

Subcutaneous Mepolizumab Injection: An Adjunctive Treatment for Recalcitrant Allergic Fungal Rhinosinusitis Patients With Asthma

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Abstract

Background: Allergic Fungal Rhinosinusitis (AFRS) is a non-invasive fungal disease that results from chronic allergic inflammation of the sinonasal mucosa. Failure to respond to mainstay medical therapies and sinus surgery leaves AFRS patients with limited alternatives and a decreased quality of life. Mepolizumab is a known IL-5 antagonist for patients with severe eosinophilic asthma.

Objective: To identify the efficacy of mepolizumab on improving Modified Lund-Kennedy (MLK) endoscopic scores in recalcitrant AFRS patients with asthma.

Methods: Retrospective chart review of 27 recalcitrant AFRS patients with asthma receiving a monthly mepolizumab injection between January 2017 and July 2019. Patients were evaluated endoscopically at baseline and at each follow-up visit every 6–8 weeks until their third visit. Secondary outcomes included SNOT-22 scores, serum eosinophil counts and the rate of prednisone rescues required in patients receiving mepolizumab compared to a retrospective control arm.

Results: Total median MLK scores improved significantly for all patients over three follow-up visits (6[4,7], 4[2,6], 5[2,6], 3.5[2.25,5]; $p = 0.04$). Amongst patients with a baseline polyposis score of 1 or more, combined MLK edema and polyposis subscores significantly improved (6[5.25,6], 3.5[2.25,5.75], 4[2.75,5.25], 4[3,4]; $p = 0.02$) versus patients with no polyposis (4[3,4], 3[1,4], 4[2,4], 3[0,4]; $p = 0.90$). Total SNOT-22 scores (56 vs 43; $p = 0.04$) and eosinophil counts ($0.40 \times 10^9/L$ vs $0.00 \times 10^9/L$; $p < 0.01$) decreased significantly when comparing baseline to last follow up. There was no significant difference in rate of prednisone rescues per 1000 person-days when comparing control to Mepolizumab population (1.19 vs 1.23; $p = 1$).

Conclusion: Mepolizumab injections administered once monthly as an adjunctive treatment for recalcitrant AFRS patients with asthma appear to significantly reduce endoscopic signs of inflammation, patient-reported symptomatology and serum eosinophil levels. Patients with evidence of more severe endoscopic inflammation appear to benefit the most. Adjunctive treatment with mepolizumab does not reduce the need for prednisone rescues.

Keywords

mepolizumab, nucala, allergic fungal rhinosinusitis, asthma, recalcitrant, anti-IL-5, MLK, SNOT-22, eosinophils, prednisone rescue

Introduction

Chronic rhinosinusitis (CRS) is an inflammatory disease of the sinonasal passage.¹ Allergic fungal rhinosinusitis (AFRS) is a subtype of CRS that accounts for 5–10% of CRS cases, involving a fungal-derived allergy-mediated

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type 2 inflammatory response.² Asthma is seen in approximately 25% of AFRS patients.^{3,4}

AFRS, diagnosed using Brent and Kuhn's criteria, may present as a failure to respond to bacterial rhinosinusitis treatments, with onset occurring in younger individuals (mean of 22 years of age), immunocompetency, asymmetrically affected sinuses and a lack of severe pain symptoms.^{5,6} AFRS patients exhibit elevated total serum IgE, IL-4 and IL-5 responses, a higher prevalence of CD8+ T cells, elevated serum IgE levels and evidence of local bone erosion.⁵⁻⁷

The treatment for AFRS involves minimizing inflammation and restoring aeration to the sinonasal mucosa.⁸ Mainstay approaches include endoscopic sinus surgery followed by topical steroids.^{1,5,6,9,10} Antifungals such as Itraconazole have mixed evidence to support their use.⁶ Failure to respond to interventions leads to recalcitrance, whereby patients are left with few therapeutic options.

