

Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies

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Summary

Background Findings from previous studies showed that mepolizumab significantly reduces the rate of exacerbations in patients with severe eosinophilic asthma. To assess the relationship between baseline blood eosinophil counts and efficacy of mepolizumab we did a secondary analysis of data from two studies, stratifying patients by different baseline blood eosinophil thresholds.

Methods We did a post-hoc analysis of data, which was completed on Sept 25, 2015, from two randomised, double-blind, placebo-controlled studies of at least 32 weeks duration (NCT01000506 [DREAM] and NCT01691521 [MENSA]) done between 2009 and 2014. In these studies, mepolizumab (DREAM: 75 mg, 250 mg, or 750 mg intravenously; MENSA: 75 mg intravenously or 100 mg subcutaneously) versus placebo was given at 4-week intervals in addition to standard care (high-dose inhaled corticosteroids plus ≥ 1 additional controller with or without daily oral corticosteroids) to patients aged 12 years or older with a clinical diagnosis of asthma, a history of at least two exacerbations in the previous year that required systemic corticosteroid treatment, and evidence of eosinophilic airway inflammation. The primary endpoint in both studies was the annual rate of clinically significant exacerbations (defined as worsening of asthma that required the use of systemic corticosteroids, or admission to hospital, or an emergency-room visit, or a combination of these occurrences). In our analysis, the primary outcome was the annualised rate of exacerbations in patients stratified by baseline eosinophil counts (≥ 150 cells per μL , ≥ 300 cells per μL , ≥ 400 cells per μL , and ≥ 500 cells per μL) and baseline blood eosinophil ranges (< 150 cells per μL , ≥ 150 cells per μL to < 300 cells per μL , ≥ 300 cells per μL to < 500 cells per μL , and ≥ 500 cells per μL). We based our analysis on the intention-to-treat populations of the two original studies, and all mepolizumab doses were combined for analysis.

Findings Of 1192 patients, 846 received mepolizumab and 346 received placebo. The overall rate of mean exacerbations per person per year was reduced from 1.91 with placebo to 1.01 with mepolizumab (47% reduction; rate ratio [RR] 0.53, 95% CI 0.44–0.62; $p < 0.0001$). The exacerbation rate reduction with mepolizumab versus placebo increased progressively from 52% (0.48, 0.39–0.58) in patients with a baseline blood eosinophil count of at least 150 cells per μL to 70% (0.30, 0.23–0.40) in patients with a baseline count of at least 500 cells per μL . At a baseline count less than 150 cells per μL , predicted efficacy of mepolizumab was reduced.

Interpretation Our analysis has shown a close relationship between baseline blood eosinophil count and clinical efficacy of mepolizumab in patients with severe eosinophilic asthma and a history of exacerbations. We noted clinically relevant reductions in exacerbation frequency in patients with a count of 150 cells per μL or more at baseline. The use of this baseline biomarker will help to select patients who are likely to achieve important asthma outcomes with mepolizumab.

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Introduction

Asthma is a heterogeneous condition, which includes several clinical phenotypes that differ in severity, natural history, and response to therapy.¹ One well defined pattern of disease in patients with severe asthma is characterised by persistent eosinophilic airway inflammation, as indicated by eosinophil counts of at least 150 cells per μL in blood, or more than 2% in sputum, or both.^{2,3} Eosinophils normally make up fewer than 5% of leucocytes in the blood,⁴ but their production is increased in response to inflammation.⁵ Eosinophils are recruited from the bloodstream to areas of inflammation by cytokines such as interleukin-5 and members of the eotaxin family of

chemokines.⁵ Studies using specific inhibitors of this process have shown an association between eosinophils and the pathogenesis of asthma exacerbations.^{6,7}

Prospective clinical studies of monoclonal antibodies inhibiting interleukin-5 have shown that baseline blood eosinophil count is predictive of response to treatment.^{8,9} However, there are differences in the blood eosinophil thresholds used in clinical trials among the various biologicals targeting the interleukin-5 pathway.^{9–11} Moreover, little is known about the relationship between blood eosinophil count and the effect of treatment on other important asthma-related outcomes, such as lung function, asthma symptoms, and quality of life.

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Research in context

Evidence before this study

Eosinophils are inflammatory cells associated with airway inflammation in asthma, and represent an important biomarker for identification of patients with eosinophilic asthma. We searched PubMed on Nov 26, 2015, for English-language articles with the terms “asthma”, “anti-interleukin-5”, and “eosinophil” in the title or abstract. Our search yielded 26 results, which included a meta-analysis of randomised placebo-controlled trials of mepolizumab in patients with asthma. On the basis of our systematic review of the literature, mepolizumab appears to be the only interleukin-5 monoclonal antibody using a blood eosinophil threshold of at least 150 cells per μL at baseline in asthma clinical trials.

Added value of this study

To our knowledge, this is the first analysis to systematically assess the clinical effects of mepolizumab in patients with different thresholds of blood eosinophil counts at baseline.

