Original Article

Long-Term Efficacy and Safety Among Patients With Severe Eosinophilic Asthma Treated With Mepolizumab and Its Effect on Small Airways

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What is already known about this topic? Mepolizumab (MP) is safe and effective in treating patients with severe eosinophilic asthma up to $4\frac{1}{2}$ years.

What does this article add to our knowledge? Our study demonstrates that MP is safe and effective up to $6\frac{1}{2}$ years. After treatment with MP, all 67 patients in our cohort revealed a 30.4% increase in forced expiratory flow at 25% to 75% ($FEF_{25\%-75\%}$) *P* less than .001. There was a 40% median increase of the $FEF_{25\%-75\%}$ in 47 super-responders with very little change in the forced expiratory volume in 1 second (FEV_1).

How does this study impact current management? To effectively manage patients treated with biologics, it is important to follow the $FEF_{25\%-75\%}$ because this is indicative of small airway disease, which is an integral part of severe eosinophilic asthma. Moreover, all research comparing different biologics, as well as attempts to define a super-responder to various biologics, should include $FEF_{25\%-75\%}$ rather than just FEV_1.

BACKGROUND: The major problem at the Cleveland Allergy and Asthma Center was the need for additional therapy for severe eosinophilic asthma patients who were steroid-dependent or required frequent bursts of prednisone.

OBJECTIVES: The objectives of this study were to determine the efficacy of monthly mepolizumab (MP) injections up to $6\frac{1}{2}$ years using Asthma Control Quesitonnaire-7 (ACQ-7), forced expiratory volume in 1 second (FEV_1), forced expiratory flow at 25% to 75% ($FEF_{25\%-75\%}$) overall and among super-responders, and to understand whether $FEF_{25\%-75\%}$ is an effective parameter to evaluate MP efficacy.

METHODS: We reviewed the charts of 67 patients with severe eosinophilic asthma and compared the results between 47 super-responders and the rest of the cohort regarding ACQ-6, ACQ-7, eosinophils, FEV_1, and $FEF_{25\%-75\%}$. The groups of super-responders and all other patients were described with respect to initial and current values of the study end points using medians and 25th and 75th percentiles. Changes from the

initial to the current values in the study end points were measured using percent changes. The Wilcoxon signed rank test was used within each group to test the null hypothesis of 0 median percent change.

RESULTS: After $6\frac{1}{2}$ years, there were no significant changes in FEV_1. The $FEF_{25\%-75\%}$, had a significant median percent increase of 40% among the super-responders ($P < .001$), which was substantially higher ($P = .026$) than the median percent increase of 13.8% observed among all other patients.

CONCLUSIONS: The use of MP up to $6\frac{1}{2}$ years was safe and effective, with significant changes to ACQ-7 and $FEF_{25\%-75\%}$ associated with MP treatment, but not the FEV_1. A higher magnitude of changes was observed among super-responders than the rest of the cohort. Changes in $FEF_{25\%-75\%}$ were more meaningful than changes in FEV_1 in evaluating pulmonary function responsiveness of severe eosinophilic asthma to MP. © 2023 American Academy of Allergy,

Abbreviations used
    ACQ-6- Asthma Control Questionnaire-6
    ACQ-7- Asthma Control Questionnaire-7 (which includes the
        forced expiratory volume in 1 second)
    BMI- Body mass index
    DREAM- Dose Ranging Efficacy And Safety with Mepolizumab
        in Severe Asthma
    $FEF_{25\%-75\%}$- Forced expiratory flow at 25% to 75%
    FEV_1- Forced expiratory volume in 1 second
    FVC- Forced vital capacity
    GINA- Global Initiative for Asthma
    ICS- Inhaled corticosteroids
    IL-5- Interleukin-5
    LABA- Long-acting beta-agonists
    MP- Mepolizumab
    OCS- Oral corticosteroids
    SAD- Small airway disease
    SEA- Severe eosinophilic asthma

INTRODUCTION

The care of asthmatics with severe eosinophilic asthma (SEA) has been revolutionized by the use of mepolizumab (MP) over the last $6^1/_2$ years in our practice with dramatic improvement clinically and manifested with a significant increase in the forced expiratory flow at 25% to 75% ($FEF_{25\%-75\%}$), revealing the importance of small airway disease (SAD).

Mepolizumab (GlaxoSmithKline, Research Triangle Park, NC) is a recombinant humanized immunoglobulin G/K monoclonal anti—interleukin-5 (IL-5) antibody that inhibits IL-5 from binding to the alpha subunit of the IL-5-receptor complex expressed on the eosinophil cell's surface.[1]

In a study by Siroux et al,[2] they discovered that small airway obstruction is assessed based on $FEF_{25\%-75\%}$ outcomes independently from the effect of large airways. Data from a real-world study are important to determine whether data from randomized control trials are effective to a broader population.

Asthma is currently thought to be a complex disease characterized by heterogeneous traits with a regard to etiology, triggers, inflammatory patterns, clinical manifestations, and therapeutic responses. Among severe different phenotypes, eosinophilic asthma occurs in more than 50% of patients with either atopic or nonatopic asthma.[3]

In an attempt to define super-responders, we used the study by Upham et al[4] that appears to be the most well-researched attempt to define a super-responder, realizing that there is no agreed-upon definition of super-responder. The aim of their study was to develop a consensus-based super-responder definition that encompassed both objective measures and patient-reported outcomes. They used a Delphi process to survey multiple severe asthma experts from numerous countries. The Delphi panel was a poll of 81 participants (94% specialists, pulmonologists, or allergists) from 24 countries and consisted of 3 iterative online voting rounds. Consensus was achieved that super-responder definition should be based on improvement across 3 or more domains accessed over 12 months. Major super-responder criteria included exacerbation elimination, a large improvement in asthma control (2 or more times the minimal clinical important difference), and cessation of maintenance oral corticosteroids (OCS) (or weaning to adrenal insufficiency). Minor super-responder criteria were composed of a 75% exacerbation reduction, having well-controlled asthma, and 500 mL or greater improvement in forced expiratory volume in 1 second (FEV_1). The super-responder definition required improvement in at least 2 major criteria.

METHODS

This is a retrospective study of severe asthmatics treated at the Cleveland Allergy and Asthma Center in Cleveland, Ohio, with MP beginning in May 2016 and concluding in November 2022. Because we planned on reviewing the patients in our study in November 2022 and felt that significant data required at least 6 months of treatment with MP, the last patients studied were those who began MP in June 2022. Written permission was granted by all patients to use the results of their treatment with MP, a monoclonal antibody directed against the IL-5 cytokine.

