Original Article

Asthma Exacerbations Associated with Lung Function Decline in Patients with Severe Eosinophilic Asthma

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What is already known about this topic? While there are some reports investigating the decline in lung function associated with asthma exacerbations, limited data exist in patients with severe eosinophilic asthma.

What does this article add to our knowledge? This study provides further evidence of the impact of frequent asthma exacerbations and related decline in lung function in patients with severe eosinophilic asthma.

How does this study impact current management guidelines? Preventing exacerbations should be one of the most important treatment goals and therefore disease management approaches, including step-down of controller therapy, should be carefully considered in patients with severe disease who are prone to exacerbations.

BACKGROUND: Limited data describe the association between the frequency of asthma exacerbations and the decline in lung function in severe asthma.
OBJECTIVE: To determine whether asthma exacerbations are associated with enhanced decline in lung function.
METHODS: Changes in lung function were analyzed retrospectively using data from the DREAM and MENSA studies of mepolizumab intervention in patients with severe asthma. Patients were either nonsmokers or former smokers. A linear regression model was used to analyze the relationship between the number of exacerbations and decline in FEV_1 across treatment groups.
RESULTS: In a combined post hoc analysis, 57% (n = 572) of patients had no exacerbations and experienced an improvement in postbronchodilator FEV_1 of 143 mL. In contrast, in patients who experienced 3 or more exacerbations, there was a decrease in postbronchodilator FEV_1 of 77 mL in the combined analysis. The linear modeling analysis estimated that for each exacerbation seen during the observational period, there was a decrease of 50 mL in FEV_1 ($P < .001$).
CONCLUSIONS: A direct relationship between the number of exacerbations in patients with severe eosinophilic asthma and decline in lung function was observed. Repeated exacerbations may be associated with accelerated loss of lung function. **(J Allergy Clin Immunol Pract 2018;■:■-■)**

Key words: *Severe asthma; Exacerbations; Decline in lung function; FEV_1*

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INTRODUCTION

Asthma is characterized by the presence of reversible airflow obstruction[1]; however, as disease severity increases, structural changes in the airways can contribute to irreversible airflow obstruction. Accelerated loss of lung function over time has been reported in longitudinal prospective and retrospective studies in patients with asthma.[2-5] However, accelerated decline in lung function does not occur in all patients.[6] Risk factors associated with an accelerated loss of lung function include age, male sex, smoking, longer duration of disease, black race, airway eosinophils, and asthma exacerbations.[5-10] The frequency of acute severe exacerbations has also been associated with a more rapid decline in FEV_1 in patients with chronic obstructive pulmonary disease (COPD).[11,12]

The prevention of structural airway wall remodeling is highly desirable in the management of asthma, as these changes lead to

Abbreviations used
COPD- Chronic obstructive pulmonary disease
FVC- Forced vital capacity
OCS- Oral corticosteroid

irreversible airflow obstruction despite prolonged steroid therapy.[10] Recurrent asthma exacerbations are a significant problem in patients with asthma, particularly in patients with severe eosinophilic asthma.[8,13-16] We hypothesized that the enhanced tendency for disease exacerbation in uncontrolled eosinophilic airway inflammation leads to progressive airway remodeling with consequent loss of lung function. Pulmonary function testing, which has been used in clinical settings and epidemiological studies, can link changes in mechanical properties of airways with airway remodeling.[17] The Dose Ranging Efficacy and Safety with Mepolizumab (DREAM) and Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma (MENSA) studies were multicenter, randomized, double-blind, placebo-controlled trials designed to assess the effect of mepolizumab on exacerbation frequency over 12 and 8 months, respectively.[14,15] These studies provide an opportunity to retrospectively assess in each study individually as well as combined whether exacerbations are associated with a loss of lung function.

