

A retrospective analysis of mepolizumab in subjects with aspirin-exacerbated respiratory disease



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Clinical Implications

- This study provides clinical evidence that IL-5 inhibition with mepolizumab improves upper airway symptoms, including anosmia and nasal congestion, and asthma control in subjects with aspirin-exacerbated respiratory disease and severe asthma.

TO THE EDITOR:

Aspirin-exacerbated respiratory disease (AERD) is the triad of chronic rhinosinusitis with nasal polyposis, asthma, and adverse reactions to aspirin and other cyclooxygenase-1 inhibitors. The pathophysiology of AERD involves dysregulated arachidonic acid metabolism and overproduction of cysteinyl leukotrienes, which further increase on exposure to cyclooxygenase-1 inhibitors.¹ Paradoxically, aspirin desensitization improves upper and lower airway symptoms in 67% to 78% of patients with AERD.² However, there are patients with AERD who are in need of additional treatment options because they cannot tolerate aspirin desensitization³ or aspirin therapy,² or do not derive sufficient benefit from aspirin therapy.

The upper and lower respiratory tracts in AERD are characterized by eosinophilic infiltration. Nasal polyps (NPs) from subjects with AERD exhibit 3 times more eosinophils compared with NPs from aspirin-tolerant subjects.⁴ They also contain higher levels of IL-5,⁵ an eosinophil maturation and differentiation factor, and soluble IL-5 receptor alpha.⁶ Bronchial mucosa biopsies demonstrate 3 times more eosinophilic cationic protein compared with aspirin-tolerant patients with asthma, suggesting eosinophilic infiltration of the lower respiratory tract in patients with AERD.⁷ In addition, peripheral eosinophilia greater than 300 cells/ μ L³ is common in AERD. These biologic characteristics suggest that patients with AERD could benefit from anti-IL-5 therapy.

Two randomized, double-blinded trials explored the utility of mepolizumab in recurrent NPs. Two doses of mepolizumab 750 mg intravenous reduced NP size⁸ and 6 monthly doses of mepolizumab 750 mg intravenous reduced the need for NP surgery and improved sino-nasal outcome test (SNOT)-22 scores.⁹ However, these results were not stratified on the basis of aspirin intolerance.

No data exist on the benefit of mepolizumab for asthma or NPs in AERD. We sought to determine the clinical efficacy of mepolizumab on the upper and lower airway symptoms and lung function in subjects with AERD.

Subjects at the Brigham and Women's Hospital AERD Center with AERD who received 3 or more mepolizumab 100-mg subcutaneous doses through May 2017 for the treatment of severe

TABLE 1. Characteristics of patients with AERD started on mepolizumab for severe eosinophilic asthma (at least 3 mepolizumab injections)

Characteristic	Value
Sex: female, n (%)	7 (50)
Age (y), median (IQR)	54 (14.8)
Weight (kg), mean $\pm$ SD	82.3 $\pm$ 16.9
Previous lifetime exposure to tobacco products (>1 pack-year), n (%)	5 (36)
Age of polyp onset (y), mean (IQR)	38.5 (15)
Age of asthma diagnosis (y), mean (IQR)	35 (14)
Number of lifetime polypectomies, mean (IQR)	2.5 (1.8)
Time to polyp regrowth (mo), median (IQR)	3 (16)
Subjects on daily oral glucocorticoids for >6 mo per year, n (%)	7 (50)
Subjects taking high-dose aspirin,* n (%)	9 (64)
AEC, before starting mepolizumab (eosinophils/ μ L), mean $\pm$ SD	842 $\pm$ 485
FEV ₁ (% predicted), before starting mepolizumab, mean $\pm$ SD	63.5 $\pm$ 24.2
Duration on mepolizumab at time of data collection (mo), median (IQR)	5.5 (6)

IQR, Interquartile range.

*High-dose aspirin: either 650 mg daily or 1300 mg daily.

asthma were included. The AERD diagnosis was physician-confirmed by aspirin challenge. This retrospective study was approved by the Partners Healthcare Institutional Review Board.