This approach used counts obtained at baseline from more than 1000 patients participating in two large-scale, randomised placebo-controlled trials of mepolizumab. Our analysis provides further evidence that blood eosinophils are a robust marker for selecting patients that would benefit from specific treatments and are also associated with the response to anti-interleukin-5 therapies such as mepolizumab.

Implications of all the available evidence

Clinical trials of other interleukin-5 inhibitors in development (ie, reslizumab and benralizumab) have used different blood eosinophil thresholds at baseline when investigating the effect of interleukin-5 inhibition on clinical outcomes, and confusion has arisen about the best cutoff point. We provide evidence from a large patient population with severe eosinophilic asthma that supports the value of blood eosinophil counts as a biomarker to guide therapy, and to provide guidance on the probable effect of that therapy in patients with severe asthma.

Findings from two large studies (Dose Ranging Efficacy And safety with Mepolizumab in severe asthma [DREAM; NCT01000506]⁸ and MEpolizumab as adjuNctive therapy in patients with Severe Asthma [MENSA; NCT01691521]⁹) have shown reductions in asthma exacerbation rates after treatment with mepolizumab compared with placebo in patients with severe eosinophilic asthma. Modelling analysis in the DREAM study identified blood eosinophils as a predictor of treatment response to mepolizumab;⁸ patients were then selected in the subsequent MENSA study on the basis of this criterion.⁹

This report describes the results of our secondary post-hoc analysis of data from these two randomised studies, which aims to provide a more robust and clinically informative analysis of the relationship between baseline blood eosinophil counts and efficacy outcomes after treatment with mepolizumab.

Methods

Included studies and patients

Criteria used for the inclusion of studies in this analysis were: placebo-controlled studies of mepolizumab in patients with severe eosinophilic asthma; duration of the study at least 32 weeks; maintenance corticosteroid use kept constant; and analysis of blood samples at a central laboratory. On the basis of these criteria, we included data from DREAM⁸ and MENSA done between 2009 and 2014.⁹ The protocol for the analysis is available from the GSK Clinical Study Register (number 204664).¹²

Enrolment criteria for the studies have been previously published.^{8,9} Briefly, patients were aged at least 12 years; required to have had a clinical diagnosis of asthma; had a history of at least two exacerbations requiring systemic corticosteroid treatment in the previous year, and met the American Thoracic Society criteria for refractory

asthma.¹³ For DREAM, patients had evidence of eosinophilic inflammation at study entry or within the previous year, as shown by one or more of the following criteria: (1) a sputum eosinophil count of at least 3%, (2) fractional exhaled nitric oxide (FE_{NO}) of at least 50 parts per billion, (3) an asthma-related peripheral blood eosinophil count of at least 300 cells per μL , or (4) a prompt deterioration in asthma control after at least 25% reduction in regular maintenance inhaled corticosteroids or oral corticosteroids. In MENSA, eosinophilic inflammation was defined as a blood eosinophil count of at least 150 cells per μL at screening or at least 300 cells per μL at some time during the previous year. Study-related blood eosinophil counts were done by a central laboratory from samples obtained in the morning. The original protocols were approved by local or study research ethics committees, and done in accordance with good clinical practice guidelines and the Declaration of Helsinki.

Treatments

Patients in DREAM were randomly assigned to one of three different doses (75 mg, 250 mg, or 750 mg) of intravenous mepolizumab or matched placebo at 4-week intervals for 52 weeks.⁸ Patients in MENSA were randomly assigned to mepolizumab, administered as either a 75 mg intravenous dose or a 100 mg subcutaneous dose, or matched placebo for 32 weeks in a double-dummy design.⁹

Outcomes

The primary outcome for both studies was the annualised rate of clinically significant exacerbations, expressed as mean exacerbations per person per year. An exacerbation was defined as worsening of asthma that required the

use of systemic corticosteroids, or admission to hospital, or an emergency-room visit, or a combination of these occurrences. Exacerbations reported from the start of treatment until completion of study or up to withdrawal (but ≤ 4 weeks after the last dose of study medication) were included in the analysis. Exacerbations separated by less than 7 days were considered a continuation of the same exacerbation.¹⁴ Hospital admissions included intubation and admittance to an intensive care unit.

In our post-hoc analysis, which was completed on Sept 25, 2015, we assessed the following thresholds of baseline blood eosinophil counts for exacerbation outcomes in DREAM, MENSA, and the combined dataset: at least 150 cells per μL , at least 300 cells per μL , at least 400 cells per μL , and at least 500 cells per μL . Baseline blood eosinophil ranges (<150 cells per μL , ≥ 150 cells per μL to <300 cells per μL , ≥ 300 cells per μL to <500 cells per μL , and ≥ 500 cells per μL) were also assessed. The use of a historical measure of blood eosinophil count (≥ 300 cells per μL in the previous year) was also assessed in patients with baseline blood eosinophil counts of less than 150 cells per μL by subgroup analysis of the DREAM study.

