

Prognostic and predictive value of blood eosinophil count, fractional exhaled nitric oxide and their combination in severe asthma: a post-hoc analysis

Rahul Shrimanker

Oliver Keene*

Gareth Hynes

Sally Wenzel~

Steven Yancey#

Ian D Pavord

Oxford Respiratory NIHR Biomedical Research Centre, Nuffield Department of Medicine, NDM Research Building, University of Oxford, Old Road Campus, Oxford OX3 7FZ, UK. *Clinical Statistics, GlaxoSmithKline, Stockley Park, Middlesex, UK. ~The Department of Pulmonary, Allergy, and Critical Care Medicine, University of Pittsburgh Asthma Institute at the University of Pittsburgh Medical Center—University of Pittsburgh School of Medicine, Pittsburgh, USA. #Respiratory Therapeutic Area. GlaxoSmithKline, Research Triangle Park, North Carolina, USA

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Correspondence to Ian D Pavord, Oxford Respiratory NIHR Biomedical Research Centre, Nuffield Department of Medicine, NDM Research Building, University of Oxford, Old Road Campus, Oxford OX3 7FZ

ian.pavord@ndm.ox.ac.uk

To the editor,

Patients with severe eosinophilic asthma have a high risk of exacerbations requiring rescue oral corticosteroid treatment. Monoclonal antibody treatments inhibiting IL-5 directly or via the IL-5R α or IL13/IL4 via the IL-4R α reduce exacerbations of severe, eosinophilic asthma with evidence to type-2 inflammation as shown by a raised peripheral blood eosinophil count or fractional exhaled nitric oxide (FeNO) (1) (2). Both of these biomarkers have been associated with an increased risk of exacerbations (3).

The key cytokine for the development of eosinophils is IL-5 whereas FENO is regulated by the IL-13 dependant inducible nitric oxide pathway (4) suggesting that their combination might provide additive prognostic and predictive information. We tested this hypothesis in a post-hoc analysis of a placebo controlled trial of anti-IL-5 (mepolizumab) in patients with severe asthma.

Methods

We undertook a *post-hoc* analysis of a phase 2b study of mepolizumab in patients with severe eosinophilic asthma (DREAM) (1). We selected this study as it was the only mepolizumab study to assess FeNO and blood eosinophils at baseline.

DREAM evaluated placebo and 3 doses of mepolizumab (75 mg, 250 mg, 750 mg IV 4 weekly) for 52 weeks. Participants had a history of 2 or more exacerbations requiring oral corticosteroids in the previous year and evidence of eosinophilic inflammation as reflected by one of more of the following: a peripheral blood eosinophil count ≥ 300 cells/ μ L; a sputum eosinophil count $\geq 3\%$; FeNO ≥ 50 ppb; and prompt deterioration of asthma control after a 25% or less reduction in regular maintenance inhaled or oral corticosteroids. As the DREAM study did not show a dose-related effect of active treatment or evidence of an interaction between dose and predictive value of biomarkers, our analysis is based on the combined effect of the different doses.

Participants were divided into subgroups depending on their baseline peripheral blood eosinophil count (PBE) and FeNO. PBE were defined as high (≥ 150 cells/ μL) or low (<150 cells/ μL) and FeNO as high (≥ 25 ppb) or low (< 25 ppb). We chose these cut points because of pre-existing evidence linking them to eosinophilic airway inflammation and response to corticosteroids(5). Baseline demographics, clinical characteristics and annualised exacerbation rates were calculated based on 4 biomarker subgroups; PBE high-FeNO high, PBE high-FENO low, PBE low-FENO high, PBE low-FeNO low. An additional analysis was carried out using a PBE cutpoint of 300 cells/ μL .

The DREAM study was a multi-centre, randomised, double blind, placebo-controlled trial. Our primary interest was severe exacerbation rate, defined as the requirement for rescue oral corticosteroids, as the main benefit of mepolizumab treatment is to reduce the rate of exacerbations and exacerbation rate was the primary outcome measure of the trial. We also present the change in pre-bronchodilator FEV₁ after 52 weeks of treatment.