METHODS

Study population

DREAM was a placebo-controlled randomized study using intravenous mepolizumab (75 mg, 250 mg, and 750 mg every 4 weeks) for 52 weeks. MENSA was a placebo-controlled double-dummy randomized study with subcutaneous (100 mg every 4 weeks) and intravenous mepolizumab (75 mg intravenous every 4 weeks) administration for 32 weeks (protocol 207348). The patients with severe asthma who participated in these studies were required to have evidence of 2 or more exacerbations requiring treatment with systemic corticosteroids in the previous 12 months despite current therapy and had direct or indirect evidence of eosinophilic inflammation. All patients had treatment requirements of at least 880 μg of inhaled fluticasone propionate equivalent per day with or without maintenance oral corticosteroids (OCSs) and required additional controller medication. Additional details are available in previous publications.[14,15] Participants provided written informed consent. The study protocols (DREAM: NCT01000506; MENSA: NCT01691521) were approved by local ethics committees.

Clinically significant exacerbations

Exacerbations were defined as worsening of asthma requiring use of systemic corticosteroids for 3 or more days and/or hospitalization and/or emergency department visit. In those on maintenance oral steroids, an exacerbation was defined as a doubling of oral steroid dose for at least 3 days and/or hospitalization and/or emergency department visit. Exacerbations were confirmed by objective changes that patients recorded daily in an electronic diary.

Lung function testing

Spirometry testing met the American Thoracic Society standards. The spirometer was calibrated in accordance with the manufacturer's instructions. FEV_1 and forced vital capacity (FVC) were measured at each corresponding visit. Spirometry was performed within 1 hour of the baseline visit. Patients were asked to withhold short-acting beta-2-agonists for 6 or more hours and long-acting beta-agonists for 12 or more hours before clinic visit. Predicted values were calculated using the Third National Health and Nutrition Examination Survey values with adjustments for ethnicity and race.[18] The maximum postbronchodilator procedure was used to conduct reversibility (up to 600 μg inhaled salbutamol).

Statistical analysis

The last pulmonary function measure that occurred at least 28 days after the most recent exacerbation was used in the analysis. This approach aimed to reduce the confounding effect of an acute exacerbation on lung function. The corresponding number of exacerbations before this last measurement of lung function was used in the analysis. A linear regression model was used to analyze the relationship between the number of exacerbations and decline in FEV_1 and FVC over the observational periods. The model for calculating the adjusted mean and linear trend in each study adjusted for covariates of exacerbation category (0, 1, 2, $\geq$3 exacerbations), treatment, baseline lung function, region, exacerbations in the year before the study (2, 3, $\geq$4) as an ordinal variable, baseline maintenance OCS (OCS vs no OCS), sex, age (as continuous variable), and log of baseline eosinophil count. Combined estimates were calculated using inverse variance weighted fixed-effects meta-analysis. The analysis allows for differences in lung function across treatment groups but assumed a common decline in lung function with each exacerbation. We also performed analysis for each treatment group separately instead of combined across treatment groups. A sensitivity analysis was conducted using the last pulmonary function measure that occurred at least 14 days after the most recent exacerbation (see this article's Online Repository at www.jaci-inpractice.org). All analyses were post hoc and were performed using SAS version 9 (SAS Institute, Cary, NC).

RESULTS

Population

A total of 1192 patients with severe asthma participated in these studies. The mean age of this patient population was 49 years, and they were predominantly women (60%). A total of 24% were former smokers (<10 pack-year history) and the rest of the patients never smoked. The mean duration of asthma was 20 years and 28% were on maintenance OCS for disease management. The mean rate of exacerbations in the previous year was 3.6. The prebronchodilator FEV_1 percent predicted was 60% and the mean FEV_1 reversibility was 26% (Table I).

The statistical analysis included a total of 1004 patients; 188 patients were excluded from analysis because of missing postbronchodilator lung function data or because of absence of any lung function measure occurring at least 28 days after an exacerbation. We also conducted a sensitivity analysis evaluating events occurring at least 14 days after an exacerbation. The results showed a similar effect as seen in events occurring at least 28 days after an exacerbation (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). Table II describes the baseline characteristics on the basis of the number of exacerbations that occurred during the observational period for the population analyzed. Patients who experienced more than 1 exacerbation during the observation period had at baseline numerically lower FEV_1, higher use of maintenance OCS, and a higher level of uncontrolled disease as measured by the Asthma Control Questionnaire, compared with those with no exacerbations. Those who experienced more exacerbations during the studies had a greater exacerbation rate in the previous year. Blood