We also did a subgroup analysis of all data on FEV_1 before and after administration of a bronchodilator, St George's Respiratory Questionnaire (SGRQ) scores to measure quality of life, and Asthma Control Questionnaire (ACQ)-5 scores by baseline eosinophil thresholds of at least 150 cells per μL , at least 300 cells per μL , and at least 500 cells per μL . We did analyses for DREAM, MENSA, and the combined dataset, apart from SGRQ scores, which were only obtained in the MENSA study. For lung function and ACQ-5 scores, the values obtained from both studies at week 32 were analysed. The ACQ-6 was administered in the DREAM study, and the ACQ-5 was used in MENSA. ACQ-5 scores for DREAM were derived from the responses to the first five questions of ACQ-6.

Statistical analysis

This post-hoc analysis was based on the intention-to-treat (ITT) population for DREAM and MENSA, including all randomly assigned patients who received at least one dose of study medication. Because DREAM and MENSA showed similar reductions in overall exacerbation rates based on a ten-fold dose range of mepolizumab,^{8,9} we combined data for all mepolizumab doses for this analysis. Pooling data from the active treatment arms of DREAM and MENSA reduced variability and allowed for a more precise estimation of the relationship between the efficacy of mepolizumab and baseline eosinophil counts.

We did a subgroup analysis of exacerbation rates based on baseline blood eosinophil thresholds using negative binomial regression. Covariate modelling was applied to each study separately and to the combined dataset, with covariates of treatment group (placebo vs mepolizumab),

geographical region, baseline maintenance oral corticosteroids (use vs no use), baseline percentage predicted prebronchodilator FEV_1 (continuous 0–100%), number of exacerbations in the year before the study (as an ordinal variable [2, 3, and ≥ 4]), and study (combined dataset only).

Additionally, exacerbation rates were modelled as a function of blood eosinophils as a continuous variable. Modelling preserves information compared with separate subgroup analysis, and is preferred when a variable is measured on a continuous scale.¹⁵ We did this analysis using negative binomial regression separately for each study and included covariates of treatment group (placebo vs mepolizumab), region, baseline maintenance oral corticosteroids (use vs no use) and number of exacerbations in the year before the study (as an ordinal variable [2, 3, and ≥ 4]) and the interaction between treatment group and baseline blood eosinophils. We investigated various functional relationships for the

	DREAM (n=616)	MENSA (n=576)	Total (ITT population; n=1192)
Sex			
Female	387 (63%)	328 (57%)	715 (60%)
Male	229 (37%)	248 (43%)	477 (40%)
Age (years)	50 (42–57)	52 (42–60)	50 (42–58)
≥ 12 to <18	1 ($<1\%$)	25 (4%)	26 (2%)
≥ 18 to <65	590 (96%)	471 (82%)	1061 (89%)
≥ 65	25 (4%)	80 (14%)	105 (9%)
Ethnic origin			
White	554 (90%)	450 (78%)	1004 (84%)
Asian	35 (6%)	106 (18%)	141 (12%)
African-American or African heritage	23 (4%)	16 (3%)	39 (3%)
Other	4 ($<1\%$)	4 ($<1\%$)	8 ($<1\%$)
Baseline blood eosinophil count			
Geometric mean (SD log)	250 (1.03)	290 (0.99)	270 (1.01)
Median (IQR)	290 (150–510)	330 (170–570)	310 (160–540)
<150 cells per μL	149 (24%)	116 (20%)	265 (22%)
150 to <300 cells per μL	165 (27%)	145 (25%)	310 (26%)
300 to <500 cells per μL	138 (22%)	118 (20%)	256 (21%)
≥ 500 cells per μL	164 (27%)	190 (33%)	354 (30%)
Missing	0	7 (1%)	7 ($<1\%$)
Patients on maintenance oral corticosteroids	188 (31%)	144 (25%)	332 (28%)
Baseline prebronchodilator % predicted FEV_1	60 (16)	61 (18)	60 (17)
Baseline % reversibility FEV_1	25 (21)	27 (22)	26 (21)
Baseline prebronchodilator FEV_1 :FVC ratio	0.63 (0.12)	0.64 (0.13)	0.64 (0.13)
Baseline ACQ-5 score	2.4 (1.1)	2.2 (1.2)	2.3 (1.2)

Data are n (%), mean (SD), or median (IQR). ACQ=asthma control questionnaire. FVC=forced vital capacity. ITT=intention-to-treat.

Table 1: Patient baseline characteristics

See Online for appendix

relationship with blood eosinophils, and the model that provided the best fit for the data was for log-transformed eosinophil counts.

We did the subgroup analysis of FEV₁ (before and after being given a bronchodilator), SGRQ scores, and ACQ-5 scores by baseline eosinophil threshold using mixed-model repeated measures analysis with covariates of treatment group (placebo vs mepolizumab), geographical region, baseline maintenance oral corticosteroids therapy (use vs no use), baseline percentage predicted prebronchodilator FEV₁ (SGRQ and ACQ-5 only), exacerbations in the year before the study, study (combined dataset only), and visit, plus interaction terms for visit by baseline and visit by treatment group. We did all analyses with SAS version 9.