Mepolizumab (Nucala) is a humanized IgG1 monoclonal antibody that acts as an interleukin-5 (IL-5) antagonist.^{11,12} It has shown great efficacy as an adjunctive therapy for severe asthma, reducing tissue eosinophil levels and thus airway inflammation and exacerbations.^{13,14} IL-5 is a key mediator in the activation of eosinophils. It has therefore been theorized that mepolizumab may be beneficial in the treatment of CRS with nasal polyps (CRSwNP). Mepolizumab has also shown significant efficacy in the reduction of Sinonasal Outcome Test (SNOT-22) scores for patients with aspirin-exacerbated respiratory disease (AERD).¹⁵ Additionally, total endoscopic sinonasal scores have improved when asthmatic patients with recurrent CRSwNP used mepolizumab.¹⁶

As no prior study has examined the impact of mepolizumab in recalcitrant AFRS patients who have concomitant severe eosinophilic asthma, this work aimed to primarily determine the effect of mepolizumab on Modified Lund-Kennedy (MLK) endoscopic scores in this patient population.

Methods

Ethical Considerations

A retrospective chart review was conducted with approval from the Providence Health Care Research Ethics Board (H19-01727).

Patient Population

Patients were included in this retrospective chart review if they were nineteen years of age or older, diagnosed with recalcitrant AFRS as defined by Bent and Kuhn criteria, demonstrated endoscopic evidence of edema or

polyposis, greater than 3 months post-functional endoscopic sinus surgery (FESS), and diagnosed with co-existing asthma by a pulmonologist.^{5,6} Recalcitrance was defined as failure to respond to standard treatment consisting of topical steroids via sinus rinses or mucosal atomization device (MAD), systemic steroids, antifungals, and did not improve or deteriorated within three months of FESS. This post-surgical time point defining recalcitrance was derived from evidence that suggests improvement in quality of life can be expected to occur within the first three months post-operatively.^{17,18}

Patients were excluded if they were diagnosed with a known autoimmune disorder, immunocompromised, diagnosed with a sinonasal tumor, or pregnant or breast-feeding.

Treatment and Study Outcomes

Patients received the recommended 100mg/mL subcutaneous injection of mepolizumab once monthly in addition to ongoing AFRS treatment including steroids, nasal rinses or other therapeutics.¹² Mepolizumab was prescribed to patients and administered by their pulmonologist as an adjunctive asthma treatment.

The primary outcome was to determine the change in MLK scores upon the addition of mepolizumab to patients' therapy. MLK scores have shown to correspond with SNOT-22 scores, a validated questionnaire that subjectively quantifies the severity of patients' sinus symptoms and impact of the disease on quality of life, thereby validating its use in research as an outcome measure in CRS.^{19,20} Retrospective MLK endoscopic scores were collated from baseline and follow-up visits spaced 6-8 weeks apart. Collection of data was stopped at the third follow-up visit due to a reduction in sample size thereafter, earlier if a patient underwent sinus surgery during the study period or if patients had less than 3 follow-up visits.

Secondary outcomes included changes to SNOT-22 scores and serum eosinophil counts over time. SNOT-22 scores and serum eosinophil levels were collected at baseline and for one follow-up visit thereafter corresponding to when data was available. SNOT-22 scores were further analyzed based on disease specific (question #1-10 and #22) and quality of life (question #11-21) sub-scores.²⁰

Finally, we compared the rate of prednisone rescues required for worsening AFRS sinonasal symptoms amongst mepolizumab patients versus patients in a retrospectively generated control arm over 74 days. All patients were matched for recalcitrant AFRS with asthma as per the stated inclusion criteria, as well as gender.²¹ The time period of 74 days corresponded to the longest follow-up time for which data was available for all patients in the mepolizumab arm. The rescue rate

was calculated in person-time, represented per 1000 person days, upon dividing the number of cases requiring prednisone rescue by the sum of days each patient contributed to the 74-day follow-up. The control arm was not used to compare any other outcome measure.