The Cleveland Allergy and Asthma Center specializes in the treatment and care of severe asthmatics. Patients received monthly subcutaneous injections of 100 mg of MP during a period of 6 months to $6^1/_2$ years. In order to qualify for the study, the patients needed to be on a high dose of inhaled corticosteroids (ICS) and long-acting beta-agonists (LABAs). In addition, they had to have had at least 2 exacerbations requiring a burst of prednisone during the past year, or be on daily prednisone. It was also required that they have an eosinophil count of 150 during the past year.

Before beginning MP, when clinically stable, attempts were made to lower the prednisone to the lowest dose that kept them reasonably well controlled. At each visit, before they received MP, they were examined. Pulmonary function tests were performed, including forced vital capacity (FVC), FEV_1, peak flow, and $FEF_{25\%-75\%}$, by nurses who were well trained doing pulmonary function tests (Puritan Bennett model PB900 Overland Park, KS and Company MIR [Medical International Research] model Spiral Lab Berlin, WI). The tests were repeated 3 times and the best 1 was used.

In addition, at each monthly visit, an Asthma Control Questionnaire (ACQ-7) was completed. It has been a longstanding policy that all new patients have inhaler technique demonstrated and this was again reviewed when beginning MP. In addition, adherence to the recommended regimen was reviewed thoroughly and repeated frequently. We made sure the patients understood the necessity of taking medications even when clinically stable. In addition, they were instructed how to treat exacerbations.

We did make the distinction between difficult-to-treat and severe asthma.[5] We addressed the importance of adherence as well as inhaler technique on multiple occasions. Thus, we feel that the patients in our cohort are severe asthmatics versus difficult-to-treat.

Statistical methods

The groups of super-responders and all other patients were described with respect to initial and current values of the study end points using medians and 25th and 75th percentiles. The initial

TABLE I. Baseline demographic and clinical characteristics (as-treated population)

	MP, 100 mg SC		
Characteristic	Total patients (n = 67)	SRs (n = 47)	NSRs (n = 20)
Age (y), mean (SD)	61.5 (15.5)	63 (16)	55 (13)
Sex			
Female, n (%)	36 (54)	27 (60)	11 (55)
Male, n (%)	31 (46)	20 (40)	9 (45)
Race, n (%)			
White (non-Hispanic)	60 (90)	42 (89.1)	18 (90)
Hispanic-Latino	3 (4)	2 (4.3)	1 (5)
African American	2 (3)	1 (2.1)	1 (5)
Other	2 (3)	2 (4.3)	0
Eosinophil counts, range (average)			
Pre-MP	150–1,690 (436)	150–1,690 (369)	150–1,200 (435)
Comorbidities, n (%)			
Allergic rhinitis	58 (87)	38 (81)	20 (100)
Nasal polyposis	3 (4)	1 (2.1)	2 (10)
GERD	8 (12)	6 (12)	2 (10)
Asthma/COPD overlap syndrome	4 (6)	3 (6.3)	1 (5)
Smoking status, n (%)			
Former	18 (27)	13 (28)	5 (25)
Current	9 (13)	2 (4.3)	7 (35)
Never	40 (60)	30 (63.8)	10 (50)
Allergy injections, n (%)	11 (16)	9 (19.1)	2 (10)
Positive allergy skin tests, n (%)	60 (89)	42 (89)	18 (90)
Age of asthma onset, median (range)	24.8 (2–73)	20 (2–70)	12 (4–73)
Duration of disease (y), range	3–65	3–65	3–62
Current therapy, n (%)			
ICS	67 (100)	47 (100)	20 (100)
LABA	67 (100)	47 (100)	20 (100)
SABA	67 (100)	47 (100)	20 (100)
LTRA	60 (90)	44 (93)	16 (80)
LAMA	19 (28)	11 (23.4)	8 (40)
Xanthine	2 (3)	2 (4)	0
Terbutaline tablets	12 (18)	7 (15)	5 (25)
Albuterol tablets	17 (25)	11 (23.4)	6 (30)
Patient responders, n (%)	47 (70)	47 (100)	0
Body mass index (BMI) (kg/m^2), n (%)			
Class I (obese; BMI 30 to < 35)	7 (13)	6	1
Class II (Severe obesity; BMI 35 to < 40)	3 (5)	3	0
Class III (morbid obesity; BMI ≥ 40)	10 (15)	6	4
OCS when beginning MB, n	21	12	9
Prednisone dose (mg), range	2.5–25	2.5–25	10–15
Average dose of prednisone (mg)	11.5	10.6	12.8
Dosage of OCS in NSR			
Daily (mg)	2.5–5		2.5–5
Average dose of prednisone (mg)	4.8		4.8

COPD, Chronic obstructive pulmonary disease; *GERD*, gastroesophageal reflux disease; *LAMA*, long-acting muscarinic antagonist; *LTRA*, leukotriene receptor antagonist; *NSRs*, non–super-responders; *SABA*, short-acting beta-agonist; *SC*, subcutaneous; *SRs*, super-responders.

value coincides with the first injection of MP and current refers to the last MP injection received in November 2022. Changes from the initial to current values of the study end points were measured using percent changes. The Wilcoxon rank sum test was used within each group to test the null hypothesis of a 0 median percent change. The Wilcoxon rank sum test was used to test the null hypothesis of equal median percent change for the 2 groups. The nonparametric Wilcoxon tests were employed to avoid any undue influence of extreme or outlying percent change values. The primary analysis was the comparison of the groups with respect to the median percent change in FEF$_{25\%-75\%}$ performed at a significance level of .05. All other tests were considered secondary analyses.

TABLE II. Averages before and after beginning MP

Variable	Mean (SD)	
	Before starting MP	Current values
ACQ-6	1.54 (0.95)	0.72 (0.73)
ACQ-7	2.09 (1.28)	1.17 (0.79)
FEV_1 (%)	74.4 (20.7)	72.5 (16.8)
$FEF_{25\%-75\%}$ (%)	52.3 (29.8)	68.2 (33.6)
Eosinophils (cells/μL)	416 (334) (range 150–1690)	54.5 (34.9) (range 0–183)

RESULTS

The results of our study for all 67 patients are listed on Table E1 (available in this article's Online Repository at www.jaci-inpractice.org).

We defined the super-responders in our study if they had no exacerbations requiring oral steroids for a year, experienced a large improvement in asthma control, and had no need for daily maintenance steroids.