Results

606 DREAM participants had baseline blood eosinophil and FeNO measurements. The study population had a mean of 3.6 exacerbations per patient per year in the year prior to study enrolment. Lung function was reduced, with a mean FEV₁ of 60% predicted and there was a high symptom burden with a mean ACQ6 score of 2.3 (<1.5 indicating good control). The baseline demographics and clinical characteristics of the study patients across biomarker subgroups and treatment are shown in table 1.

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The risk of exacerbations was highest in placebo treated patients with high baseline PBE and FeNO. The efficacy of active treatment was most marked in this group with mepolizumab showing 61% exacerbation rate reduction, compared to 33% exacerbation rate reductions in the PBE high-FeNO group. Mepolizumab did not have a significant effect on exacerbation rate in the PBE low subgroups regardless of FeNO. Similar findings were seen for change in pre-bronchodilator FEV₁ (figure) and when patients were stratified by a PBE of 300 cells/ μ L (online figure).

Discussion

We found that in patients with severe asthma treated with placebo who had high blood eosinophil counts and FeNO the rate of severe exacerbations requiring oral corticosteroid treatment was up to twice that seen in placebo treated patients with low or discordant biomarker results. The different biomarker groups had similar baseline lung function, symptom scores and exacerbation risk indicating that the increased risk of exacerbation events is independent of these other markers of asthma control and risk indicating that biomarker profiling of patients with severe asthma adds predictive value to a traditional risk assessment.

To evaluate the relationship between biomarker profile and treatment efficacy, we compared our findings with published results of the phase 3 trial of monoclonal antibody dupilumab (QUEST), a monoclonal antibody that blocks IL-13 and IL-4 by binding to the IL-4 receptor- α (2). This study evaluated 2 doses of dupilumab (200mg or 300mg SC 2 weekly) for 52 weeks in 1902 patients with moderate-severe persistent, uncontrolled asthma as per the GINA guidelines (6). Both doses had equivalent efficacy and, as combined data is not available, we present data from the 934 patients randomised to dupilumab 200 mg every two weeks or matched placebo. Information on change in pre-bronchodilator FEV₁ by biomarker profile was not available for QUEST (figure). The efficacy of dupilumab on exacerbations was most marked in the PBE high-FENO high group with a 68% reduction. There was also an exacerbation rate reduction of 33% in the PBE high-FeNO low group

which was similar to the effect seen in this subgroup with mepolizumab treatment. In the PBE low-FeNO low group neither biologic had a significant effect on exacerbations. In the PBE low-FeNO high group a 39% exacerbation rate reduction was seen with dupilumab. Although not statistically significant, this finding contrasts to the absence of effect seen with mepolizumab in this subgroup.

The study populations differed significantly with the DREAM population having a higher exacerbation risk and a higher proportion of patients using high dose inhaled or regular oral corticosteroids. However, the higher risk of exacerbation in patients with higher blood eosinophils and FeNO was seen in both populations suggesting a true effect seen across a range of asthma severity. This is in keeping with earlier studies showing that a composite profile of biomarkers of type-2 airway inflammation provides prognostic information over and above a assessment of risk of exacerbation based on traditional asthma measures although this earlier study used a composite score of blood eosinophils, serum periostin and FeNO biomarkers (7). We extend these earlier findings by showing that patients with both high blood eosinophil counts and FeNO also had the greatest response to biological treatment with mepolizumab and dupilumab, indicating that biomarker profiles have predictive as well as prognostic value.