Role of the funding source

The funder of this combined analysis and the primary studies had a role in study design, data collection, data analysis, data interpretation, and writing of the report. The funder did not place any restrictions on access to the data or statements made in the report. The decision to submit for publication was that of the authors alone. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The ITT population included 616 patients in DREAM and 576 in MENSA, totalling 1192 patients. Of these, 846 received mepolizumab and 346 received placebo. Demographic characteristics were similar in both studies (table 1). The cumulative distributions of baseline blood

eosinophil counts were similar across the two studies (appendix), with geometric mean (SD logs) blood eosinophil counts of 250 cells per μL (1.03) and 290 cells per μL (0.99) in DREAM and MENSA, respectively. 467 (76%) of 616 patients in DREAM and 453 (80%) of 569 in MENSA had a baseline count of at least 150 cells per μL . Seven patients had missing baseline eosinophil values in MENSA and were therefore excluded from this analysis.

In the integrated analysis of all doses of mepolizumab from DREAM and MENSA, the overall rate of mean exacerbations per person per year was reduced from 1.91 with placebo to 1.01 with mepolizumab (47% reduction; rate ratio [RR] 0.53, 95% CI 0.44–0.62, $p < 0.0001$). Exacerbation rate reductions with mepolizumab versus placebo increased from 52% (0.48, 0.39–0.58) for patients with a baseline eosinophil threshold of at least 150 cells per μL to 70% (0.30, 0.23–0.40) for patients with a baseline eosinophil threshold of at least 500 cells per μL (table 2). When specific baseline blood eosinophil ranges were assessed (<150 cells per μL , ≥ 150 to <300 cells per μL , ≥ 300 to <500 cells per μL , and ≥ 500 cells per μL), exacerbation rate reductions increased progressively from 26% (RR 0.74, 95% CI 0.52–1.04) to 70% (0.30, 0.23–0.40; appendix).

The figure shows the predicted exacerbation rate (ie, based on the modelling analyses described in the methods) against baseline blood eosinophils as a continuous variable based on multivariate modelling of DREAM and MENSA. Greater reductions occurred in the predicted rates of exacerbations with mepolizumab compared with placebo with increasing baseline blood

	DREAM (n=616)		MENSA (n=569)		Combined* (n=1185)	
	Placebo (n=155)	Mepolizumab (n=461)	Placebo (n=189)	Mepolizumab (n=380)	Placebo (n=344)	Mepolizumab (n=841)
≥ 150 cells per μL						
n (%)	121 (78%)	346 (75%)	157 (83%)	296 (78%)	278 (81%)	642 (76%)
Exacerbation rate per year	2.47	1.13	1.65	0.78	1.94	0.92
Rate ratio vs placebo (95% CI)	..	0.46 (0.35–0.60)	..	0.47 (0.35–0.63)	..	0.48 (0.39–0.58)
≥ 300 cells per μL						
n (%)	86 (55%)	216 (47%)	106 (56%)	202 (53%)	192 (56%)	418 (50%)
Exacerbation rate per year	2.66	1.11	1.98	0.78	2.19	0.89
Rate ratio vs placebo (95% CI)	..	0.42 (0.31–0.56)	..	0.39 (0.28–0.55)	..	0.41 (0.33–0.51)
≥ 400 cells per μL						
n (%)	64 (41%)	149 (32%)	87 (46%)	161 (42%)	151 (44%)	310 (37%)
Exacerbation rate per year	3.12	1.03	2.06	0.66	2.36	0.81
Rate ratio vs placebo (95% CI)	..	0.32 (0.23–0.46)	..	0.32 (0.22–0.46)	..	0.34 (0.27–0.44)
≥ 500 cells per μL						
n (%)	50 (32%)	114 (25%)	66 (35%)	124 (33%)	116 (34%)	238 (28%)
Exacerbation rate per year	3.34	0.92	2.11	0.58	2.49	0.75
Rate ratio vs placebo (95% CI)	..	0.27 (0.19–0.39)	..	0.27 (0.18–0.41)	..	0.30 (0.23–0.40)
Data are from the intention-to-treat populations from the DREAM and MENSA studies. All mepolizumab doses were combined for the analysis. *Seven patients had missing baseline eosinophil values in MENSA and were excluded from this analysis.						
Table 2: Reduction in exacerbation rate stratified by baseline blood eosinophil count						

eosinophil counts. Reductions in exacerbation frequency of at least 30% (highest RR 0·70, 95% CI 0·53–0·93) were apparent from the discrete point of 150 cells per μL at baseline (table 3). At less than 150 cells per μL , predicted efficacy was reduced, particularly for the DREAM study.

When exacerbation rates were analysed according to dose and then further stratified by baseline eosinophil threshold in the DREAM study, exacerbation rates and rate reductions were similar for different doses of mepolizumab irrespective of baseline eosinophil counts (appendix). When exacerbation rate reductions were analysed according to historical blood eosinophil counts in DREAM, patients with a historical blood eosinophil count of at least 300 cells per μL , and a baseline eosinophil count of less than 150 cells per μL , had a reduction in exacerbation rate of 20% (RR 0·80, 95% CI 0·38–1·68) with mepolizumab compared with placebo. For patients with low baseline eosinophil counts (<150 cells per μL) and no evidence of a historical count of at least 300 cells per μL , exacerbation rates were only reduced by 10% (RR 0·90, 95% CI 0·49–1·64) with mepolizumab compared with placebo (DREAM study only; appendix).