TABLE I. Baseline characteristics of the study population (DREAM and MENSA, ITT population)

Characteristic	DREAM (N = 616)	MENSA (N = 576)	Total (N = 1,192)
Sex, n (%)			
Female	387 (63)	329 (57)	716 (60)
Age (y), mean ± SD	49 ± 11	50 ± 14	49 ± 13
12-17, n (%)	1 (<1)	25 (4)	26 (2)
18-64, n (%)	590 (96)	471 (82)	1,061 (89)
≥65, n (%)	25 (4)	80 (14)	105 (9)
Race category, n (%)			
White	554 (90)	450 (78)	1004 (84)
Other	62 (10)	126 (22)	188 (16)
Smoking status, n (%)			
Never	483 (78)	417 (72)	900 (76)
Former	133 (22)	159 (28)	292 (24)
Duration of the disease, mean ± SD	19.1 ± 14.3	19.9 ± 13.8	19.5 ± 14.1
Exacerbation rate in the past year, mean ± SD	3.6 ± 3.1	3.6 ± 2.6	3.6 ± 2.8
Baseline blood eosinophils (cells/μL), geometric mean ± SD log	253 ± 1.03	295 ± 0.99	272 ± 1.01
Patients on maintenance OCS, n (%)	188 (31)	144 (25)	332 (28)
Baseline ACQ-5 score, mean ± SD	2.4 ± 1.1	2.2 ± 1.2	2.3 ± 1.2
Baseline prebronchodilator, mean ± SD			
% predicted FEV_1	60 ± 16	61 ± 18	60 ± 17
FEV_1 (mL)	1,878 ± 660	1,816 ± 666	1,848 ± 663
FVC (mL)	2,989 ± 944	2,856 ± 901	2,925 ± 926
FEV_1/FVC ratio	0.63 ± 0.12	0.64 ± 0.13	0.63 ± 0.13
Baseline postbronchodilator, mean ± SD			
% predicted FEV_1	71 ± 18	71 ± 19	71 ± 18
Baseline % reversibility FEV_1	25 ± 21	27 ± 22	26 ± 22

ACQ, Asthma Control Questionnaire; *ITT*, intent-to-treat.

eosinophil count at baseline was slightly higher among those with no exacerbations during the trials compared with those with 3 or more exacerbations (291 cells/μL vs 225 cells/μL; $P = .023$ across all groups) (Table II).

Changes in postbronchodilator FEV_1

Patients in the DREAM study with no exacerbations (n = 283) had a 108 mL FEV_1 improvement from baseline over the period of observation. However, there was a progressive loss in postbronchodilator FEV_1 as the number of exacerbations increased. Patients who had 3 or more exacerbations (n = 69) experienced an adjusted FEV_1 mean change of −65 mL (95% CI, −160 to 29 mL per year) (Table III). The linear regression model data suggest that for every additional exacerbation seen, there was a decrease of 43 mL (95% CI, −67 to −18; $P < .001$).

Patients in the MENSA study with no exacerbations (n = 289) had a 181 mL FEV_1 improvement from baseline over the period of observation. Patients who had 3 or more exacerbations (n = 21) experienced an adjusted mean FEV_1 change of −117 mL (95% CI, −293 to 60) (Table III). The linear regression model data suggest that for every additional exacerbation seen there was a decrease of 68 mL (95% CI, −107 to −28; $P < .001$).

In the combined analysis of the 2 studies, those with no exacerbations (n = 572) had a 143 mL FEV_1 improvement from baseline over the observational period. Patients who had 3 or more exacerbations (n = 90) experienced an adjusted mean FEV_1 change of −77 mL (95% CI, −160 to 6) (Table IV). The linear regression model data suggest that for every additional exacerbation seen, there was a decrease of 50 mL (95% CI, −71 to −28; $P < .001$) (Table IV; Figure 1).

Changes in postbronchodilator FVC

We explored changes in postbronchodilator FVC. Figure 1 illustrates the linear change trend in the combined (DREAM/MENSA) analysis. Overall, the changes were similar (46 mL; 95% CI, −71 to −22; $P < .001$) to the changes observed in postbronchodilator FEV_1.