Statistical Analysis

Clinical data was collected from baseline to the third follow-up visit. Continuous explanatory variables following a normal distribution were described using parametric tests. Non-parametric tests were used otherwise. Categorical explanatory variables were summarized by count. The Friedman rank-sum test was used to compare MLK scores between baseline and follow-up visits. Secondary outcomes were analyzed using paired Wilcoxon signed rank tests with each patient serving as their own control. Results were considered statistically significant with $p < 0.05$. Given the overall significance found in the Friedman rank-sum test, a post-hoc multiple comparison analysis of MLK scores was conducted using paired Wilcoxon signed rank tests. A new significance level of $p < 0.008$ was defined accordingly (p of 0.05 divided by 6 different comparisons required) using the Bonferroni adjustment. An unpaired Wilcoxon signed-rank test was employed to compare the rates of prednisone rescues between both arms. All statistical analyses were performed using RStudio version 3.4.1 (RStudio, Boston, MA, USA).

Results

A total of 27 patients were included in this study, demographics from whom are summarized in Table 1. Two patients underwent sinus surgery during the study period resulting in cessation of their data collection, and 3 patients had fewer than 3 follow-up visits.

MLK Analysis

A significant improvement was found in the total MLK score change over 3 visits from baseline to the end of follow-up (6[4,7], 4[2,6], 5[2,6], 3.5[2.25,5]; $p = 0.04$) (Figure 1). Post-hoc analysis revealed a trend towards significant reductions between baseline and each follow-up visit. However, upon correcting for multiple comparisons, no post-hoc significance was found.

To ascertain whether the MLK score changes could be predicted by the baseline severity of sinonasal inflammation, patients were stratified into 2 groups. Amongst patients with a polyposis sub-score of 1 or more at baseline, combined edema and polyposis MLK scores significantly improved over the 3 follow-up visits (6[5.25,6], 3.5[2.25,5.75], 4[2.75,5.25], 4[3,4]; $p = 0.02$), whereas patients with no polyposis at baseline showed a

Table 1. Patient Demographic Data.

Characteristics	Result
Mean age (SD)	57 (11)
Median total baseline MLK score (IQR)	6 (4,7)
Co-morbidities	
Hyper eosinophilia	2 (7.4%)
COPD	1 (3.7%)
Bronchiectasis	1 (3.7%)
Eustachian tube dysfunction	1 (3.7%)
Last sinus surgery prior to commencing mepolizumab	
Within 1 year	6 (22.2%)
Over 1 year	21 (77.8%)
Total prior surgeries	
1 surgery	19 (70.3%)
2 or more surgeries	8 (29.6%)
Concurrent medication	
Intranasal corticosteroid (pulmicort)	24 (88.9%)
0.08% topical betadine	14 (51.9%)
Montelukast	14 (51.9%)
Bronchodilator $\pm$ inhaled corticosteroid	8 (29.6%)
Saline rinse	8 (29.6%)
Oral antifungal (sporanox)	7 (25.9%)
Oral corticosteroid (prednisone)	6 (22.2%)
Culture-directed antibiotic	4 (14.8%)
Antihistamine	2 (7.4%)
Omalizumab	1 (3.7%)
Manuka honey	1 (3.7%)
Topical antifungal	21 (3.7%)

Abbreviations: COPD, chronic obstructive pulmonary disease; IQR, inter-quartile range; MLK, modified Lund-Kennedy; SD, standard deviation.

non-significant change to their edematous process (4[3,4], 3[1,4], 4[2,4], 3[0,4]; $p = 0.90$) (Figure 1).

SNOT-22 Analysis

Total SNOT-22 scores alongside disease-specific and quality of life sub-scores between baseline and a final follow-up visit were compared amongst 15 patients from whom SNOT-22 data was available (Figure 2). Total SNOT-22 scores (56 vs 43; $p = 0.04$) as well as disease-specific sub-scores (34 vs 17; $p < 0.01$) decreased significantly, equating to a MCID of 1.46 in the total score reduction (one MCID = 8.9 points).²⁰ The change in quality of life SNOT-22 sub-score was non-significant (22 vs 22; $p = 0.25$).