There were 67 patients with severe eosinophilic asthma in our cohort (Table I). The average age was 61.5 years, there were 36 females and 31 males, there were 60 white (non-Hispanic), 3 Hispanic-Latino, 2 African-American, and 2 other patients. The eosinophil count pre-MP ranged from 150 to 1690 (with an average of 436). The comorbidities were 58 had allergic rhinitis, 3 had nasal polyposis, 8 had gastroesophageal disease, and 4 had asthma/chronic obstructive pulmonary disease overlap syndrome. Smoking status revealed that 18 were former smokers, 9 were current smokers, and 40 had never smoked. There were 11 patients receiving allergy injections (immunotherapy), and 60 had positive skin tests. The median age of onset was 24.8 years, with a range of 2 to 73. The duration of the disease ranged from 3 to 65 years, with an average of 33 years. Regarding current therapy, 67 were taking ICS, LABAs, and short-acting beta-agonists, 60 received leukotriene receptor antagonists, and 19 received long-acting beta-agonists, with 2 on xanthine, 12 on terbutaline tablets, and 17 on albuterol tablets. The number of patients defined as super-responders was 47 (70%). Regarding weight, the number of patients whose body mass index (BMI) was class I obesity (BMI 30 to < 35) was 7, class II severe obesity (BMI 35 to < 40) was 3, and class III morbid obesity (BMI ≥ 40) was 10. Twenty-one patients were receiving OCS when beginning MP. The range of prednisone was 2.5 to 25 mg. The average dose was 11.5 mg. For the dosage of OCS in our non—super-responder, the daily dose was 2.5 to 5 mg, and the average daily dose was 4.8 mg.

The average ACQ-6 score before starting MP was 1.54 and the current ACQ-6 is 0.72 ($P < .001$) (Table II). The average ACQ-7 score before starting MP was 2.09 and the current ACQ-7 is 1.17 ($P < .001$). The average FEV_1 before starting MP was 74.36% of predicted. The average current FEV_1 is 72.49%, a 2.5 decrease in percent of predicted ($P = .42$). The average initial $FEF_{25\%-75\%}$ was 52.3% of predicted and the average current $FEF_{25\%-75\%}$ is 68.2% of predicted (a 30.4% increase; $P < .001$). Forty-seven of the 67 patients were considered super-responders by criteria based on the Upham et al study.[4] They did not require daily prednisone or bursts of prednisone and were well controlled on ICS and LABAs.

In our cohort, we identified 10 patients (14.9%) who were super-responders, while only receiving montelukast for over a year, and 2 patients who had not received any other medication for a year and were totally asymptomatic. We had 5 patients in our study that were older than 82 years. All 5 of them became super-responders.

Two patients died during the 6½-year period of our study unrelated to MP: 1 patient died from suicide and the other from esophageal cancer.

While on MP, patients frequently reported feeling significantly better with an increased quality of life and increased energy.

Mepolizumab, during the 6½ years, was remarkably well tolerated. Other than occasional itching, there were no significant reactions at the injection site. Three patients developed mild cases of herpes zoster. One patient developed urticaria on 2 separate occasions. She was treated before her next injections over the next 6 months with prednisone, diphenhydramine, and cetirizine before each injection. She tolerated it well. We discontinued the medications and she continued to tolerate the MP injections without an issue. There were no episodes of angioedema or anaphylaxis.

Super-responders and non—super-responders

Comparisons of super-responders and all other patients with respect to study end points.
We do have 47 of 67 patients who achieved super-responder status, whereas 20 out of 67 (30%) did not achieve super-responder status; 3 patients were on 5 mg of prednisone daily and 1 patient was receiving 2.5 mg/d, besides ICS, LABAs, and other controller medications, including montelukast, albuterol tablets, terbutaline tablets, long-acting muscarinic antagonists, and the use of albuterol inhalers and albuterol aerosols (Table III). Comparing the 2 groups, the super-responders had a 66.4% decrease in the ACQ-6, and other patients had a 58.2% decrease. Regarding the ACQ-7, the super-responders had a 47.1% decrease, and the other patients had 42.6% decreases. Regarding eosinophils, there was an 83% decrease in the super-responders and a 91% decrease in the other patients. The FEV_1% showed a decrease of 1.35% in the super-responders and all other patients had a 3.2% decrease. Most important is the $FEF_{25\%-75\%}$ with the % increase in the super-responders of 40.0 while there was a 13.8% increase in the other patients.

The most significant spirometry finding at the end of 6½ years was the 40% median increase in the $FEF_{25\%-75\%}$ in 47 super-responders in the face of very little change in the FEV_1 (Table III and Figures 1–5).

Table IV shows number of patients treated with MB in regard to duration of treatment.

DISCUSSION
Small airway dysfunction

The SAD asthma phenotype is characterized by narrowing of the airways to less than 2 mm in diameter between generations 8 and 23 of the bronchial tree.[6] They do not contain cartilage in their walls. The chronic inflamed infiltrate consists of eosinophils plus lymphocytes, neutrophils, and macrophages. Moreover, transbronchial biopsy findings show small airway inflammation and remodeling in all severities of asthma.[7] The involvement of the peripheral small airways[8] has recently gained greater

TABLE III. Comparisons of super-responders and all other patients with respect to study end points

| | Median (25th, 75th percentiles) | | Wilcoxon rank sum |
| | Super-responders (n = 47) | All other patients (n = 20) | |
Study end point			P value*
ACQ-6			
Initial	1.42 (0.71, 2.00)	2.00 (1.03, 2.57)	.11
Current	0.42 (0, 1.07)	0.86 (0.50, 1.14)	.14
% Decrease, P†	66.4 (2.10, 100), <.001	58.2 (26.3, 78.8), <.001	.50
ACQ-7			
Initial	1.86 (1.28, 2.64)	2.00 (1.57, 3.14)	.56
Current	0.93 (0.57, 1.64)	1.14 (0.68, 1.54)	.50
% Decrease, P†	47.1 (2.47, 69.0), <.001	42.6 (30.4, 54.8), .002	.73
Eosinophils (cells/μL)			
Initial	245 (170, 588)	305 (215, 502)	.38
Current	54.0 (38.0, 71.5)	50.0 (30.0, 74.5)	.73
% Decrease, P†	83.0 (70.8, 91.2), <.001	91.0 (77.0, 93.2), <.001	.28
FEV_1 (%)			
Initial	72.4 (62.0, 89.2)	79.7 (58.0, 95.0)	.51
Current	72.0 (61.5, 81.5)	79.5 (64.3, 87.8)	.20
% Decrease, P†	1.35 (−22.6, 16.4), .67	3.27 (−6.83, 14.2), 0.35	.78
$FEF_{25\%-75\%}$ (%)			
Initial	39.1 (28.0, 68.0)	61.0 (41.0, 84.5)	.07
Current	60.0 (44.5, 92.0)	71.0 (45.0, 88.8)	.57
% Increase, P†	40.0 (16.8, 81.1), <.001	13.8 (-2.62, 26.4), .19	.026