Changes in postbronchodilator FEV_1 and FVC by treatment

We also conducted an exploratory analysis to evaluate the differential response by treatment assignment in the combined analysis. Figure 2 shows improvements in FEV_1 (179 mL; 95% CI, 142-215) and FVC (153 mL; 95% CI, 110-195) in patients who received mepolizumab and did not have any exacerbations during the study. In contrast, patients who received placebo plus standard of care and without exacerbations had a modest improvement in FEV_1 (37 mL; 95% CI, −30 to 105) and loss in FVC (−15 mL; 95% CI, −90 to 60). In patients with 1 or more exacerbation, decline in lung function occurred in both groups, mepolizumab and placebo, although the changes were more pronounced in the placebo group, particularly for FVC (Figure 2). The difference between mepolizumab and placebo was statistically significant for FEV_1 ($P = .040$), but not for FVC ($P = .116$).

TABLE II. Baseline characteristics of the analysis population based on number of exacerbations

Characteristic	No. of exacerbations				*P* value*
	0 (N = 572)	1 (N = 233)	2 (N = 109)	≥3 (N = 90)	
Sex, n (%)					
Female	325 (57)	137 (59)	77 (71)	66 (73)	<.001
Age (y), mean ± SD	50 ± 14	50 ± 11	48 ± 13	47 ± 11	.043
Race category, n (%)					
White	487 (85)	201 (86)	89 (82)	70 (78)	
Other	85 (15)	32 (14)	20 (18)	20 (22)	.088
Duration of the disease, mean ± SD	18.9 ± 13.6	19 ± 14.6	20.4 ± 13.5	20.6 ± 15.6	.185
Exacerbation rate in the past year, mean ± SD	3.2 ± 2.1	3.4 ± 2.4	3.9 ± 3.2	5.0 ± 4.7	<.001
Smoking status, n (%)					
Never	451 (79)	161 (69)	87 (80)	70 (78)	
Former	121 (21)	72 (31)	22 (20)	20 (22)	.581
Baseline blood eosinophils (cells/μL)					
Geometric mean ± SD log	291 ± 0.96	268 ± 0.95	268 ± 1.13	225 ± 1.13	.023
Patients on maintenance OCS, n (%)	128 (22)	65 (28)	40 (37)	41 (46)	<.001
Baseline ACQ-5 score, mean ± SD	2.1 ± 1.1	2.4 ± 1.1	2.6 ± 1.1	2.8 ± 1.1	<.001
Baseline prebronchodilator, mean ± SD					
% predicted FEV_1,	62 ± 17	60 ± 16	59 ± 18	57 ± 18	.007
FEV_1 (mL)	1,907 ± 684	1,859 ± 666	1,748 ± 605	1,688 ± 639	<.001
FVC (mL)	3,018 ± 937	2,969 ± 969	2,779 ± 847	2,603 ± 868	<.001
FEV_1/FVC ratio	0.63 ± 0.13	0.63 ± 0.12	0.63 ± 0.12	0.65 ± 0.13	.668
Baseline postbronchodilator, mean ± SD					
% predicted FEV_1	72 ± 18	71 ± 18	71 ± 19	69 ± 19	.179
Baseline % reversibility FEV_1	25 ± 21	27 ± 20	25 ± 18	28 ± 28	.453

ACQ, Asthma Control Questionnaire.
**P* value for linear trend.

TABLE III. Mean and linear change trend in postbronchodilator (mL) FEV_1 in DREAM and MENSA studies*

Parameters	Study							
	DREAM				MENSA			
No. of exacerbations	0	1	2	≥3	0	1	2	≥3
N	283	136	68	69	289	97	41	21
Mean change (95% CI)	106 (57 to 154)	−23 (−85 to 40)	−34 (−152 to 85)	−37 (−132 to 59)	174 (125 to 224)	64 (−38 to 166)	86 (−75 to 246)	−17 (−179 to 145)
Adjusted mL mean change (95% CI)	108 (63 to 153)	−10 (−75 to 54)	−39 (−131 to 53)	−65 (−160 to 29)	181 (134 to 227)	76 (−5 to 157)	64 (−61 to 189)	−117 (−293 to 60)
Linear mL change trend (95% CI)	−43 (−67 to −18)				−68 (−107 to −28)			
P value	<.001				<.001			

