

Characterisation of an OCS-dependent severe asthma population treated with mepolizumab

A subpopulation of patients with asthma treated with maximal inhaled treatments is unable to maintain asthma control and requires additional therapy with oral corticosteroids (OCS); a subset of this population continues to have frequent exacerbations. Alternate treatment options are needed as daily use of OCS is associated with significant systemic adverse effects that affect many body systems and have a direct association with the dose and duration of OCS use. We compared the population demographics, medical conditions and efficacy responses of the OCS-dependent group from the DREAM study of mepolizumab with the group not managed with daily OCS.

Trial Registration Number NCT01000506.

Mepolizumab, an anti-interleukin 5 monoclonal antibody under development for severe asthma, has been shown to reduce peripheral and sputum eosinophils.^{1 2} Mepolizumab is hypothesised to work by reducing eosinophilic driven airway inflammation. Mepolizumab has previously been shown to be steroid sparing in a small study.¹ The DREAM study (NCT01000506) reported that mepolizumab can reduce the exacerbation rate by 39–52% in a severe asthma population.² Approximately a third of the subjects (n=188) who participated in the DREAM study were using daily oral corticosteroids (OCS) at baseline in addition to using high dose inhaled corticosteroid and an additional controller to treat their asthma. This group reported an average duration of OCS use of 4.1 years, a mean OCS dose of 17 mg/day and a median peripheral blood baseline eosinophil level of 280 cells/ μ L, which was similar to that for the non-OCS dependent subgroup (290 cells/ μ L) (table 1). Sputum

eosinophils levels were also similar between the OCS-dependent and non-OCS dependent groups, although only measured in a subset of subjects. Consistent with a recent finding from Severe Asthma Research Program (SARP), the OCS group also had greater baseline airway inflammation, as assessed by median FE_{NO} (table 1).³

Mean baseline ACQ scores indicated both subgroups were not controlled; the OCS-group had a mean ACQ-6 score of 2.5 compared with 2.3 (p=0.077) for the non-OCS group (table 2). Despite being on maximal therapy, the OCS group had a lower baseline mean FEV₁, and lower FVC, and FEV₁/FVC ratio when compared with the non-OCS group (table 1). The majority of subjects (75%) in the OCS group reported having three or more exacerbations in the year prior to the study compared with 44% of the non-OCS group; 49% of the OCS group had severe exacerbations that required asthma-related hospitalisation(s), intubation, or were considered near-fatal asthma events (table 3).

Table 1 Characteristics of the non-OCS and OCS dependent subgroups

Variables	Non-OCS dependent (n=428)	OCS dependent (n=188)	p Value
Mean age, years (SD)	47.6 (11.72)	51.0 (9.81)	<0.001*
Sex, female % (n)	65 (279)	57 (108)	0.067†
Body mass index (kg/m ²) (SD)	28.4 (6.05)	28.5 (5.74)	0.875*
Race, white % (n)	89 (380)	89 (167)	0.228†
FEV ₁ % predicted (SD)			
Prebronchodilator	60.7 (14.58)	57.3 (18.35)	0.014*
Postbronchodilator	72.3 (16.87)	67.7 (19.38)	0.003*
FEV ₁ L (SD)			
Prebronchodilator	1.91 (0.62)	1.80 (0.73)	0.045*
Postbronchodilator	2.28 (0.72)	2.12 (0.79)	0.014*
FVC L (SD)			
Prebronchodilator	3.03 (0.92)	2.89 (1.00)	0.076*
Postbronchodilator	3.38 (0.97)	3.26 (1.06)	0.161*
FEV ₁ /FVC ratio (SD)			
PreBronchodilator	0.63 (0.12)	0.62 (0.13)	0.159*
PostBronchodilator	0.68 (0.13)	0.66 (0.18)	0.079*
Reversibility			
Mean % reversibility (SD)	24.1 (19.74)	26.1 (25.82)	0.282*
Inflammation characteristics			
Median baseline FE _{NO} ppb (IQR)	27.5 (17–52)	38 (22–65)	<0.001‡
Median baseline sputum eosinophil count % (IQR) [§]	n=46 11.25 (2.75–30.75)	n=40 13.88 (4.00–40.25)	0.436‡
Median baseline peripheral blood eosinophil count, cells/ μ L (IQR)	290 (150–510)	280 (130–510)	0.372‡
Inflammation criteria at study entry			
Peripheral eosinophils \geq 300 cells/ μ L in previous 12 months % (n)	71 (256/359)	65 (109/168)	0.136†
Peripheral eosinophils \geq 150 cells/ μ L at baseline % (n)	77 (328)	74 (139)	0.471†
Sputum eosinophils \geq 3% in previous 12 months % (n)	41 (36/88)	61 (28/46)	0.028†
FE _{NO} \geq 50 ppb at baseline or in previous 12 months % (n)	44 (174/392)	52 (88/168)	0.082†
Patient-reported outcomes			
Mean ACQ-6 score (SD)	2.3 (1.06)	2.5 (1.17)	0.077*
Mean overall AQLQ (SD)	4.2 (1.17)	4.2 (1.24)	0.993*

*p-value from a t-test.

