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/μL, which was similar to that for the non-OCS dependent subgroup (290 cells/μL) (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 FEV_1, and lower FVC, and FEV_1/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)δ	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/μL (IQR)	290 (150–510)	280 (130–510)	0.372‡
Inflammation criteria at study entry			
Peripheral eosinophils≥300 cells/μL in previous 12 months % (n)	71 (256/359)	65 (109/168)	0.136†
Peripheral eosinophils≥150 cells/μL at baseline % (n)	77 (328)	74 (139)	0.471†
Sputum eosinophils≥3% in previous 12 months % (n)	41 (36/88)	61 (28/46)	0.028†
FE_{NO}≥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.
δInterquartile 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 Ortega[1]

[1]GlaxoSmithKline, Research Triangle Park, North Carolina, USA
[2]Division of Pulmonary, Allergy and Critical Care, Department of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, USA
[3]Respiratory Medical Franchise, GSK, Uxbridge, UK
[4]The William Harvey Research Institute, Barts, London, UK
[5]The London School of Medicine and Dentistry, London, UK
[6]Department of Allergy and Immunology, The Royal Melbourne Hospital and The University of Melbourne, Parkville, Victoria, Australia
[7]GlaxoSmithKline, 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

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Competing interests None.

Patient consent Obtained.

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Statistical Analysis

FEV_1 in the OCS dependent and non-OCS dependent subgroups was examined using two repeated measures analyses. The models had covariates for treatment group, region, number of exacerbations in the year prior to the study (on the basis of patient recall and case-note review), visit, and baseline pre-bronchodilator FEV_1, visit by baseline pre-bronchodilator FEV_1 and visit by treatment group interactions we also included. All data up to the time of study discontinuation were included for patients who withdrew prematurely.

As described previously, the number of exacerbations per year in the OCS dependent and non-OCS dependent populations were analysed with separate negative binomial generalized linear models with log-link functions.[3] The models had covariates for treatment group, region, exacerbations in the year prior to the study (on the basis of patient recall and case-note review), and baseline percentage of predicted pre-bronchodilator FEV_1, time on treatment was included as an offset variable. A separate model was used to assess the interaction between treatment and baseline OCS therapy, this model included the same covariates as the subgroup models plus covariates for baseline maintenance OCS therapy and an interaction term between baseline maintenance OCS therapy and treatment group. All analysis were conducted with SAS (versions 9.1.3 and 9.2; SAS Institute, Cary, NC, USA).

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