Analysis was performed using analysis of covariance with covariates of exacerbations in study group (as a categorical variable), baseline lung function, region, baseline maintenance OCS therapy (OCS vs no OCS), exacerbations in the year before the study (2, 3, 4+) as an ordinal variable, treatment, sex, age (as a continuous variable), and log of baseline blood eosinophils. Linear change trend by replacing covariate of exacerbations in the study group with that of exacerbations in study (as a continuous variable).
*Analysis conducted ≥28 d after an exacerbation.

DISCUSSION

The results from this post hoc analysis of data from 2 large studies in severe asthma demonstrate that frequent exacerbations requiring systemic corticosteroids are associated with a decline in lung function compared with patients who do not exacerbate. This decline was consistent for each individual study and associated with the number of exacerbations, with a greater impact in those with 3 or more exacerbations. The adjusted mean change from this meta-analysis showed that each exacerbation resulted in a 50 mL decline in FEV_1. The data in our study showed that exacerbations could be linked temporally to accelerated decline in lung function in patients with severe asthma who do not smoke.

While the average rate of decline in FEV_1 in nonsmoking healthy adults is 15 to 20 mL/y,[19] the long-term effects of chronic inflammation and frequent exacerbations on lung function in patients with severe asthma are poorly understood. Severe exacerbations and decline in FEV_1 may both be manifestations of a more severe asthma phenotype. Patients who experienced more exacerbations during the observation period had at baseline lower lung function, a more pronounced history of smoking, higher use of maintenance OCS, and higher level of uncontrolled disease as

TABLE IV. Adjusted mean and linear change trend (mL) in postbronchodilator FEV_1 in a combined DREAM/MENSA analysis*

Parameters	Combined DREAM/MENSA studies			
No. of exacerbations	0	1	2	≥3
N	572	233	109	90
Adjusted mL mean change (95% CI)	143 (111 to 176)	23 (−27 to 74)	−3 (−77 to 72)	−77 (−160 to 6)
Linear mL change trend (95% CI)	−50 (−71 to −28)			
P value	.001			

Combined estimates across DREAM and MENSA were calculated using inverse variance weighted fixed-effects meta-analysis of the estimates from the individual studies.
*Analysis conducted ≥28 d after an exacerbation.

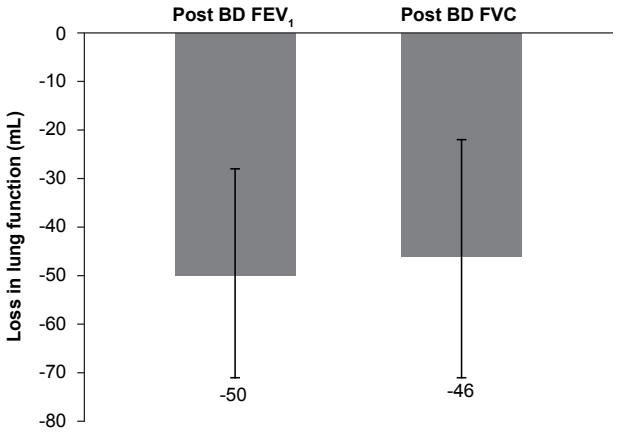

FIGURE 1. Linear trend change in lung function (mL) in a combined DREAM/MENSA analysis. *BD*, Bronchodilator. Error bars represent 95% CIs. *Analysis conducted ≥28 days after an exacerbation.