†p-value from a chi-squared test.

‡p-value from a Wilcoxon test.

§Interquartile range.

ACQ-6, asthma control questionnaire; AQLQ, asthma quality of life questionnaire; OCS, oral corticosteroids.

Table 2 Exacerbation rate

	Non-OCS dependent		OCS dependent	
	Placebo (n=110)	Mepolizumab (n=318)	Placebo (n=45)	Mepolizumab (n=143)
Exacerbation rate/year	1.90	1.07	3.12	1.54
Rate ratio (95% CI)	0.56 (0.42 to 0.76)		0.49 (0.35 to 0.70)	
Interaction p value	0.503			

OCS, oral corticosteroids.

Table 3 Exacerbation History and Related Healthcare Utilization Events

	Non-OCS dependent	OCS dependent
% population with history in the past 12 months of:		
2 exacerbations	55	25
>2 exacerbations	44	75
Reporting 1 or more prior hospitalization for an exacerbation	22	25
Reporting prior intubation(s) for exacerbation	3	7
Reporting prior near fatal event for exacerbation	8	17

*one subject in the non-OCS dependent population had reported only one exacerbation at baseline and was considered a protocol violator.

Mepolizumab reduced the peripheral eosinophils within 4 weeks of treatment and the effect was maintained for the duration of the study and was effective at reducing the frequency of exacerbations in the non-OCS and OCS groups during the 52-week treatment period with a numerically greater reduction noted in the OCS group (table 2).² This difference was not statistically different. Placebo treated subjects in the OCS group had the highest exacerbation rate during the study. These results demonstrate that despite daily OCS use the OCS group continues to have severe disease impairment with persistent eosinophils, airway inflammation, reduced lung function, and are also at high risk for future exacerbations. These clinical parameters were reflected by the poor control status and poor quality of life reported at baseline. The efficacy results demonstrate that mepolizumab

treatment of a population using OCS daily was able to reduce peripheral eosinophils and exacerbation risk to a similar extent as a non-OCS dependent group.

C M Prazma,¹ S Wenzel,² N Barnes,^{3,4,5} J A Douglass,⁶ B F Hartley,⁷ H Ortega¹

¹GlaxoSmithKline, Research Triangle Park, North Carolina, USA

²Division of Pulmonary, Allergy and Critical Care, Department of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

³Respiratory Medical Franchise, GSK, Uxbridge, UK

⁴The William Harvey Research Institute, Barts, London, UK

⁵The London School of Medicine and Dentistry, London, UK

⁶Department of Allergy and Immunology, The Royal Melbourne Hospital and The University of Melbourne, Parkville, Victoria, Australia

⁷GlaxoSmithKline, Uxbridge, UK

Correspondence to Dr Hector Ortega, GlaxoSmithKline, 5 Moore Drive, PO Box 3317.3A, Research Triangle Park, NC 27709-3398, USA; hector.g.ortega@gsk.com

Contributors CMP and HO contributed to the conception and design of the work and in the acquisition, analysis, or interpretation of data. BFH, SW, JAD and NB contributed to the analysis, or interpretation of data. All authors contributed towards drafting the research letter and revising it critically for important intellectual content and provided final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding This study was funded by GlaxoSmithKline.

Competing interests None.

Patient consent Obtained.

Ethics approval The data presented within was a global clinical trial and various independent Ethics committees and IRBs reviewed and approved prior to study initiation.

Provenance and peer review Not commissioned; internally peer reviewed.



CrossMark

To cite Prazma CM, Wenzel S, Barnes N, *et al.* *Thorax* 2014;**69**:1141–1142.

Received 18 April 2014

Accepted 22 April 2014

Published Online First 16 May 2014

Thorax 2014;**69**:1141–1142.

doi:10.1136/thoraxjnl-2014-205581

REFERENCES

- 1 Nair P, Pizzichini MM, Kjarsgaard M, *et al.* Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. *N Engl J Med* 2009;**360**:985–93.
- 2 Pavord ID, Korn S, Howarth P, *et al.* Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet* 2012; **380**:651–9.
- 3 Wysocki K, Park SY, Bleecker E, *et al.* Characterization of factors associated with systemic corticosteroid use in severe asthma: Data from the Severe Asthma Research Program. *J Allergy Clin Immunol* 2014;**133**:915–18.