Serum Eosinophils Count

Amongst 15 patients from whom data was available, serum eosinophil levels decreased significantly between the baseline visit and a subsequent follow-up visit ($0.40 \times 10^9/\text{L}$ vs $0.00 \times 10^9/\text{L}$; $p < 0.01$) (Figure 3).

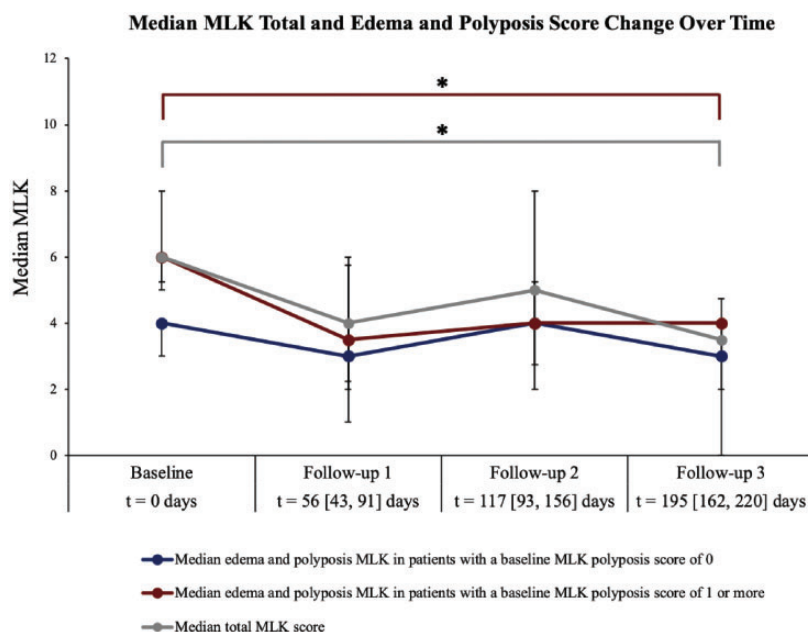


Figure 1. Median total MLK score changes between baseline and follow-up visits (baseline $n = 27$, final follow-up $n = 22$, $*p = 0.04$) (grey). Comparison of combined median MLK edema and polyposis subscores between patients with a baseline MLK polyposis score of 1 or more (baseline $n = 10$, final follow-up $n = 7$, $*p = 0.02$) (red) and patients with a baseline MLK polyposis score of 0 (baseline $n = 17$, final follow-up $n = 15$, $p = 0.90$) (blue). Time displayed in median days from baseline with interquartile range. Error bars indicate interquartile range.

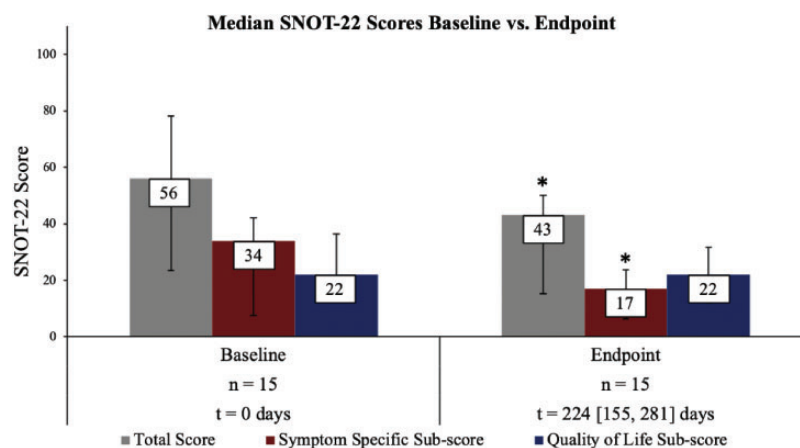


Figure 2. Median total SNOT-22 change ($*p = 0.04$), alongside symptom-specific ($*p < 0.01$) and quality of life ($p = 0.25$) sub-score changes between baseline and endpoint. Time displayed in median days from baseline with interquartile range. Error bars indicate interquartile range.