*P values reported that assess whether medians are different between super-responders and all other patients are based on the Wilcoxon rank sum test.
†P values reported within groups that assess whether median %increase or %decrease is different from 0 are based on the Wilcoxon signed rank test.
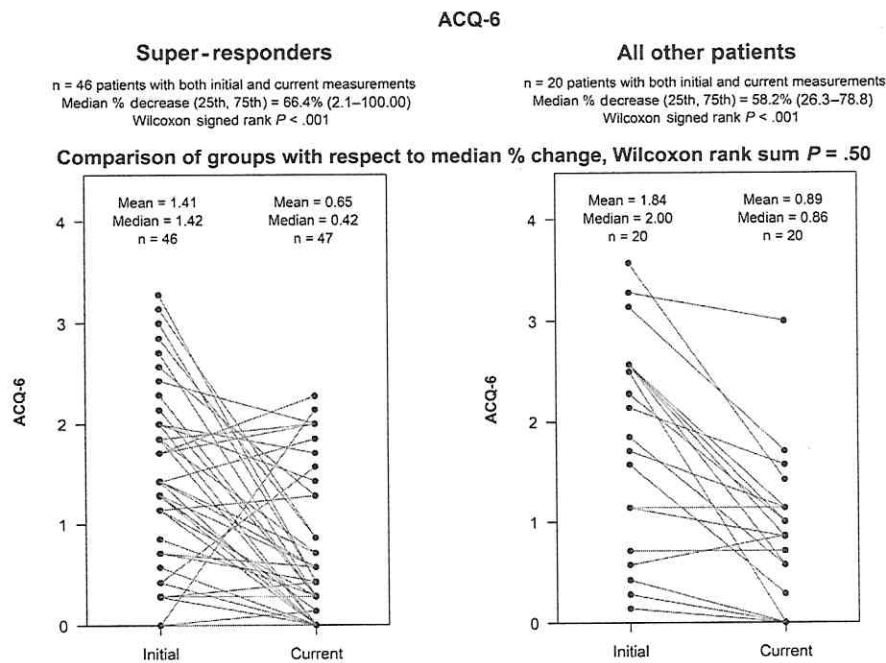
FIGURE 1. Evaluation of changes in ACQ-6 between initial and current time points among super-responders and all other patients.

recognition in asthma, and many studies suggest that persisting inflammation in these sites lead to SAD, strongly contributing to worse asthma control.

Riley et al[9] studied whether $FEF_{25\%-75\%}$ relates to clinical or biological outcomes independently of the FEV_1 or the FEV_1/FVC reaction. After they controlled for demographic variables, FEV_1 and FEV_1/FVC, the reduced $FEF_{25\%-75\%}$ is independently associated with previous intensive care unit admissions, persistent symptoms, blood eosinophilia, and bronchial hypersensitivity. Their findings suggest that, in some

ACQ-7

Super-responders

n = 42 patients with both initial and current measurements
Median % decrease (25th, 75th) = 47.1% (2.5–69.0)
Wilcoxon signed rank P < .001

All other patients

n = 16 patients with both initial and current measurements
Median % decrease (25th, 75th) = 42.6% (30.4–54.8)
Wilcoxon signed rank P < .002

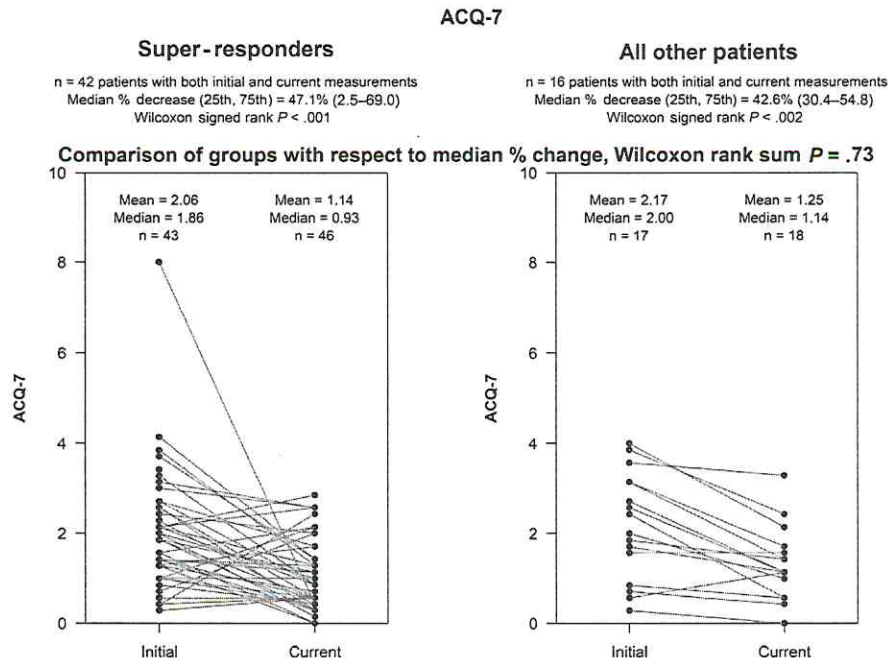**Comparison of groups with respect to median % change, Wilcoxon rank sum P = .73**

FIGURE 2. Evaluation of changes in ACQ-7 between initial and current time points among super-responders and all other patients.

Eosinophil

Super-responders

n = 42 patients with both initial and current measurements
Median % decrease (25th, 75th) = 83.0% (70.8–91.2)
Wilcoxon signed rank P < .001

All other patients

n = 19 patients with both initial and current measurements
Median % decrease (25th, 75th) = 91.0% (77.0–93.2)
Wilcoxon signed rank P < .001