For lung function outcomes, at week 32, the mean increase from baseline in FEV_1 with mepolizumab compared with placebo was similar in patients with a baseline eosinophil count of at least 150 cells per μL and at least 300 cells per μL , and higher for patients with a count of at least 500 cells per μL (64–68 mL vs 106 mL, respectively, for prebronchodilator FEV_1 ; table 4). We also noted improvements in quality of life, and asthma control across all blood eosinophil thresholds (≥ 150 cells per μL , ≥ 300 cells per μL , and ≥ 500 cells per μL ; table 4). ACQ-5 scores were increased (based on increased blood eosinophil counts) in the mepolizumab group compared to placebo, with a response below the minimally important clinical difference (0·5) in patients with baseline eosinophil count of at least 150 cells per μL and at least 300 cells per μL , and higher for patients with a count of at least 500 cells per μL (0·61). Improvements in SGRQ from placebo were greater than the minimal clinically important difference of four units.

Discussion

In this analysis, mepolizumab produced a clinically meaningful reduction in the exacerbation rate, and improvements in quality of life (as measured by the SGRQ) and asthma control, in patients with severe eosinophilic asthma at a baseline blood eosinophil threshold of at least 150 cells per μL . Importantly, this benefit was achieved in patients who were already receiving intensive therapy per asthma treatment guidelines and had at least two exacerbations in the previous year.¹⁶ Patients with a baseline blood eosinophil count of at least 150 cells per μL who were treated with mepolizumab approximately halved their exacerbation risk compared with placebo (the mean response for all patients with at least 150 cells per μL at baseline).

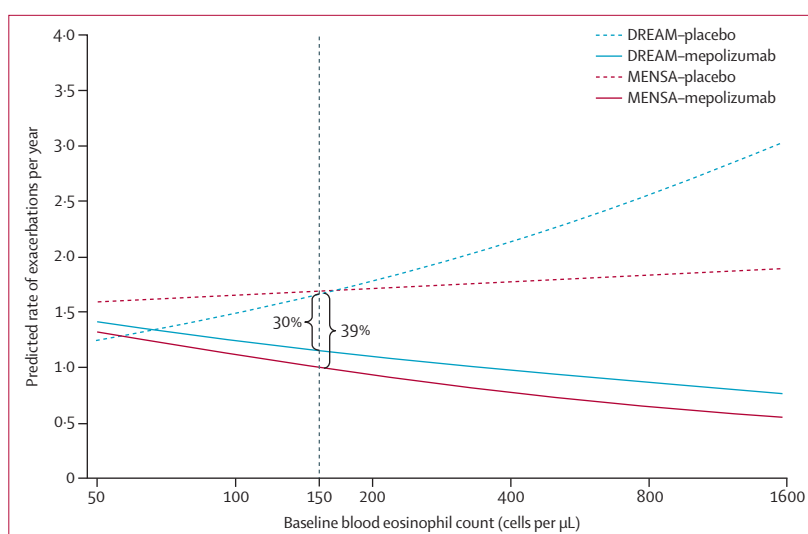


Figure: Predicted rate of clinically significant exacerbations per year against baseline blood eosinophil counts. Data are from the intention-to-treat populations from the DREAM and MENSA studies. Graph shows the percentage differences in exacerbation rates (mean per person per year) between placebo and mepolizumab at the baseline blood eosinophil count of 150 cells per μL .

	DREAM (n=616)		MENSA* (n=569)	
	Placebo	Mepolizumab	Placebo	Mepolizumab
150 cells per μL				
Exacerbation rate per year	1·65	1·16	1·65	1·00
Rate ratio vs placebo (95% CI)	..	0·70 (0·53–0·93)	..	0·61 (0·45–0·82)
300 cells per μL				
Exacerbation rate per year	1·98	1·03	1·74	0·85
Rate ratio vs placebo (95% CI)	..	0·52 (0·41–0·65)	..	0·49 (0·38–0·63)
400 cells per μL				
Exacerbation rate per year	2·13	0·98	1·78	0·79
Rate ratio vs placebo (95% CI)	..	0·46 (0·36–0·58)	..	0·45 (0·34–0·58)
500 cells per μL				
Exacerbation rate per year	2·26	0·94	1·81	0·75
Rate ratio vs placebo (95% CI)	..	0·42 (0·32–0·54)	..	0·42 (0·31–0·55)

Data are from the intention-to-treat populations from the DREAM and MENSA studies. All mepolizumab doses were combined for the analysis. ..=not available. *Seven patients had missing baseline eosinophil values in MENSA and were excluded from this analysis.