These greater prognostic value of the combined biomarker profile make biological sense given the biomarkers relate to different aspects of type-2 immune responses in the airway. The peripheral blood eosinophil count reflects airway and systemic IL-5 production and is reduced markedly by anti-IL-5 (1) but not dupilumab (2). In contrast, FeNO reflects airway IL-13 activity as it is reduced markedly by anti-IL-13 and dupilumab (2) but not anti-IL-5 (1). Thus, the two measures provide a more complete assessment of type-2 immune responses in the airway. It is also likely that the combination of a systemic and local airway measure adds precision to an assessment in only one of these compartments. We did not find a point estimate improvement for mepolizumab in patients

with high FeNO but low PBE as might be expected as FeNO is a marker of IL-13 activity in the airway. In contrast, there was a trend for benefit of dupilumab in this group.

Caution is required in interpreting this post-hoc subgroup analysis since the number of patients in some subgroups is small and the populations studied in DREAM and QUEST were different. We acknowledge that the relative efficacy of mepolizumab and dupilumab treatment in subgroups may reflect the play of chance or differences in patient populations as well as the different cytokine associations of the biomarkers. However, it is striking that the relative exacerbation rate reductions in three of the four subgroups were very similar. Our findings suggest that biomarker profiles might have value in identifying patients suitable for different biological agents. Formal head-to-head studies in similar patient populations are needed to assess this possibility prospectively. Future studies should also model the relationship between biomarker values and exacerbations more completely, allowing more accurate inferences to be drawn on individual patient responses.

Legend to figure

Annualised exacerbation rates and improvement in pre-bronchodilator FEV₁ with 52 weeks treatment with mepolizumab or placebo. Equivalent exacerbation rates for Dupilumab 200 mg every 2 weeks and placebo are shown for comparison.

Legend to on-line supplement figure

Annualised exacerbation rates and improvement in pre-bronchodilator FEV₁ with 52 weeks treatment with mepolizumab or placebo with a peripheral blood eosinophil cutpoint of 300 cells/ μ L

Reference List

1. Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, Ortega H, Chanez P. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet* 2012; 380: 651-659.
2. Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF, Busse WW, Ford L, Sher L, FitzGerald JM, Katelaris C, Tohda Y, Zhang B, Staudinger H, Pirozzi G, Amin N, Ruddy M, Akinlade B, Khan A, Chao J, Martincova R, Graham NMH, Hamilton JD, Swanson BN, Stahl N, Yancopoulos GD, Teper A. Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma. *N Engl J Med* 2018; 378: 2486-2496.
3. Malinovschi A, Fonseca JA, Jacinto T, Alving K, Janson C. Exhaled nitric oxide levels and blood eosinophil counts independently associate with wheeze and asthma events in National Health and Nutrition Examination Survey subjects. *The Journal of allergy and clinical immunology* 2013; 132: 821-827.e821-825.
4. Arron JR, Choy DF, Scheerens H, Matthews JG. Noninvasive biomarkers that predict treatment benefit from biologic therapies in asthma. *Ann Am Thorac Soc* 2013; 10 Suppl: S206-213.
5. Pavord ID, Afzalnia S, Menzies-Gow A, Heaney LG. The current and future role of biomarkers in type 2 cytokine-mediated asthma management. *Clin Exp Allergy* 2017; 47: 148-160.
6. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. www.ginasthma.org. 2016 [cited 2016 11th May].
7. Heaney LG, Djukanovic R, Woodcock A, Walker S, Matthews JG, Pavord ID, Bradding P, Niven R, Brightling CE, Chaudhuri R, Arron JR, Choy DF, Cowan D, Mansur A, Menzies-Gow A, Adcock I, Chung KF, Corrigan C, Coyle P, Harrison T, Johnston S, Howarth P, Lordan J, Sabroe I, Bigler J, Smith D, Catley M, May R, Pierre L, Stevenson C, Crater G, Keane F, Costello RW, Hudson V, Supple D, Hardman T. Research in progress: Medical Research Council United Kingdom Refractory Asthma Stratification Programme (RASP-UK). *Thorax* 2016; 71: 187-189.

Table. Baseline demographics and disease characteristics of DREAM patients divided by baseline PBE and FeNO subgroup and randomised treatment.