Comparison of groups with respect to median % change, Wilcoxon rank sum P = .28
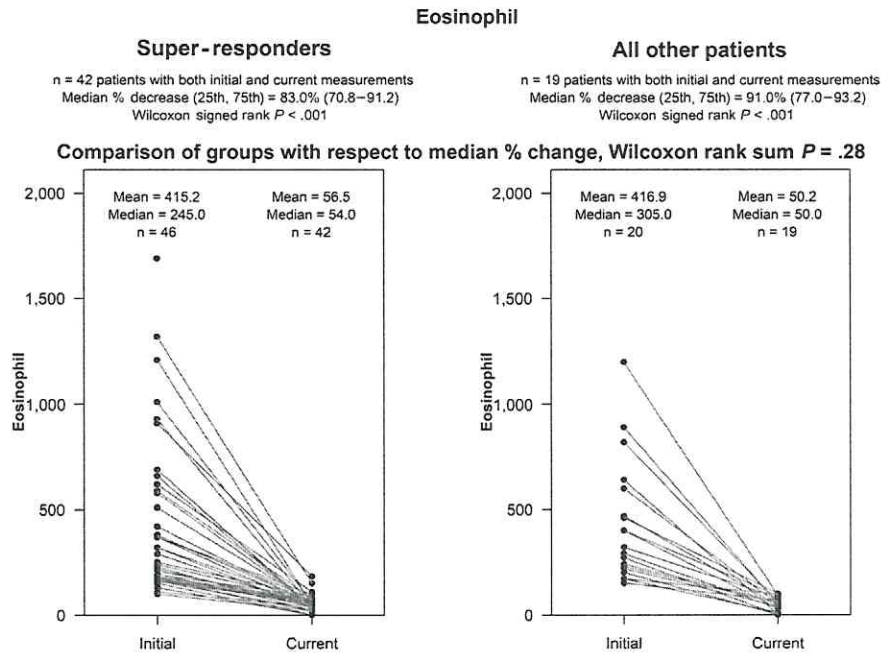
FIGURE 3. Evaluation of changes in eosinophils between initial and current time points among super-responders and all other patients.

asthmatics, the reduced $FEF_{25\%-75\%}$ is an independent biomarker for more severe asthma. Our study has certainly shown this.

Lipworth et al[6] were prescient in their article, Unlocking the quiet zone, the small airway asthma phenotype, in discussing small airways in the distal lung that they referred to, as mentioned, as the quiet zone because of the difficulty of assessing this in treating patients with asthma who have a disproportionate

impairment of small airway function. They felt that evidence was accumulating to support a distinct clinical phenotype for patients with asthma with impaired small airway function. The small airway asthma phenotype, which is prevalent in patients at all steps of the management guidelines, seems to be associated with poor disease control. Many of these patients have a preserved FEV_1, have evidence of impaired $FEF_{25\%-75\%}$ of FVC lower than 60% of predicted. We are mentioning this only because this
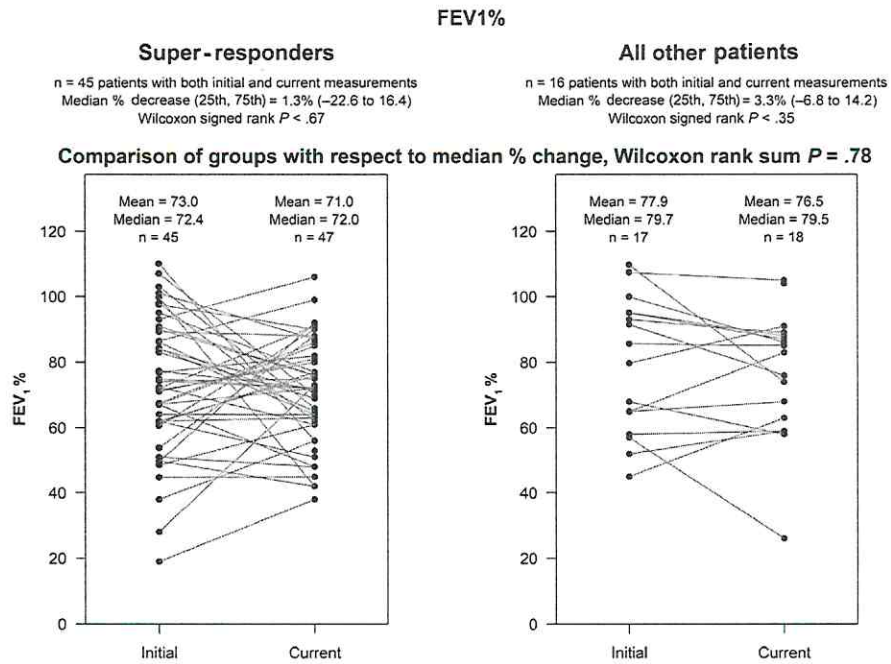
FEV1%

Super-responders

n = 45 patients with both initial and current measurements
Median % decrease (25th, 75th) = 1.3% (−22.6 to 16.4)
Wilcoxon signed rank *P* < .67

All other patients

n = 16 patients with both initial and current measurements
Median % decrease (25th, 75th) = 3.3% (−6.8 to 14.2)
Wilcoxon signed rank *P* < .35

Comparison of groups with respect to median % change, Wilcoxon rank sum *P* = .78

FIGURE 4. Evaluation of changes in FEV_1 between initial and current time points among super-responders and all other patients.

$FEF_{25\%-75\%}$

Super-responders

n = 45 patients with both initial and current measurements
Median % increase (25th, 75th) = 40.0% (16.8 to 81.1)
Wilcoxon signed rank *P* < .001

All other patients

n = 16 patients with both initial and current measurements
Median % increase (25th, 75th) = 13.8% (−2.6 to 26.4)
Wilcoxon signed rank *P* = .19

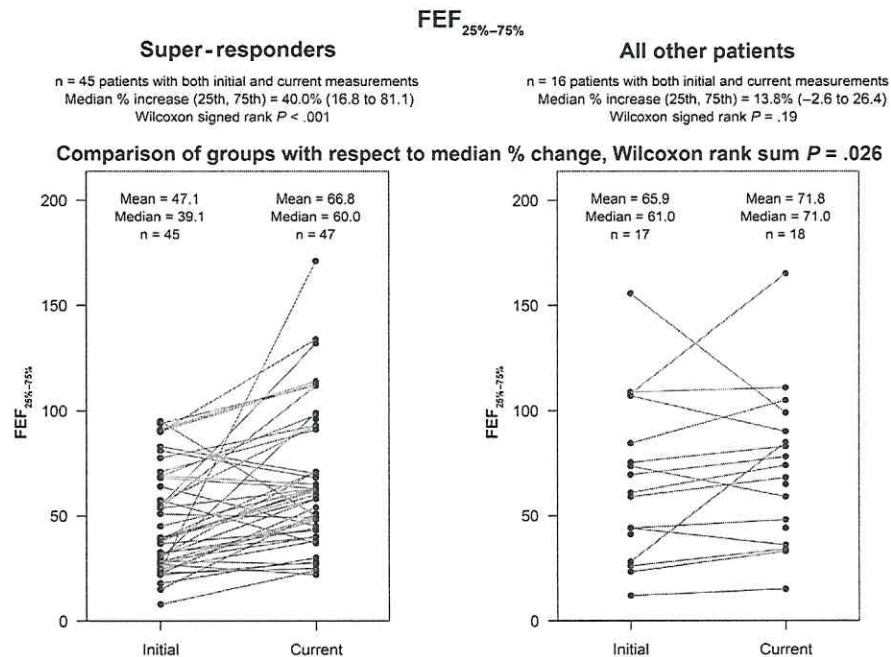**Comparison of groups with respect to median % change, Wilcoxon rank sum *P* = .026**

FIGURE 5. Evaluation of changes in $FEF_{25\%-75\%}$ between initial and current time points among super-responders and all other patients.

was written in 2014 and most of the studies of severe asthmatics and the use of MP did not test for SAD.