Table 3: Multivariate modelling of predicted exacerbation rates at different baseline blood eosinophil counts

These results build upon and support the previous results from the DREAM study by including a similar cohort from the MENSA study, allowing for more confident predictions across a range of pretreatment blood eosinophil counts.⁸ The reduction in exacerbation

	DREAM (n=616)	MENSA (n=569)	Combined* (n=1185)
Prebronchodilator FEV₁ (mL [95% CI]; n [%])			
≥150 cells per µL	2 (-93 to 97); 418 (68%)	113 (28 to 198); 423 (74%)	64 (1 to 127); 841 (71%)
≥300 cells per µL	-4 (-123 to 116); 274 (44%)	128 (25 to 232); 290 (51%)	68 (-10 to 146); 564 (48%)
≥500 cells per µL	72 (-105 to 248); 149 (24%)	113 (-24 to 250); 181 (32%)	106 (-2 to 214); 330 (28%)
Postbronchodilator FEV₁ (mL [95% CI]; n [%])			
≥150 cells per µL	22 (-71 to 114); 403 (65%)	172 (77 to 267); 386 (68%)	101 (35 to 168); 789 (67%)
≥300 cells per µL	18 (-101 to 138); 264 (43%)	202 (90 to 315); 268 (47%)	108 (26 to 191); 532 (45%)
≥500 cells per µL	83 (-90 to 255); 144 (23%)	247 (102 to 392); 166 (29%)	161 (50 to 272); 310 (26%)
SGRQ change in score (95% CI); n (%)			
≥150 cells per µL	..	-8.1 (-11.2 to -5.1); 420 (74%)	..
≥300 cells per µL	..	-10.4 (-14.2 to -6.7); 288 (51%)	..
≥500 cells per µL	..	-11.3 (-16.3 to -6.4); 179 (31%)	..
ACQ-5 change in score (95% CI); n (%)			
≥150 cells per µL	-0.14 (-0.36 to 0.08); 401 (65%)	-0.52 (-0.70 to -0.34); 402 (71%)	-0.35 (-0.49 to -0.20); 803 (68%)
≥300 cells per µL	-0.24 (-0.51 to 0.03); 262 (43%)	-0.73 (-0.95 to -0.50); 274 (48%)	-0.49 (-0.67 to -0.31); 536 (45%)
≥500 cells per µL	-0.44 (-0.83 to -0.06); 144 (23%)	-0.76 (-1.07 to -0.46); 171 (30%)	-0.61 (-0.85 to -0.37); 315 (27%)

Data are from the intention-to-treat populations from the DREAM and MENSA studies. All mepolizumab doses were combined for the analysis. n includes patients treated with either mepolizumab or placebo who provided data at week 32. *Seven patients had missing baseline eosinophil values in MENSA and were excluded from this analysis. ACQ=asthma control questionnaire. ..=not available. SGRQ=St George's Respiratory Questionnaire.

Table 4: Changes in FEV₁, SGRQ, and ACQ-5 by baseline blood eosinophil counts

rate was positively associated with increasing blood eosinophil count at baseline. Therefore, understanding the predicted benefit for patients at the lower end of the predefined threshold of at least 150 cells per µL at baseline is important. For patients at this lowest blood eosinophil count (150 cells per µL), the estimated benefit was a reduction in the exacerbation rate of 30% and 39% in the DREAM and MENSA studies, respectively. This result raises an important question as to whether this expected benefit for patients at the lower end of the biomarker threshold is large enough to warrant treatment with a biological therapy.

Currently, no guidelines exist that establish a particular threshold of reduction in asthma exacerbation rate as clinically meaningful. However, available evidence suggests that a rate reduction of at least 30% is important. For example, combination treatment with long-acting β₂-agonists (LABAs) and inhaled corticosteroids has been shown to reduce exacerbation frequency by 23% (RR 0.77, 95% CI 0.68–0.87) compared with inhaled corticosteroids alone.¹⁷ Additionally, in two randomised clinical trials, omalizumab added to high dose inhaled corticosteroids plus a LABA reduced clinically significant

exacerbations by 26% (RR 0.74, 95% CI 0.55–1.00) and 25% (0.75, 0.61–0.92) compared with placebo.^{18,19} LABAs added to inhaled corticosteroids and omalizumab are both accepted as preferred treatments in relevant populations and are recommended in asthma guidelines.¹⁶ The effect of mepolizumab on reducing exacerbations should also be interpreted in light of the high baseline exacerbation frequency (an average of 3.6 exacerbations per year);^{8,9} the well recognised relationship between reduced exacerbation rates and the reduced risk of being admitted to hospital; the costs associated with severe exacerbations;^{20,21} the possibility that a reduction in exacerbations will mitigate untoward structural changes in the airway;²² and evidence that such an effect is seen despite reductions in the dose of oral corticosteroids.²³

A wide range of mean blood eosinophil counts have been measured in heterogeneous asthma populations as predictive of exacerbation risk, resulting in different thresholds for defining eosinophilic disease.^{24–27} These populations vary in severity of disease, and have included patients who were not on intensive treatment and did not have a history of frequent exacerbations. Comparison between studies is also complicated by the fact that eosinophil counts have been given as arithmetic means or geometric means in different analyses. However, median eosinophil counts of 250 cells per µL and 240 cells per µL have been previously reported in patients with severe asthma and frequent exacerbations,^{24,26} which are consistent with the median blood eosinophil count of 310 cells per µL reported in this analysis. This finding also showed that eosinophil counts should not be assessed in isolation when identifying who might benefit from mepolizumab treatment; disease severity, treatment intensity, and exacerbation history are also key considerations.

