Published in final edited form as:

Ann Allergy Asthma Immunol. 2020 January ; 124(1): 102–104. doi:10.1016/j.anai.2019.09.023.

Poor Control of Asthma Symptoms with interleukin-5 Inhibitors in four Patients with Aspirin-Exacerbated Respiratory Disease

Ryan C Eid, MD¹, Eden Wudneh, MD², Soombal Zahid, DO³, Katherine Cahill, MD⁴, Elina Jerschow, MD, MSc⁵

¹Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts.

²NYC Health + Hospitals, Jacobi Medical Center, New York, New York.

³Lenox Hill Hospital, Northwell Health, New York, New York.

⁴Vanderbilt University Medical Center, Nashville, Tennessee.

⁵Montefiore Medical Center/Albert Einstein College of Medicine, Bronx, New York.

Introduction:

Aspirin-exacerbated respiratory disease (AERD) is a condition of the respiratory tract characterized by rhinosinusitis, asthma, eosinophilia, and respiratory reactions to nonsteroidal anti-inflammatory drugs. The pathophysiology of AERD involves a baseline dysregulation of arachidonic acid metabolism leading to the overproduction of leukotrienes.¹ Leukotrienes are inducers of bronchoconstriction and also attract eosinophils into the airways.² The overproduction of leukotrienes in AERD is further exacerbated by cyclooxygenase-1 inhibitors.¹ Paradoxically, aspirin desensitization improves respiratory symptoms in 67–78% of patients.³ However additional treatments are needed as some patients fail to improve cannot tolerate aspirin.^{3, 4}

The respiratory tract in AERD is characterized by eosinophilic infiltration with nasal polyps and bronchial biopsies demonstrating more eosinophils and higher levels of interleukin-5 (IL-5), than aspirin-tolerant-asthmatics.^{5, 6} IL-5 is an eosinophilic maturation and differentiation factor contributing to tissue and peripheral eosinophilia.⁷ These characteristics suggest that patients with AERD should benefit from therapies that target eosinophilic inflammation.

Mepolizumab, a monoclonal antibody against IL-5, has been shown to decrease asthma exacerbations and blood eosinophilia in patients with asthma.⁸ While IL-5 antagonists are of interest in AERD, data on anti-IL-5 treatment in this group is scarce. To date, only one study has explored the role of mepolizumab in AERD and described improvement of asthma, nasal symptoms and peripheral absolute eosinophil count (AEC) during the first several months of treatment.⁹ Here we describe 4 patients with AERD who were treated with mepolizumab for severe glucocorticoid-dependent asthma and experienced poor asthma control and elevation of AEC months after treatment.

Methods:

Subjects at Brigham and Women's Hospital AERD Center and Montefiore Hospital AERD Center who received mepolizumab for at least 2 months were included. The AERD diagnosis was confirmed by aspirin challenge in all patients. This retrospective study was approved by the Partners healthcare and Montefiore Institutional Review Board. Data was extracted from Partners Healthcare and Montefiore electronic medical record (Epic Systems, Verona, Wisconsin). Data reported are means $\pm$ standard deviation.

Results:

Of the 4 subjects with AERD, 2 (50%) were maintained on aspirin for AERD, while the others could not tolerate aspirin due to side effects. Three (75%) were female, 3 identified as African American (AA) and all were obese. The average age was 46.8 ± 7.7 years. At baseline, AEC ranged from 800 cells/uL to 2800 cells/uL. Average peripheral AEC was 1800 cells/uL and all had poorly controlled glucocorticoid-dependent asthma with 2 (50%) requiring daily oral corticosteroids and 2 (50%) requiring six or more oral corticosteroid bursts per year prior to mepolizumab. The average number of lifetime polypectomies was 2.75 ± 5 and the average FEV1% prior to mepolizumab was 61 ± 19.7 . Mepolizumab was initiated with an oral glucocorticoid burst. Prior to starting mepolizumab all patients were not receiving other biologics. Subject 4 had been on omalizumab which was discontinued 20 months prior to mepolizumab due to the lack of effectiveness. All patients were treated with standard mepolizumab dosage for asthma at 100 mg subcutaneous every 4 weeks and initially had a decrease in AEC and did not require additional steroids (Table-1).