measured by the Asthma Control Questionnaire compared with those with no exacerbations. Several cohort studies and cross-sectional studies have suggested that, over time, some patients with asthma lose lung function at a greater rate than do subjects without asthma, and that increased loss of lung function is not seen in all patients.[2,4,5,8] A study reported by Bai et al[9] evaluated the decline in FEV_1 in a cohort of 93 nonsmoking patients with asthma with moderate-to-severe disease followed for 5 or more years (median, 11 years). The decline in mean FEV_1 was 31.5 mL/y in those with more frequent exacerbations and 14.6 mL/y in patients with asthma with less frequent exacerbations; the difference was 16.9 mL/y ($P = .03$). The investigators concluded that 1 exacerbation per year was associated with a 30.2 mL greater annual decline in FEV_1.[9] Similarly, data reported by Matsunaga et al[20] examined the changes in FEV_1 over a 3-year period in patients who experienced exacerbations while having well-controlled asthma at baseline. Overall, patients with 2 or more exacerbations had greater decline in FEV_1 than did patients with no exacerbations. Specifically, those with no exacerbations (n = 100) had a 13.6 mL/y decline, whereas those with 1 exacerbation (n = 10) had a 41.3 mL/y decline and those with 2 or more exacerbations (n = 18) had a 58.3 mL/y decline in FEV_1. The same author also reported data[21] from a retrospective analysis of lung function changes over a 10-year period in 54 patients with severe asthma. The results showed that the faster changes detected by decline in FEV_1 were accompanied by excessive loss of FVC ($r = 0.85$; $P < .0001$) and this decline was 1.2 times larger than the FEV_1 decline. In his analysis, age, baseline FVC, use of OCS, and annual exacerbation rate showed negative correlations with the rate of annual change in FVC. These data suggest that small airway susceptibility may be associated with a rapid disease progression. The current data are consistent with previous reports, despite differences in disease severity, showing a trend in lung function decline in both FEV_1 and FVC, which was associated with an increase in the number of exacerbations, where each exacerbation resulted in 50 mL/y decline in FEV_1. The exploratory analysis showed that patients without exacerbations improved their lung function with mepolizumab treatment, whereas those with increased number of exacerbations experienced decline in lung function in both treatment groups, although more accentuated in patients with 3 or more exacerbations. Speculatively this might suggest different mechanisms, with reversal of eosinophilic inflammation improving lung function but that repeated exacerbations, potentially related to mechanotransductive signals and independent of eosinophilic inflammation, override this benefit and induce remodeling changes that result in loss of lung function.

These results point to similarities with COPD; for example, in the Study to Understand Mortality and Morbidity (SUMMIT) study, patients who received placebo (N = 4,111) had a mean rate of decline in FEV_1 of 46 mL/y.[11] Donaldson et al[12] also reported a 40.1 mL/y decline in FEV_1 in patients with COPD and frequent exacerbations (median, 4.2/y), compared with 32.1 mL/y in those with less frequent exacerbations (median, 1.9/y). More recently, the same group of investigators reported that in patients with COPD who have 1 or more nonrecovered exacerbation within 99 days, a 33.6 mL/y decline in FEV_1 was observed.[22] Overall, our results are consistent with data from both asthma and COPD studies, supporting the concept that frequent exacerbations contribute significantly to the progressive loss of lung function.

We speculate that loss of FEV_1 may be due to airway narrowing triggered by recurrent exacerbations with consequent loss of lung elasticity or by structural airway wall remodeling leading to airway wall thickening[17] and associated with enhanced airway collagen deposition.[23] Eosinophils have been implicated in airway remodeling through the production of cytokines and growth factors, such as transforming growth factor-β.[8,24,25] Activated eosinophils, via release of eosinophil granule proteins, can damage the airway epithelium[26] and, as part of the epithelial repair response, promote epithelial mesenchymal signaling that enhances airway collagen deposition.[27] Furthermore, exacerbations predisposed by airway eosinophilic inflammation will also have mechanotransductive effects of relevance to airway remodeling.[28]