Several aspects of our study require further discussion. First, we focused on blood eosinophil count as a predictive marker of response to mepolizumab. This focus was justified because findings from previous studies had shown a clearer relationship between blood eosinophils and efficacy of treatment, compared with FE_{NO} and sputum eosinophils. This result, and the fact that dose-dependent suppression of sputum eosinophils with mepolizumab does not correlate with exacerbation rate reductions, suggests that the main method of action of mepolizumab is to deplete circulating eosinophils, potentially reducing recruitment to the airway in response to transient exacerbation-related stimuli.³ Our analysis only provides information about outcomes during treatment. The available evidence suggests that the effects of mepolizumab on blood eosinophil counts disappear 3 months after treatment is discontinued, when counts return to pretreatment baseline levels, and asthma exacerbation rates return to pretreatment baseline levels 3 to 6 months after treatment withdrawal.²⁸ These time trends support a direct and causal link between the blood eosinophil count and exacerbation reduction.

Second, use of a single measurement of blood eosinophil count can be justified by findings from a study by Katz and colleagues,²⁹ which established that a single measurement of at least 150 cells per μL predicted the average of subsequent measurements being at least 150 cells per μL in 85% of patients.

Third, the population of patients with a blood eosinophil count less than 150 cells per μL at baseline might not be fully representative of the wider population of patients with severe asthma and a low blood eosinophil count, because patients were either required to have other markers of eosinophilic airway inflammation before recruitment (ie, the DREAM study required patients to have a $\text{FE}_{\text{NO}} \geq 50$ parts per billion, a sputum eosinophil count $>3\%$, or a prompt deterioration in asthma control with a 25% decrease in inhaled corticosteroids or oral corticosteroids) or a history of blood eosinophils of at least 300 cells per μL in the previous year. Therefore, the treatment response seen in this population might not represent the efficacy of mepolizumab in the wider population of patients with a blood eosinophil count less than 150 cells per μL .

Fourth, in this analysis we combined different doses and routes of administration of mepolizumab based on the absence of a dose–response association with exacerbation rate shown in the original studies.^{8,9} When data were analysed by dose, similar reductions in exacerbation rates occurred among subgroups defined by baseline blood eosinophils, irrespective of dose. This provides evidence that higher doses of mepolizumab would not confer additional benefit in patients with high blood eosinophil counts.

Fifth, the ratio of female to male patients was 60 to 40. This finding is consistent with previous clinical studies in this patient population.^{8,9,23} In all analyses, the sex of the patient was not identified as a confounding factor for the relationship between baseline blood eosinophil counts and the efficacy of mepolizumab.

A final aspect of the study is that its size allowed us to investigate the relationship between the blood eosinophil count and other asthma-related outcome measures. Our integrated analysis showed a progressive benefit of mepolizumab on postbronchodilator FEV_1 and ACQ-5 score with increasing baseline eosinophil count. This was noted more in MENSA than in DREAM, perhaps because DREAM included a population with more severe asthma than MENSA, as reflected by the higher proportion of patients requiring daily oral corticosteroids to treat exacerbations in the placebo group. As a consequence, measurements of ACQ-5 score and postbronchodilator FEV_1 were more likely to be confounded by the recent use of oral corticosteroids.

In conclusion, blood eosinophil count is an easily accessible and sensitive biomarker of asthma for health-care providers, and the results can be available rapidly after collection. The use of this baseline biomarker

at a threshold of at least 150 cells per μL will select patients with the phenotype that is likely to achieve important reductions in the rate of exacerbations and resultant improvements in QoL and asthma control with mepolizumab.

Contributors

HGO, ONK, BM, SWY, CEB, ERB, and IDP conceived and designed the study. CEB, ERB, and IDP acquired the data. HGO, ONK, BM, NBG, SWY, CEB, ERB, and IDP analysed and interpreted the data. All authors had access to the data from the study. HGO wrote the first draft of the manuscript. All authors participated in the development of all stages of the manuscript, revising it for intellectual content. All authors provided final approval of the version submitted for publication and are accountable for the accuracy and integrity of the work.

Declaration of interests

SWY, BM, ONK, and NBG are employees of GlaxoSmithKline (GSK) and own stock or stock options in GSK. HGO is a former employee of GSK and owns stock or stock options in GSK, and is now employed by Genentech. IDP received advisory board fees and speaker fees from AstraZeneca, Boehringer Ingelheim, Aerocrine, Almirall, Novartis, Genentech, Regeneron, Teva, Roche, and GSK. CEB has received consultancy and research income via his institution from GSK, AstraZeneca/MedImmune, Novartis, Genentech/Roche, Chiesi, and Boehringer Ingelheim. ERB has undertaken clinical trials through his employer, Wake Forest School of Medicine, for AstraZeneca, MedImmune, Boehringer Ingelheim, Pfizer, Cephalon/Teva, Forest, Genentech, GSK, Johnson & Johnson (Janssen), Novartis, and Sanofi. He has also served as a paid consultant for AstraZeneca, MedImmune, Boehringer Ingelheim, Pfizer, GSK, Forest, Novartis, Regeneron, and Sanofi.