Data were extracted from the Partners Healthcare electronic medical record (Epic Systems, Verona, Wis). Clinical demographic characteristics, medications, absolute eosinophil count (AEC), SNOT-22 scores, asthma control test (ACT) scores, and FEV₁ were extracted from the medical record at the visit before initiation and after 3 or more doses of mepolizumab. The SNOT-22 is a validated questionnaire quantifying upper respiratory tract symptoms and scores range from 0 to 110, with higher scores indicating greater symptoms. A change of 8.9 or more points represents a minimally important difference.¹⁰ The ACT is an asthma questionnaire with possible scores of 0 to 25, with higher scores indicating better asthma control and a change of 3 points or more representing a minimally important difference.¹¹

All analyses were performed using GraphPad Prism (GraphPad, La Jolla, Calif). Data reported are means $\pm$ SEM unless otherwise noted. Paired *t* test and Wilcoxon signed rank test were used when appropriate for parametric or nonparametric data, respectively. All *P* values are 2-sided, with a *P* value of less than .05 considered statistically significant.

Of the 22 subjects with AERD treated through May 2017, 14 subjects received at least 3 doses of mepolizumab (Table 1). At baseline, subjects reported a mean number of 2.5 lifetime polypectomies, median time to polyp recurrence of 3 months, current (64%) or previous (100%) high-dose aspirin therapy, and mean AEC of 842/ μ L. Fifty percent (7) of the subjects were taking a daily oral glucocorticoid at the time mepolizumab was prescribed.