The assessment of small airway involvement in an asthma study[10] was a multinational 1-year prospective cohort study that includes people with asthma of all severities and control participants without airway disease. The study comprised 773 patients with asthma and 99 controls without airway obstruction. It was particularly designed to determine the prevalence and effect of

SAD in patients with asthma. The results show the clinical relevance established is present across all severity stages of asthma. The SAD is particularly present in severe disease, likely reflecting structural changes that are not responsive to the use of OCS, high-dose ICS, or both. Moreover, SAD relates to asthma severity (assessed by Global Initiative for Asthma [GINA] scale), quality of life, exacerbation frequency, and health care use, and this disease can be delineated by easy-to-conduct clinically

TABLE IV. Duration of MP treatment

Duration of MP treatment	Number of patients
0–6 mo	1
6 mo–2 y	7
2–5 y	29
5–6 y	22
>6 y	8

applicable measures such as impulse oscillometry and spirometry. They state that this aspect of asthma needs further consideration in the management of the disease; we hope our study gives some insight into their questions.

So, here is another study besides Lipworth et al[6] to emphasize the importance of SAD and it seems ironic that this was not part of so many of the studies of MP as well as many of the other biologics.

Regarding SAD, the essential premise here is that the systemic route would facilitate delivery of biologics to the entire lung including the peripheral airways, the same way that OCS in patients who are refractory to high-dose ICS. Given that the airway mucosal surface is proportionately much greater in the distal than in the proximal lung, systemic delivery of biologics appears to be an excellent way for treating all type 2 inflammation asthmatic airways. This may be one of the reasons why systemic biologics were so successful at improving control in severe asthma despite the use of high-dose ICS.[11]

Malerba et al[12] interestingly found that the $FEF_{25\%-75\%}$ but not the FEV_1 correlated with sputum eosinophilic count in patients with SAD. Therefore, they felt $FEF_{25\%-75\%}$ more accurately represents the effect of asthma in lung functions in patients having only SAD, and FEV_1 did not reflect the disease conditions.

An interesting study by Qin et al,[13] titled $FEF_{25\%-75\%}$, was a more sensitive measure reflecting airway dysfunction in patients with asthma, a comparison study using $FEF_{25\%-75\%}$ and FEV_1. They state that the assessment of small airway impairment should be an important step in the management of severe asthmatic patients as well as the evolution of response to biologic therapy. They felt that $FEF_{25\%-75\%}$, but not FEV_1, was correlated with airway inflammation and disease control in patients with SAD.

What we found absolutely fascinating was the work by Minshall et al.[14] The tissue they examined for evidence of major inflammatory cytokines revealed that the number of cells expressing mRNA was increased; that is, IL-5 mRNA was greater in the small airways than in the large airways. They also found an increased expression of IL-5 and IL-4 mRNA in the distal airways of asthmatics compared with nonasthmatic controls.

A few other studies relate to SAD.[15] Farah et al[15] state that this was the first study to show an improvement in small airway function following the initiation of anti–IL-5 treatment with MP in severe eosinophilic asthma. Their results suggest that biologic therapy might be effective because of its systemic delivery that might access the small airway in subjects with severe asthma.

In support of this are 2 retrospective studies that independently demonstrate a significant improvement in $FEF_{25\%-75\%}$ with MP in severe eosinophilic asthma patients. Both studies used the Wilcoxon signed rank test, as we did, to assess patients

before and after treatment with MP. Maglio et al[16] investigated the effect of MP on lung function in severe eosinophilic asthma patients. This was a retrospective study that analyzed 105 patients with severe eosinophilic asthma treated with MP that was administered subcutaneously in doses of 100 mg every 4weeks and analyzed patients who had completed at least 6 months of therapy. Data were selected at baseline and after 6, 12, and 18 months of MP treatment. The mean percentage value of FEV_1 increased almost to the maximum improvement level after 6 months of therapy without further significant improvement over the course of observation. The $FEF_{25\%-75\%}$ showed a highly significant gradual and persistent increase (from 32.7% ± 18.2% at baseline to 48.6% ± 18.4% after 18 mo [r = 0.566; $P <$ .0001]). This effect correlated with clinical benefits and, thus, may represent an accessible parameter through which to evaluate therapeutic responses.

Sposato et al[17] studied the effect of MP on 130 patients with asthma for up to 11 months ± 3.7 months. Mean $FEF_{25\%-75\%}$ was 37.4 before and 47.2 after treatment ($P <$ .0001). They too felt that this significant improvement was a possible expression of MP's effect on small airways.

To our knowledge, this is the first study treating SEA with monoclonal antibodies, except for omalizumab, up to $6^1/_2$ years with almost no change in the FEV_1, but a 30% increase in the $FEF_{25\%-75\%}$.

Forced expiratory volume 1 second

Ozturk et al's study[18] was a retrospective chart review of patients with SEA treated with MP. Data were collected at baseline and at 6 and 12 months. The mean FEV_1 at baseline was 2.102 L. There was an increase of 0.373 L at 6 months and 0.596 L at 12 months.

In other studies, an increase in FEV_1 ranged from 177 mL to 600 mL.[19-24] There was tremendous variation in the increase of FEV_1 as well as the timing. Some were within 1 month, some were within 6 months. In a study from Austria[20] consisting of 35 patients, a 90-mL increase was found in FEV_1 in the first month, but could not be maintained at the 20th week. Wide variation in increase in FEV_1 as well as the timing, pointed to a lack of consistency to be used to determine whether a patient is a super-responder. Determining the minimal improvement value for measures may be helpful to interpret changes.[25] Improvements in FEV_1 should be interpreted in context if they do not exceed the minimal clinical important difference of 230 mL. In addition, as mentioned in Khatri et al,[26] at 200 weeks the FEV_1 was similar to what it was at baseline.

In our study, after 6 months to $6^1/_2$ years, there was little difference in the FEV_1 between the super-responders and the non–super-responders.