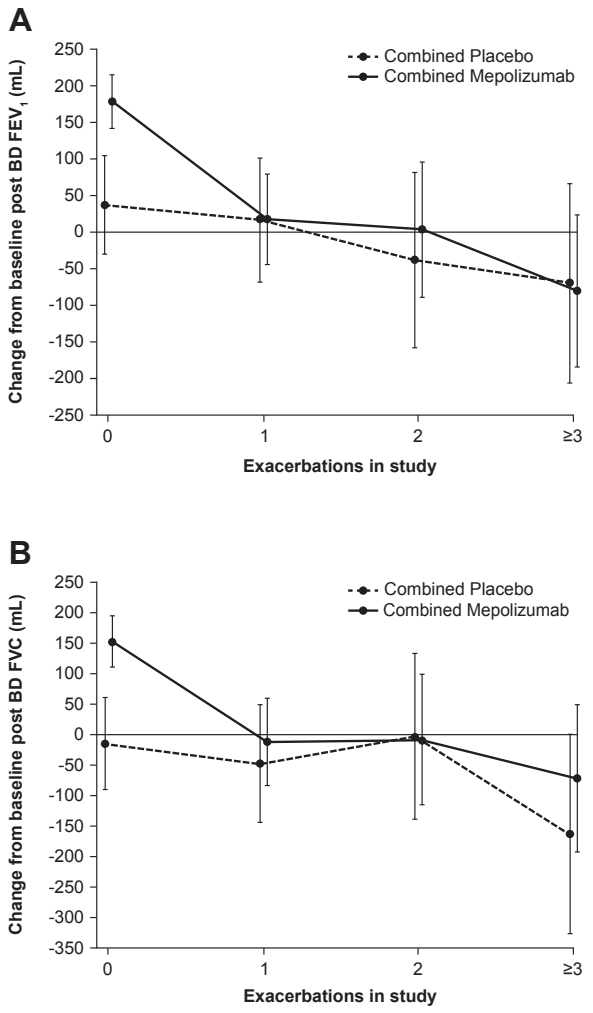

FIGURE 2. Changes from baseline FEV_1 (**A**) and change from baseline FVC (**B**) in patients treated with mepolizumab or placebo by number of exacerbations. *BD*, Bronchodilator. Error bars represent 95% CIs. Difference between groups for changes in FEV_1 was statistically significant ($P = .040$); nonstatistical significant difference between groups for changes in FVC ($P = .116$).

The consequences of the remodeling, namely, airway wall thickening and collagen deposition, can stiffen the subepithelial matrix and make the airways less responsive to treatment.[29-32] Newby et al[16] followed 97 patients with severe asthma for approximately 6 years. Patients experienced an FEV_1 decline of 25.7 mL/y in the overall population. Postbronchodilator FEV_1 was dependent on exacerbations, age of onset, height, age, sex, and sputum eosinophil percentages. They identified 3 clusters: (1) noneosinophilic with low eosinophil variation (mean decrease in lung function, 14.0 mL/y), (2) hypereosinophilic with low eosinophil variation (mean decrease, 19.2 mL/y), and (3) eosinophilic with high eosinophil variation (mean decrease, 40.9 mL/y). These data suggest that the high variability rather than the actual level of airway eosinophils is associated with accelerated FEV_1 decline. The cluster with highly variable eosinophils might reflect fluctuation in immune activation of key effector cytokines and chemokines, natural biological variation, and/or the rate of passage from the tissue compartment to the luminal airway compartment likely influenced by exacerbations. All patients enrolled in DREAM and MENSA had features of eosinophilic inflammation and therefore may be at a greater risk for this type of structural change. We recently reported the frequency of exacerbations by eosinophil count thresholds in the DREAM and MENSA studies.[33] The rate of exacerbations in the placebo group varied per baseline blood eosinophil counts: 1.94 per year (≥150 cells/μL), 2.19 per year (≥300 cells/μL), 2.36 per year (≥400 cells/μL), and 2.49 per year (≥500 cells/μL). The analysis showed greater reductions in exacerbations following mepolizumab treatment with increased blood eosinophil count. In the current analysis, those patients who experienced 3 or more exacerbations had on average 5 exacerbations in the previous year, compared with those with 0, 1, or 2 exacerbations who had on average 3.2, 3.4, and 3.9 events, respectively.

In the current study, we conducted an exploratory analysis by treatment; patients who received mepolizumab and did not have any exacerbations during the study had improvements in FEV_1 and FVC compared with patients who received placebo and without exacerbations. However, this benefit was not observed in patients with 3 or more exacerbations. A decline in lung function occurred in both mepolizumab and placebo groups. We speculate that in those patients treated with mepolizumab who had frequent exacerbations and associated decline in lung function, other noneosinophilic mechanisms (eg, noneosinophilic type 2 inflammation) are involved in the pathogenesis of these exacerbations. It is notable that the patients with 3 or more exacerbations had slightly lower baseline blood eosinophil counts compared with those with less exacerbations.