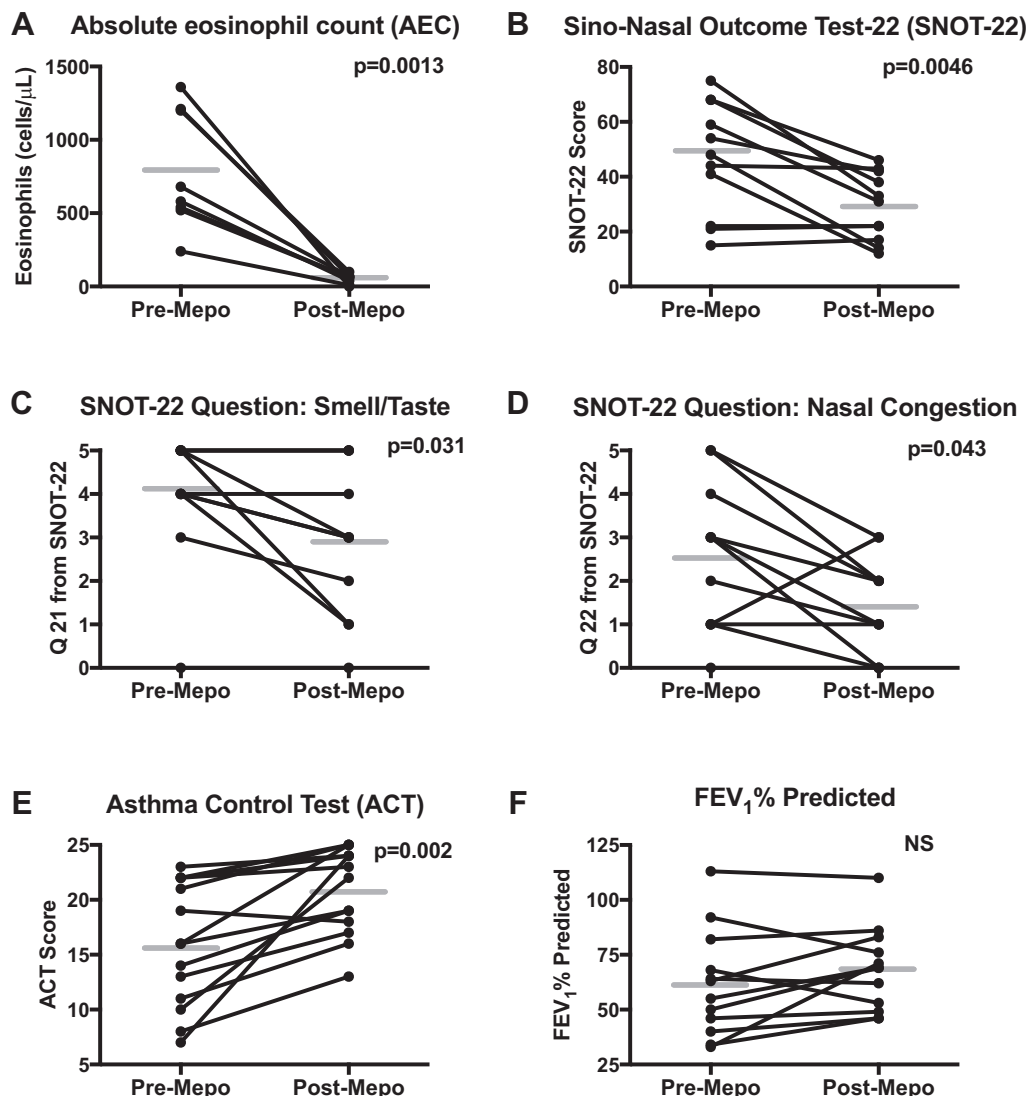


FIGURE 1. Treatment with 3 or more doses of mepolizumab decreased AEC and SNOT-22 scores, whereas ACT scores increased. **A**, AEC and **B**, total SNOT-22 scores, including **C**, symptoms of anosmia (question 21) and **D**, nasal congestion (question 22), declined and **E**, total ACT scores increased on mepolizumab. **F**, No statistically significant change in FEV₁% of predicted. Analysis performed using a paired *t* test (Figure 1, **A**, **B**, and **E**) or a Wilcoxon signed-rank test (Figure 1, **C**, **D**, and **F**). *Mepo*, Mepolizumab. Gray horizontal lines represent group means.

After 3 or more mepolizumab doses (range, 3-11 doses), AEC decreased significantly ($N = 8$; $P < .01$; Figure 1, **A**). SNOT-22 scores decreased by 17.7 points (± 4.9 ; $N = 11$; $P < .01$; Figure 1, **B**), indicating significant improvement in sinonasal symptoms. Anosmia (SNOT-22 question 21, Figure 1, **C**) and nasal congestion (SNOT-22 question 22, Figure 1, **D**) significantly decreased (both $P < .05$) after treatment with mepolizumab. Treatment with mepolizumab significantly increased overall ACT scores by 5.1 (± 1.3 ; $N = 14$; $P = .002$; Figure 1, **E**). There was a trend toward improvement in mean FEV₁% predicted (baseline, $62.9\% \pm 6.3\%$; post mepolizumab, $68.3\% \pm 5.5\%$; $N = 14$; $P = .16$; Figure 1, **F**).

No subjects required sinus surgery, and there were no increases in or initiation of oral glucocorticoids during the study period. Five of the 7 subjects on oral glucocorticoids for greater

than 6 months per year before mepolizumab initiation decreased their daily oral glucocorticoid dose; 2 of these 5 subjects on oral glucocorticoids were also able to reduce their daily inhaled corticosteroid-long-acting beta-agonist dose (data not shown).

Physicians have a small therapeutic arsenal to treat the severe nasal polyposis, sinonasal congestion, and anosmia characteristic of AERD. To our knowledge, this is the first study to specifically examine the role of IL-5 inhibition in a cohort of subjects with AERD. Treatment with mepolizumab, 100 mg subcutaneous every 4 weeks for 3 or more doses, decreased AEC and significantly improved both upper and lower airway symptoms. Specifically, mepolizumab improved subject-reported outcomes of nasal congestion and sense of smell, important quality-of-life measures. The overall SNOT-22 score improved by 17 points, whereas Bachert et al⁹ reported a 13.2-point increase in their

study of mepolizumab in severe NPs, indicating that subjects with AERD may respond better to mepolizumab than aspirin-tolerant subjects with chronic rhinosinusitis with NP.

This retrospective, pragmatic analysis of mepolizumab in AERD has limitations. It is not randomized, blinded, or placebo-controlled and involves subject-reported data. Not all patients with AERD meet criteria for severe asthma, which limits the generalizability of our results to all patients with AERD.

Subjects with AERD treated with mepolizumab for more than 3 months exhibited improvement in nasal congestion, anosmia, and asthma control, providing evidence that AERD represents an endotype of eosinophilic asthma and nasal polyposis responsive to IL-5 inhibition. Double-blinded, controlled studies that screen and report on aspirin intolerance in patients with asthma and recurrent nasal polyposis are necessary to confirm these data, and to properly identify the responder endotype.

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Conflicts of Interest: T. M. Laidlaw has served on scientific advisory boards for GlaxoSmithKline and Allakos and has received consultancy fees from Knopp Biosciences and Sanofi-Genzyme. K. N. Cahill is on the advisory boards of Teva and Optinose. The rest of the authors declare that they have no relevant conflicts of interest.

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