Despite compliance with mepolizumab, all patients developed a rise in AEC with concomitant asthma exacerbations requiring oral glucocorticoids after 3.5 ± 1.3 months of treatment. Sputum eosinophilia, and sino-nasal symptoms were not evaluated in these patients. Patients were treated with mepolizumab for 8.0 ± 4.5 months prior to discontinuation of mepolizumab. All subjects were trialed on alternative biologics but continued to have poor asthma control requiring courses of oral glucocorticoids.

Discussion:

Our study identifies a subset of AERD patients who failed to have a prolonged response to mepolizumab despite an initial decrease in AEC. All subjects developed asthma exacerbations requiring steroids after months of treatment. To date there is only one other study, by Tuttle and colleagues, examining the efficacy of mepolizumab in AERD. Our findings contradict those by Tuttle despite similarity of subjects. Both studies comprised of overweight females with a similar number of lifetime polypectomies (2.75 vs 2.5) and similar FEV1 % predicted prior to starting mepolizumab (61 ± 19.7 vs. 63.5 ± 24.2). In addition, 50% of subjects in both studies were on daily oral glucocorticoids. Subjects in our study were younger, (46.8 ± 7.7 vs 54 ± 14.8) had a higher average AEC prior to starting mepolizumab (1800 vs 842) and were mostly AA. Racial demographic data was not included in the study by Tuttle. While the focus of Tuttle and colleagues was on the sino-nasal symptoms in AERD, they found that subjects with AERD treated with mepolizumab

had decreased AEC without the need for increase of oral glucocorticoids.⁹ At the time of data collection, subjects had been on mepolizumab for an average of 5.5 months.

In contrast, subjects in our studies required oral glucocorticoids months after initiation of mepolizumab. Subjects required multiple courses of oral glucocorticoids and continued to have asthma exacerbations and increases in AEC. All subjects discontinued mepolizumab months after stating the medication. At the time of data collection, subjects had been on mepolizumab for an average of 8 months.

This report has its limitations. It involves a small number of subjects with AERD. In our study, mepolizumab was initiated together with a steroid burst, therefore making it less clear if the initial reduction in AEC was due to mepolizumab alone. In addition, sputum eosinophilia was not measured in these patients.

Nevertheless, our findings are relevant because sparse data exists from clinical practice on the effect of anti-IL-5 pathway biologics in AERD and our findings challenge the conclusion of the only study exploring mepolizumab in AERD. One reason why our findings are different may be the demographics of our subjects. Aspirin desensitization in minority populations have been found to be less successful than in Caucasians.¹⁰ It is possible that minority patients may have a poor response to mepolizumab. Further studies are needed to explore this phenomenon. Lastly, all subjects were trialed on alternative biologics but continued to have poor asthma control requiring glucocorticoids. As biologics become common in clinical practice, it is important for clinicians to recognize the limitations of these medications. Future studies are needed to explore the efficacy of mepolizumab and other biologics in patients with AERD.

