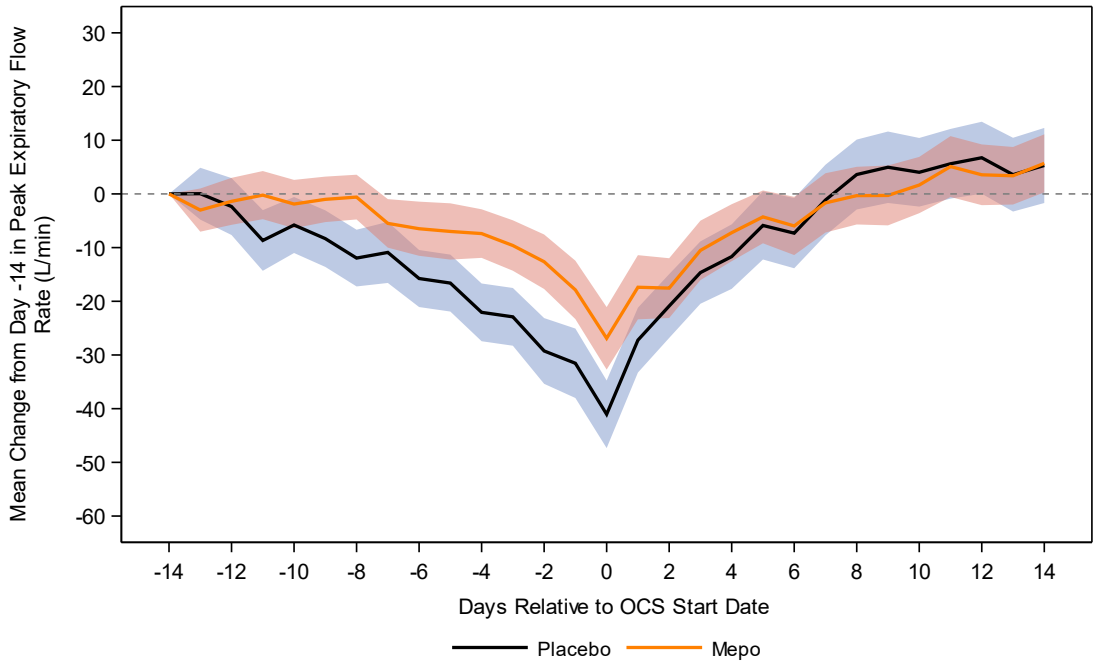
- Patients completed a daily diary card including a 6 point symptom score assessing asthma symptoms in the previous 24 hours and a best-of-three morning peak expiratory flow (PEF)
- Exacerbations requiring rescue oral corticosteroids (OCS) with at least 20 days of diary data in the period from 14 days prior to starting OCS (Day -14) to 14 days (Day 14) after starting OCS were included in the analysis

Results

- 1026 exacerbations were included in the analysis. 476 occurred in 248 subjects on placebo treatment and 550 occurred in 338 subjects on mepolizumab treatment

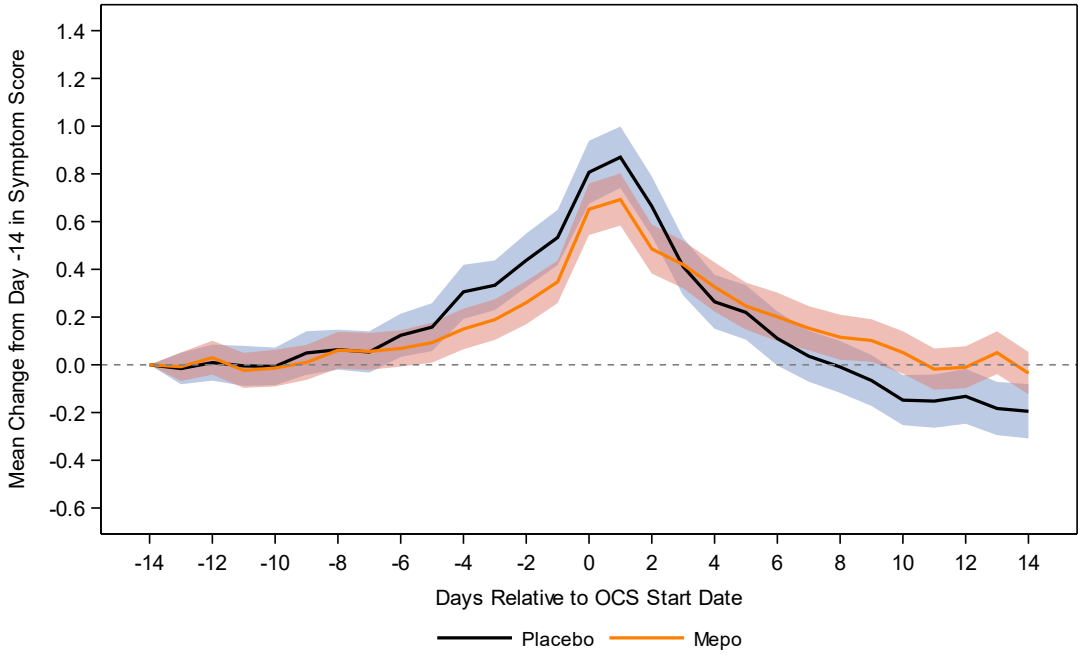
Effect on PEF

- Exacerbations on placebo were associated with a larger drop in PEF (-41.0 L/minutes [95% CI -47.3, -34.7]) compared to mepolizumab (-26.9 L/minutes [-32.7, -21.1]) over the 14 days prior to starting OCS (figure)



Effect on symptoms

- Exacerbations on placebo also tended to have a larger increase in daily symptom score compared to mepolizumab (0.81 points [0.68, 0.94] *vs* 0.65 points [0.54, 0.76] respectively)



Summary

- Exacerbations on mepolizumab appear different in nature and less severe compared to those on placebo
- Exacerbations on mepolizumab are associated with
  - Lower sputum eosinophils
  - Lower symptoms as measured by the VAS or daily symptom score
  - Smaller falls from baseline PEF
  - A potentially differential response to prednisolone treatment
- Prospective studies are underway to further investigate these differences

Discussion