Prednisone Rescue

Of the 27 included patients, 4 in the mepolizumab arm were already receiving prednisone and were thus excluded from the comparison. The incidence of prednisone rescues required for sinonasal AFRS exacerbations over 74 days was compared between the mepolizumab arm ($n = 23$) and the control arm ($n = 23$). The rate of prednisone rescues (per 1000 person-days) within the mepolizumab arm was 1.23 compared to 1.19 within the control group ($p = 1$).

Discussion

The discovery of AFRS being a clinically distinct entity has led to controversy regarding effective management for this disease.¹ Surgical intervention followed by a limited range of evidence-based medical therapies is the current proposed management regime. However, disease recurrence rates range from 10–100%.⁹ For this reason, an effective adjunctive treatment is still required for the management of recalcitrant AFRS.

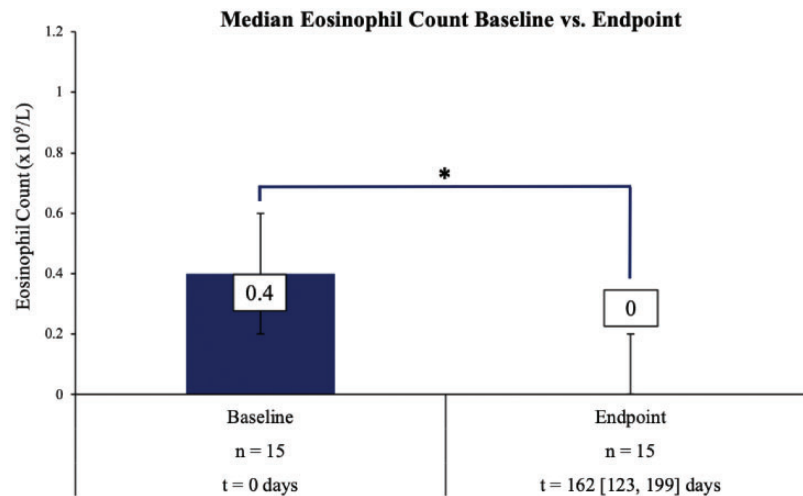


Figure 3. Median serum eosinophil counts change between baseline and endpoint (* $p < 0.01$). Time displayed in median days from baseline with interquartile range. Error bars indicate interquartile range.

Mepolizumab is currently prescribed as an adjunctive treatment for patients with severe eosinophilic asthma.¹² It is administered subcutaneously as a 100mg/mL dose every four weeks.¹² Mepolizumab has a high dissociation constant for cytokine IL-5, which is released by T_H2 cells for the activation and maturation of eosinophils responsible for inflammation. Binding of mepolizumab to IL-5 prevents its critical role, thereby reducing inflammation.^{13,16} Asthma, CRSwNP and AFRS are all mediated by this type-2 inflammatory response, providing a rationale for the use of mepolizumab as a novel treatment in AFRS.^{2,9}

Three randomized double-blind placebo-controlled studies have demonstrated the efficacy and safety of mepolizumab for severe eosinophilic asthma.^{12,22–25} In these studies, patients received either subcutaneous or intravenous injections of mepolizumab once every four weeks as an adjunctive treatment to their standard asthma medication. Compared to control groups, mepolizumab significantly reduced the number of asthma exacerbations. Side effects reported include headaches, injection site reaction, back pain and arthralgias.

No studies to our knowledge have examined the impact of mepolizumab in the AFRS subgroup of patients. Given the promising and safe solution offered by this biologic therapeutic agent in eosinophilic asthma, we aimed to investigate the role of mepolizumab as a potential adjunctive treatment for recalcitrant AFRS patients with asthma.