References

1. Laidlaw TM, Boyce JA. Aspirin-Exacerbated Respiratory Disease--New Prime Suspects. *N Engl J Med* 2016; 374:484–8. [PubMed: 26840139]
2. Dahlen SE, Hansson G, Hedqvist P, Björck T, Granström E, Dahlen B. Allergen challenge of lung tissue from asthmatics elicits bronchial contraction that correlates with the release of leukotrienes C₄, D₄, and E₄. *Proc Natl Acad Sci U S A* 1983; 80:1712–6. [PubMed: 6300870]
3. Berges-Gimeno MP, Simon RA, Stevenson DD. Long-term treatment with aspirin desensitization in asthmatic patients with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol* 2003; 111:180–6. [PubMed: 12532116]
4. Cahill KN, Bensko JC, Boyce JA, Laidlaw TM. Prostaglandin D₂: a dominant mediator of aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol* 2015; 135:245–52. [PubMed: 25218285]
5. Bachert C, Wagenmann M, Hauser U, Rudack C. IL-5 synthesis is upregulated in human nasal polyp tissue. *J Allergy Clin Immunol* 1997; 99:837–42. [PubMed: 9215253]
6. Cowburn AS, Sladek K, Soja J, Adamek L, Nizankowska E, Szczeklik A, et al. Overexpression of leukotriene C₄ synthase in bronchial biopsies from patients with aspirin-intolerant asthma. *J Clin Invest* 1998; 101:834–46. [PubMed: 9466979]
7. Sanderson CJ. Interleukin-5, eosinophils, and disease. *Blood* 1992; 79:3101–9. [PubMed: 1596561]
8. Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet* 2012; 380:651–9. [PubMed: 22901886]
9. Tuttle KL, Buchheit KM, Laidlaw TM, Cahill KN. A retrospective analysis of mepolizumab in subjects with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol Pract* 2018; 6:1045–7. [PubMed: 29501519]

10. Jerschow E, Pelletier T, Zhen R, Tamayev R, Abuzeid W, Fried M, et al. Unsuccessful Aspirin Desensitization in Minority Patients with AERD: Association with Increased Eosinophilia and Sinus Surgery Timing. *Journal of Allergy and Clinical Immunology* 2016; 137:AB211.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Characteristics of the 4 patients at the time of treatment with mepolizumab and follow-up eosinophil counts

Characteristic	Case 1	Case 2	Case 3	Case 4
Sex	Female	Female	Female	Male
Age (y)	30	52	68	33
Race	White	AA	AA	AA
BMI	50	40	30	38
Lifetime Sinus polypectomy	2	3	3	3
Medications	Aspirin 650mg twice a day Fluticasone/salmeterol 500–50µg twice a day Montelukast 10mg once a day Albuterol prn	Aspirin 650mg twice a day Fluticasone/vilanterol 200–25µg twice a day Montelukast 10mg Daily Albuterol prn	Fluticasone/vilanterol 500–50µg twice a day Albuterol prn	Mometasone/formoterol 200/5µg twice a day Omalizumab 300mg every 4 weeks Albuterol prn
Oral Steroid Use ***	7 prednisone tapers in 12 months prior to initiation with mepolizumab	Prednisone 20 mg daily with 4 prednisone tapers 12 months prior to mepolizumab	8 prednisone tapers in 12 months prior to mepolizumab	Prednisone 20mg daily with 6 prednisone tapers 12 months prior to mepolizumab
Blood eosinophil count prior to mepolizumab (cells/uL)	2800	800	1600	2100
Fev1 (% predicted)	81%	62%	67%	34%
Blood eosinophil count nadir on mepolizumab (cells/uL)	200	0	100	0
Blood eosinophil count peak on mepolizumab (cells/uL)/ number of months until peak AEC and discontinuation of mepolizumab	600 / 8 months	300 / 3 months	300 / 14 months	400 / 7 months
Months until first steroids taper	3	2	5	4
Total number of steroid tapers on mepolizumab	6	1	3	8
Course after mepolizumab failure	Switched to reslizumab, then 7 prednisone tapers	Switched to dupilumab then was lost to follow-up as she moved away from the area	Switched to benralizumab then 4 prednisone tapers in 6 months, applied for dupilumab at the time of manuscript	Switched to benralizumab, then had 2 prednisone tapers in 4 months, while continuing hydrocortisone daily, applied for dupilumab at the time of manuscript
Blood eosinophil count nadir on alternative biologic (cells/uL)	100	0	0	100

AA, African American; BMI, body mass index; prn, as needed.

Prednisone tapers prescribed to these patients were starting at 40 mg, lowering the dose by 10 mg every 3 days, finishing with 5 mg for 3 days, with a total of 15 days