There are some limitations to our study. The retrospective nature of the design and the subsequent uncertainty about the cause-effect relation represent a weakness of our study. It is possible that some patients who are more prone to loss of lung function are more susceptible to have exacerbations and therefore, the exacerbations may be the result and not the cause of loss of lung function. The patients enrolled in the mepolizumab asthma studies were either former smokers, with a less than 10 pack-year history (24%), or never smoked (76%). Therefore, we cannot extrapolate the results to a smoker population where there is a well-known association between decline in lung function and exposure to cigarette smoke. The population studied included only patients with markers of eosinophilic inflammation and therefore these findings may not be applicable to other asthma phenotypes. We were unable to determine the nature of the exacerbations (ie, eosinophilic, neutrophilic, other); therefore, our assumptions are based on the baseline phenotype of the population. Our analysis is based on studies of 12 and 8 months of duration, preventing the assessment of long-term effects of disease progression. However, the key variable identified in our analysis was the frequency of exacerbations, independent of study duration.

CONCLUSIONS

Collectively, these results suggest that in patients with severe asthma, severe exacerbations may be an important contributor to an accelerated decline in lung function. Prevention of exacerbations should be one of the most important goals of treatment and therefore disease management approaches, including step-down of controller therapy, should be carefully considered in patients with severe disease who are prone to exacerbations. Prospective studies are needed to determine whether reduction in asthma

exacerbations by attenuating the eosinophilic variability could slow or reduce the loss of lung function and potentially mitigate irreversible structural alternations in the lung.

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APPENDIX

TABLE E1. Adjusted mean and linear change trend in postbronchodilator FEV_1 (mL) in a combined DREAM/MENSA analysis

	Study							
Parameters	**DREAM**				**MENSA**			
No. of exacerbations	0	1	2	≥3	0	1	2	≥3
N	277	138	68	80	289	104	46	27
Mean change (95% CI)	106 (57 to 156)	−27 (−89 to 35)	−24 (−141 to 94)	−38 (−132 to 56)	174 (125 to 224)	71 (−28 to 170)	72 (−76 to 219)	6 (−133 to 144)
Adjusted mean change (95% CI)	110 (64 to 157)	−11 (−76 to 54)	−28 (−121 to 66)	−74 (−163 to 15)	180 (133 to 227)	79 (1 to 157)	55 (−64 to 173)	−54 (−209 to 100)
Linear change trend (95% CI)	−41 (−65 to −18)				−50 (−86 to −14)			
P value	.001				.007			

Sensitivity analysis based on last pulmonary function measure that occurred at least 14 d after an exacerbation. Analysis was performed using analysis of covariance with covariates of exacerbations in study group (as a categorical variable), baseline lung function, region, baseline maintenance OCS therapy (OCS vs no OCS), exacerbations in the year before the study (2, 3, 4+) as an ordinal variable, treatment, sex, age (as a continuous variable), and log of baseline blood eosinophils. Linear change trend by replacing covariate of exacerbations in study group with that of exacerbations in study (as a continuous variable).
Note: Sensitivity analysis conducted ≥14 d after an exacerbation.

TABLE E2. Adjusted mean and linear change trend in postbronchodilator FEV_1 (mL) in a combined DREAM/MENSA analysis

Parameters	Combined DREAM/MENSA studies			
No. of exacerbations	0	1	2	≥3
N	566	242	114	107
Adjusted mean change (95% CI)	145 (112 to 178)	26 (−24 to 76)	4 (−69 to 77)	−69 (−146 to 9)
Linear change trend (95% CI)	−44 (−64 to −24)			
P value	.001			

Sensitivity analysis based on last pulmonary function measure that occurred at least 14 d after an exacerbation. Combined estimates across DREAM and MENSA were calculated using inverse variance weighted fixed-effects meta-analysis of the estimates from the individual studies.
Note: Sensitivity analysis conducted ≥14 d after an exacerbation.