In this study, 27 recalcitrant AFRS patients with asthma were retrospectively examined to determine the effect of mepolizumab on MLK endoscopic scores. The results indicated a significant improvement in total median MLK endoscopic scores between baseline and the final follow-up visit. This is akin to a median of 6

doses of mepolizumab (IQR range of 5 to 7 doses). Post-hoc analysis concluded that there was a significant trend towards improvement between baseline to follow-up 1, baseline to follow-up 2, and baseline to follow-up 3. However, upon correcting for the multiple analyses, this trend was found to be non-significant, likely due to this study's small sample size limiting the detection of significance after multiple comparisons. Nevertheless, the results of this study correlate with previous research conducted by our group that determined omalizumab, an anti-IgE biologic, reduced MLK endoscopic scores, improved SNOT-22 scores and reduced the need for corticosteroid treatment in AFRS patients.²⁶

Given the significant improvement of total MLK endoscopic scores, further analyses were carried out to determine whether the severity of edematous disease correlated with MLK changes. In contrast to patients with no endoscopic evidence of polyposis at baseline, patients with a baseline MLK polyposis score of 1 or more exhibited a significant improvement in combined median edema and polyposis sub-scores. While an overall improvement was observed in the total MLK score as well as edema and polyposis combined subscore, we observed an increase in MLK between follow up 1 and follow up 2. This observation can be attributed to the fluctuation in mucosal edema that occurs easily with environmental fungal exposure as seen in follow-up 2 and 3 in Figure 1. Even in this very recalcitrant group, despite the natural ebbs and flows, a significant decreasing trend in edema and polyposis is seen between baseline and follow-up 3 for the most inflamed group as well as for the total MLK score. This suggests that, similar to the efficacy in severe eosinophilic asthma, mepolizumab may also be most beneficial to recalcitrant AFRS patients with a more severe edematous disease process.

These findings are comparable to previous studies that also demonstrate how biologics effectively improve sinonasal inflammation in AFRS.

One study concluded that mepolizumab significantly reduced nasal polyp size and volume after two doses, as determined by endoscopic and CT radiographic findings.²⁷ Another study determined that omalizumab decreased endoscopic nasal polyp scores in patients with CRSwNP.²⁸ Given the promising findings in this study, future work further investigating both nasal polyp size and endoscopic polyposis scores should be conducted to examine the role of mepolizumab in reducing severe edema in recalcitrant AFRS.

Amongst 15 patients, total median SNOT-22 scores and symptom specific sub-scores decreased significantly, whereas no significant change was observed in the quality of life symptom sub-score. It is difficult to determine why the SNOT-22 quality of life subscore did not change between the baseline and endpoint, especially when the total scores and symptom specific scores decreased significantly. Given the complexity of AFRS, these patients may have many underlying issues that likely play a role in their overall quality of life. These findings suggest mepolizumab may be beneficial at improving subjective sinonasal symptoms associated with AFRS rather than overall quality of life. In contrast, our research group has previously determined that omalizumab improved both quality of life and disease-specific symptom scores in patients suffering from CRSwNP and AFRS.^{26,28} Accordingly, larger prospective trials are required to validate the effects of mepolizumab on these SNOT-22 sub-score changes amongst AFRS patients.

Analysis of the change in median serum eosinophil counts revealed a significant decrease between baseline and endpoint. Similarly, one study previously determined that amongst asthmatics with nasal polyps, blood eosinophils and serum IL-5 were significantly reduced by the eighth week in patients receiving mepolizumab in comparison to a placebo group.²⁷ Reslizumab, another IL-5 antagonist, was found to significantly decrease eosinophil counts in both serum and nasal secretions within 8 weeks of initiation.²⁹ Our results, supported by the literature, suggests that mepolizumab offers an effective solution at reducing serum eosinophil levels in recalcitrant AFRS patients with asthma.

Finally, a non-significant difference of 0.04 prednisone rescues per 1000 person-days were required for the mepolizumab group compared to the control group. All the prednisone rescues required in both groups were for sinonasal exacerbation as opposed to lower airway exacerbation. At our clinic, prednisone is routinely used as a rescue therapy for individuals exhibiting significantly worse sinonasal symptoms. Our results altogether suggest that adjunctive mepolizumab treatment did not cause any worsening of sinonasal

symptoms compared to the control group who did not use mepolizumab. On the other hand, an alternate study has demonstrated that after twenty-four weeks, mepolizumab does in fact significantly reduce the dose of oral corticosteroid therapy required in patients with eosinophilic asthma.²⁵ Thus, additional long-term analyses are required to further determine the effectiveness of mepolizumab at reducing corticosteroid rescue therapy in AFRS patients with asthma.