Review of the original studies showing that MP was effective in severe eosinophilic asthma included DREAM (Dose Ranging Efficacy And Safety with Mepolizumab in Severe Asthma)[27]— regarding FEV_1, they noted small effects on FEV_1 that generally did not differ significantly from those reported with placebo. In the SIRIUS study[28] at week 24, there was a nonsignificant trend toward greater change with baseline in the FEV_1 before and after bronchodilation in the MP group than in the placebo. In the MENSA study by Ortega et al,[29] there was indeed an increase in FEV_1 of 98 mL, which was greater than in the placebo group. They felt there was a large placebo effect and the increase in FEV_1 was quite modest. Upham et al[4] suggested that a 500-mL

increase would be significant. Finally, in the MUSCA study by Chupp et al[30] found, at week 24, the mean change from baseline in post-bronchodilator FEV_1 between the MP-treated group and the placebo group was nonsignificantly higher, although the data were not shown.

Thus, FEV_1 is of limited value and the $FEF_{25\%-75\%}$ needs to be evaluated in treatment of SEA because it involves SAD. The spirometry value $FEF_{25\%-75\%}$ was significant, as shown by Maglio et al,[16] Sposato et al,[17] Siroux et al,[2] as well as our study, with a 40% median increase in the $FEF_{25\%-75\%}$ with MP.

Eosinophilic asthma

In patients with eosinophilic asthma, eosinophils accumulate within the bronchial tract where they release cytotoxic proteins, lipid mediators, cytokines, and chemokines and significantly contribute to airway inflammation and remodeling.[31] Peripheral blood eosinophils are biomarkers of asthma. The level of eosinophilia frequently characterizes the disease severity and risk for asthma exacerbation, thus, suggesting that this is a participant in these phenotypic characteristics.

Eosinophilic inflammation is closely related to SAD. Small airway dysfunction is highly prevalent in the asthmatic population and occurs across all degrees of severity, particularly in patients with severe disease.[10] Patients with SAD may experience poor disease control with poor response to inhalation therapy[10,15] and may, thus, benefit from anti–IL-5 treatment. Therefore, the assessment of small airways impairment should be an important step in the management of severe asthmatic patients as well as in evaluation response to biologic therapy.

With a new drug, there are always concerns. Mepolizumab was the first anti–IL-5 monoclonal antibody to be approved in 2015. Several reports have discussed the long-term safety, including Agachi et al[32] and Khurana et al,[33] as well as safety and tolerability.[31] Khatri et al[26] showed the long-term safety of MP as well as the durability of the clinical response.

What is interesting is that the 4 major studies that showed that Nucala was excellent for severe eosinophilic asthma, (1) DREAM,[27] (2) SIRIUS,[28] (3) MENSA,[29] and (4) MUSCA[30] looked at FEV_1, but not at $FEF_{25\%-75\%}$.

COLUMBA (Open-Label Long Term Extension Safety Study of Mepolizumab in Asthmatic Subjects) was an open-label extension study in patients with SEA previously enrolled in DREAM. Khatri et al[26] studied 347 patients and demonstrated the long-term durability of this pharmacodynamic effect, that is, the suppression of eosinophils, and provided no evidence of tolerance in MP during long-term treatment. Continuing with Khatri et al's study,[26] as mentioned earlier, the initial improvement in FEV_1 gradually decreased to approximately baseline value at 200 weeks. A possible explanation for this gradual decrease in lung function, even when exacerbations and eosinophil counts remained controlled, is that FEV_1 might not be directly associated with improvement in eosinophilic airway inflammation. This implies that, in patients with severe asthma, there is a disassociation between lung function and risk of exacerbations. The COLUMBA study might have benefitted from looking at $FEF_{25\%-75\%}$ in severe eosinophilic asthma with associated SAD, as mentioned by Lipworth et al as early as 2014.[6] An appropriate $FEF_{25\%-75\%}$ might have shown significant improvement, as in our study. The fact that FEV_1 was unchanged is consistent with our results.

Thus, the impact of MP on small airway obstruction could be explained by its systemic delivery allowing an adequate concentration of the drug at distal sectors of the respiratory tree where eosinophilic inflammation is most prominent. Thus, in the terminal bronchioles, the small airways, the presence of IL-5, the target for MP as mentioned, could explain its significance. Thus, through the blood stream, MP is able to reach the distal airways. An analogy might be ICS, which are unable to reach the distal small airways and prednisone is thus more effective.

Super-responders

In their well-written Rostrum essay on super-responders, Super-responders to biological treatment in type 2 high severe asthma: passing fad or meaningful phenotype?, Portacci et al[34] review the various attempts to define a super-responder and distinguish between super-responder status and remission and determine whether super-responder is actually a true phenotype. It has been determined that up to 91% of asthmatics in the GINA spectrum have evidence of SAD.[10] Thus, the use of FEV_1 by Menzies-Gow et al,[5] Harvey et al,[24] Kavanaugh et al,[35] Eger et al,[36] Sposato et al,[17] and even Upham et al[4] who used FEV_1 as a minor criteria is inconsistent with defining a super-responder. We know conclusively from Abdo et al[37] and Chan et al[38] that monoclonal antibodies are effective in improving SAD in patients with T helper 2–high severe asthma and $FEF_{25\%-75\%}$ seems to improve faster than FEV_1, which again is not related to SAD.

CONCLUSIONS

The significance of our study reveals that the use of MP after $6^1/_2$ years was safe and effective. We found the ACQ-7 revealed significant improvement with MP treatment. There was significant improvement in the $FEF_{25\%-75\%}$, but not in the FEV_1. There were more significant changes in the ACQ-7 and the $FEF_{25\%-75\%}$ with super-responders versus the rest of the cohort. The most significant finding at the end of $6^1/_2$ years of MP treatment was a 40% median increase in the $FEF_{25\%-75\%}$ in the 47 super-responders. Furthermore, if future studies look at severe eosinophilic asthma in SAD, they should look at $FEF_{25\%-75\%}$ instead of FEV_1. This would be a real paradigm shift.

Regarding the strength of our study, we had a high adherence to MP because it was given in the office. There was a monthly assessment clinically with ACQ scores. Physicians examined patients most of the time, allowing for a change in medications, either increasing or decreasing, depending on the clinical status. This may have helped achieve a 70% rate of super-responders. We were able to perform monthly pulmonary function tests. Review of medications allowed verification of adherence.

Limitations were that there were only 2 African-Americans in the study, which reflects the community location of the Cleveland Allergy and Asthma Center. There was no placebo. We found reduction of asthma exacerbations—many of them had been recorded during the coronavirus disease 2019 (COVID-19) epidemic.