	PBE <150 cells/μL, FeNO <25 ppb		PBE <150 cells/μL, FeNO ≥25 ppb		PBE ≥150 cells/μL, FeNO <25 ppb		PBE ≥150 cells/μL, FeNO ≥25 ppb		Total	
	Placebo (N=18)	Mepolizumab (N=57)	Placebo (N=14)	Mepolizumab (N=57)	Placebo (N=35)	Mepolizumab (N=127)	Placebo (N=84)	Mepolizumab (N=214)	Placebo (N=151)	Mepolizumab (N=455)
Age, years, mean (SD)	44.3 (12.07)	52.7 (11.79)	45.5 (10.55)	50.6 (8.27)	45.9 (11.05)	48.0 (10.99)	46.9 (11.54)	49.2 (11.49)	46.2 (11.33)	49.5 (11.10)
Female, n (%)	11 (61)	38 (67)	7 (50)	34 (60)	29 (83)	83 (65)	49 (58)	132 (62)	96 (64)	287 (63)
ICS Dose (μg/day) ¹ , mean (SD)	1053 (356)	1108 (434)	1033 (115)	1077 (567)	1175 (464)	1150 (523)	1169 (608)	1094 (447)	1145 (523)	1109 (483)
Maintenance OCS use, n (%)	2 (11)	18 (32)	5 (36)	22 (39)	8 (23)	25 (20)	27 (32)	75 (35)	42 (28)	140 (31)
Pre-bronchodilator FEV1, mL, mean (SD)	2253 (812.2)	1747 (631.1)	2105 (811.7)	1888 (647.0)	1611 (506.3)	1845 (636.2)	1919 (605.8)	1911 (678.8)	1905 (656.9)	1869 (657.4)
Pre-bronchodilator %predicted FEV1, mean (SD)	66.3 (17.05)	59.2 (14.99)	58.2 (12.90)	60.6 (15.22)	53.9 (12.77)	59.3 (16.57)	60.5 (15.54)	60.3 (16.24)	59.4 (15.21)	59.9 (16.01)
Post-bronchodilator FEV1, mL, mean (SD)	2688 (821.8)	2008 (706.1)	2648 (948.3)	2178 (725.5)	1927 (652.8)	2154 (680.0)	2311 (725.0)	2297 (764.4)	2298 (777.1)	2206 (733.8)
ACQ-6 Score, mean (SD)	2.6 (1.20)	2.1 (1.02)	2.5 (0.82)	2.5 (0.98)	2.4 (1.11)	2.1 (1.13)	2.5 (1.08)	2.4 (1.11)	2.5 (1.07)	2.3 (1.10)
PBE count, cells/μL, geometric mean (SD logs)	80 (0.57)	50 (0.95)	50 (0.89)	80 (0.72)	350 (0.66)	350 (0.54)	450 (0.61)	410 (0.63)	280 (1.01)	240 (1.03)
FeNO count, ppb, geometric mean (SD logs)	14.6 (0.39)	12.3 (0.45)	42.3 (0.49)	54.0 (0.47)	14.4 (0.34)	15.2 (0.42)	55.5 (0.55)	51.2 (0.50)	33.7 (0.79)	30.7 (0.79)
Exacerbations in year prior to study, mean (SD)	2.7 (1.87)	3.3 (2.50)	3.5 (1.99)	3.9 (3.06)	2.9 (1.09)	3.0 (2.03)	4.4 (4.87)	3.8 (3.16)	3.8 (3.83)	3.5 (2.81)
Requiring hospitalization, n (%)	4 (22)	20 (35)	3 (21)	17 (30)	7 (20)	28 (22)	25 (30)	44 (21)	39 (26)	109 (24)

1. ICS doses are presented as ex-valve/metered doses and are based on conversions to an FP equivalent dose.

ACQ, asthma control questionnaire; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 second; ICS, inhaled corticosteroids; OCS, oral corticosteroids;

PBE, peripheral blood eosinophil count; ppb, parts per billion; SD, standard deviation.