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References

- Wenzel S. Severe asthma: from characteristics to phenotypes to endotypes. *Clin Exp Allergy* 2012; **42**: 650–58.
- Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014; **43**: 343–73.
- Ortega H, Katz L, Gunsoy N, Keene O, Yancey S. Blood eosinophil counts predict treatment response in patients with severe eosinophilic asthma. *J Allergy Clin Immunol* 2015; **136**: 825–26.
- Fulkerson PC, Rothenberg ME. Targeting eosinophils in allergy, inflammation and beyond. *Nat Rev Drug Discov* 2013; **12**: 117–29.
- Mukherjee M, Sehmi R, Nair P. Anti-IL5 therapy for asthma and beyond. *World Allergy Organ J* 2014; **7**: 32.
- Green RH, Brightling CE, McKenna S, et al. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. *Lancet* 2002; **360**: 1715–21.
- Nadif R, Siroux V, Oryszczyn MP, et al. Heterogeneity of asthma according to blood inflammatory patterns. *Thorax* 2009; **64**: 374–80.
- Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet* 2012; **380**: 651–59.
- Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med* 2014; **371**: 1198–207.
- Castro M, Wenzel SE, Bleecker ER, et al. Benralizumab, an anti-interleukin 5 receptor alpha monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study. *Lancet Respir Med* 2014; **2**: 879–90.
- Castro M, Zangrilli J, Wechsler ME, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet Respir Med* 2015; **3**: 355–66.

- 12 GlaxoSmithKline. Meta-analysis in sponsored studies MEA112997, MEA115588, and MEA115575 and a proof of concept investigator sponsored study CRT110184 of mepolizumab in severe asthma. http://www.gsk-clinicalstudyregister.com/study/204664?study_ids=204664#ps (accessed May 15, 2015).
- 13 American Thoracic Society. Proceedings of the ATS workshop on refractory asthma: current understanding, recommendations, and unanswered questions. American Thoracic Society. *Am J Respir Crit Care Med* 2000; **162**: 2341–51.
- 14 Reddel HK, Taylor DR, Bateman ED, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med* 2009; **180**: 59–99.
- 15 Altman DG, Royston P. The cost of dichotomising continuous variables. *BMJ* 2006; **332**: 1080.
- 16 Global Initiative for Asthma. Pocket guide for asthma management and prevention. http://www.ginasthma.org/wp-content/uploads/2016/01/GINA_Pocket_2015.pdf (accessed April 28, 2016).
- 17 Ducharme FM, Ni Chroinin M, Greenstone I, Lasserson TJ. Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children. *Cochrane Database Syst Rev* 2010; **5**: CD005535.
- 18 Hanania NA, Alpan O, Hamilos DL, et al. Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial. *Ann Intern Med* 2011; **154**: 573–82.
- 19 Humbert M, Beasley R, Ayres J, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. *Allergy* 2005; **60**: 309–16.
- 20 O'Neill S, Sweeney J, Patterson CC, et al. The cost of treating severe refractory asthma in the UK: an economic analysis from the British Thoracic Society Difficult Asthma Registry. *Thorax* 2015; **70**: 376–78.
- 21 Zeiger RS, Schatz M, Dalal AA, et al. Utilization and costs of severe uncontrolled asthma in a managed-care setting. *J Allergy Clin Immunol Pract* 2015; **4**: 120–29.
- 22 O'Byrne PM, Pedersen S, Lamm CJ, Tan WC, Busse WW. Severe exacerbations and decline in lung function in asthma. *Am J Respir Crit Care Med* 2009; **179**: 19–24.
- 23 Bel EH, Wenzel SE, Thompson PJ, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med* 2014; **371**: 1189–97.
- 24 Amelink M, de Groot JC, de Nijs SB, et al. Severe adult-onset asthma: A distinct phenotype. *J Allergy Clin Immunol* 2013; **132**: 336–41.
- 25 Price DB, Rigazio A, Campbell JD, et al. Blood eosinophil count and prospective annual asthma disease burden: a UK cohort study. *Lancet Respir Med* 2015; **3**: 849–58.
- 26 Schleich F, Brusselle G, Louis R, et al. Heterogeneity of phenotypes in severe asthmatics. The Belgian Severe Asthma Registry (BSAR). *Respir Med* 2014; **108**: 1723–32.
- 27 Zeiger RS, Schatz M, Li Q, et al. High blood eosinophil count is a risk factor for future asthma exacerbations in adult persistent asthma. *J Allergy Clin Immunol Pract* 2014; **2**: 741–50.
- 28 Haldar P, Brightling CE, Singapuri A, et al. Outcomes after cessation of mepolizumab therapy in severe eosinophilic asthma: a 12-month follow-up analysis. *J Allergy Clin Immunol* 2014; **133**: 921–23.
- 29 Katz LE, Gleich GJ, Hartley BF, Yancey SW, Ortega HG. Blood eosinophil count is a useful biomarker to identify patients with severe eosinophilic asthma. *Ann Am Thorac Soc* 2014; **11**: 531–36.