We believe, from our study, that following the $FEF_{25\%-75\%}$ would be an important spirometry parameter to help in the care of patients. In conclusion, we have shown, in a real-world study, the efficacy of MP in the care of asthmatics with SEA and SAD to be safe and effective for over $6^1/_2$ years with retaining of FEV_1. As we look at the significant improvement in our super-responders versus other patients, the $FEF_{25\%-75\%}$ should

probably become part of the evaluation of the patient's clinical condition versus the FEV$_1$.

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TABLE E1. Results of all 67 patients in the study

Patient n	Initial ACQ-6	Current ACQ-6	Initial ACQ-7	Current ACQ-7	Initial FEV$_1$	Current FEV$_1$	Initial FEF$_{25\%-75\%}$	Current FEF$_{25\%-75\%}$	Initial eosinophil	Current eosinophil
1	2.57	1.28	2.71	1.71	95	77	95	50	910	183
2	1.71	2	1	2.14	71	81	68	63	192	40
3	0.57	0	0.85	0.428	107	70	83	70	170	50
4	2.5	0	NP	0	NP	104	NP	44	460	100
5	1.14	0.28	1.28	0.71	90	76	91	114	160	26
6	2	0	2.71	0.86	67	48	22	28	320	30
7	1.43	0.71	NP	1.43	NP	53	NP	50	180	0
8	3.14	0.86	3.71	1.43	103	66	45	63	420	50
9	0.42	0	1	0.57	86	65	31	58	150	42
10	0.42	1.57	0.71	2	84	71	38	63	190	90
11	0	2.14	0.42	2.43	NP	77	NP	96	162	60
12	1.29	0.57	1.86	1.14	83	69	28	49	170	19
13	2.57	1.14	3.14	1.71	45	63	26	34	600	50
14	0.71	0.71	1.57	1.57	57	26	12	15	240	60
15	2.57	0.57	3.14	1.43	52	59	23.3	33	400	90
16	0.14	0	0.85	0.57	65	68	44	48	220	40
17	3.28	0.42	4.14	1.43	28	73	15	51	590	78
18	3.28	3	3.57	3.29	93	89	28	85	200	0
19	2.57	1	NP	1.43	NP	76	NP	65	270	0
20	0.28	0.42	NP	1.14	62	51	64	45	220	40
21	1.43	0.57	2.14	1.29	110	56	32	44	370	80
22	2.71	0.28	3.28	0.86	62	63	25	38	660	32
23	1.14	0	1.28	0	93	106	54	112	162	73
24	0.57	0.86	0.57	1.14	95	87	59	68	890	50
25	1.85	0	2.28	0.42	74.2	72	26.5	48	180	60
26	2	1.43	2.43	2	76.8	82	93.9	112	380	58
27	0	0.14	0.428	0.57	74.2	75	56.5	93	1,320	150
28	0.42	0	8	0.428	62	76	71	91	150	0
29	2	1.71	3.14	2.57	19	38	7.9	24	1,010	62
30	2.57	0.85	2.57	1.14	100	86	109	111	469	42
31	3.57	1.42	4	2.14	68	58	44	36	640	0
32	2	0	2.57	0.286	53.9	88	24	171	160	70
33	0.71	0.57	1.42	1.14	48.6	61	32.6	40	620	110
34	1.85	2	2.14	2.85	72	91	69	65	590	NP
35	0	0.14	0.28	0.57	90.9	76	53.7	63	210	60
36	1.71	2.28	NP	2.57	101	87	90.2	113	150	0
37	0.42	0	0.71	0.428	109.7	74	73.6	59	290	30
38	1.57	0.286	2.43	0.57	85.6	85	69.4	78	1,200	90
39	2.43	2	3	2.57	49.7	92	30.9	71	1,690	NP
40	1.85	0.71	2.14	0.86	60.6	90	54.7	132	1,210	50
41	2.28	1	2.71	1.14	79.7	91	108	165	170	11
42	1.14	0.85	1.71	1.14	64.9	83	155.6	99	400	30
43	0.286	0.28	1	1	38	56	17.9	30	690	38
44	1.28	0.14	2	1	51	48	27	22	160	60
45	1.71	1.14	1.85	1.43	95.1	88	75.3	83	150	69
46	1.29	0.14	1.85	0.57	61.5	77	68.8	98	180	77
47	1.85	0.57	2	1	91.5	76	84.5	105	230	54
48	0.71	0.428	1.42	1.28	44.8	45	22.8	25	250	91
49	1.42	1.85	2.14	2.57	99.7	42	57.5	37	170	72
50	1.42	0	1.42	0.286	97.5	90	77.5	93	370	97
51	1.42	0	1.57	0	86.4	99	89.9	134	1,340	68

(continued)

TABLE E1. *(Continued)*

Patient n	Initial ACQ-6	Current ACQ-6	Initial ACQ-7	Current ACQ-7	Initial FEV$_1$	Current FEV$_1$	Initial FEF$_{25\%-75\%}$	Current FEF$_{25\%-75\%}$	Initial eosinophil	Current eosinophil
52	1.42	1.85	1.57	2.14	89.2	88	22.6	54	240	22
53	0	0	0.57	0.57	64.1	64	39.1	58	690	30
54	2.85	0.86	3.42	NP	84.3	64	36.8	43	930	40
55	2.14	1.57	NP	NP	NP	NP	NP	NP	320	80
56	1.42	0	2	0.14	98	62	51	49	320	63
57	3.14	1.71	3.86	2.43	58	59	61	74	200	NP
58	0.85	0.286	1.42	0.57	67.2	85	39.1	71	230	15
59	1.28	0	1.86	0.286	67.6	86	29.9	99	290	40
60	NP	0.428	NP	0.86	75	72	81	68	470	NP
61	1.14	1.28	1.29	1.71	67.2	72	39.1	62	214	NP
62	0.28	0	1	0.428	77.3	72	28.6	40	510	59
63	0.28	0	0.28	0	107.4	105	107.1	90	820	59
64	2.14	0.28	2.57	0.57	71.4	80	39.7	60	580	50
65	2.29	0.28	2.71	0.86	72.4	61	22.8	54	370	38
66	3	0.428	3.85	1.29	49.8	42	28.6	27	170	51.5
67	1.14	1.14	1.85	NP	57	NP	41	NP	150	98
Averages	1.54	0.72	2.09	1.17	74.36	72.49	52.3	68.2	435	54

ACQ-6, Asthma Control Questionnaire; *ACQ-7*, Asthma Control Questionnaire-7; *FEF$_{25\%-75\%}$*, forced expiratory flow at 25% to 75%; *FEV1*, forced expiratory volume in 1 second; *NP*, data no longer available.