While this retrospective chart review is the first to capture the effects of mepolizumab on recalcitrant AFRS patients, a few limitations could be considered. While our study represents a 'real-life' setting, the unique effect of mepolizumab may be masked by the confounding effects of concurrent therapies, with an overarching lack of postoperative treatment standardization given the retrospective nature. In spite of this, it is important to recognize that these patients are recalcitrant and thus have not previously responded to aggressive evidence-based treatment options. It could therefore be conceded that our results likely stem from the added effects of mepolizumab. Further linear regression models to elucidate the effect of concurrent modifications as a predictor of MLK score changes with larger predictor variable sample sizes are indicated. This study is also limited by the lack of blinding and a control group for all outcome measures, thereby introducing the potential for selection bias. Moreover, the small sample size, largely due to the lack of recalcitrant AFRS patients with severe eosinophilic asthma at our centre being treated with mepolizumab, limits the statistical analysis of the presented outcomes. Furthermore, as the mepolizumab injections were administered outside of our center by the patients' pulmonologist, the baseline and follow up dates for the data presented do not coincide with the mepolizumab injection date. A margin of one month prior to and post mepolizumab injection was thus implemented to include more patients. Finally, not all patients completed SNOT-22 questionnaires at each follow-up or received complete blood counts as these metrics were not previously included in regular visit measurements. This data would have further validated the trends in improvement observed in this study. Future prospective, larger scaled blinded studies are thus indicated to address the limitations of our work. Nonetheless, the observed outcomes could still be associated with the known anti-eosinophilic effects of mepolizumab, providing insight into the potential value of mepolizumab injections as an adjunctive agent to manage patients with recalcitrant AFRS and asthma.

Conclusion

The use of mepolizumab as an adjunctive treatment for asthmatics with recalcitrant AFRS appears to provide a

significant improvement in total MLK endoscopic scores, SNOT-22 scores and in serum eosinophil counts. Patients suffering from worse endoscopic inflammation at baseline could experience the greatest benefit. Mepolizumab may not reduce the need for prednisone rescues. Future studies are required to validate these results.

Authors' Note

Presented on September 14th, 2019 at the American Rhinologic Society 65th Annual Meeting.

Acknowledgments

The authors would like to thank Sumaiya Muathen and Laura Samson for their contributions.

Authors' Contribution

JK: Study design, data collection, statistical and data analysis, manuscript preparation

ID: Data collection, statistical and data analysis, manuscript review

RP: Statistical and data analysis, manuscript review

ARJ (Primary investigator): Concept, study design, manuscript review.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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References

1. Hamilos D. Chronic rhinosinusitis: epidemiology and medical management. *J Allergy Clin Immunol.* 2011; 128(4):693–707.
2. Hamilos DL. Allergic fungal rhinitis and rhinosinusitis. *Proc Am Thorac Soc.* 2010;7:245–252.
3. Bachert C, Akdis C. Phenotypes and emerging endotypes of chronic rhinosinusitis. *J Allergy Clin Immunol.* 2016;4(4):621–628.
4. Promsopa C, Kansara S, Citardi MJ, Fakhri S, Porter P, Luong A. Prevalence of confirmed asthma varies in chronic rhinosinusitis subtypes. *Int Forum Allergy Rhinol.* 2016;6:373–377.
5. Glass D, Amedee RG. Allergic fungal rhinosinusitis: a review. *Ochsner J.* 2011;11:271–275.
6. Tyler MA, Luong AU. Current understanding of allergic fungal rhinosinusitis. *World J Otorhinolaryngol Head Neck Surg.* 2018;4:179–185.
7. Luong A, Davis LS, Marple BF. Peripheral blood mononuclear cells from allergic fungal rhinosinusitis adults express a Th2 cytokine response to fungal antigens. *Am J Rhinol Allergy.* 2009;23(3):281–287.
8. Zhang Z, Han D, Zhang S, et al. Biofilms and mucosal healing in postsurgical patients with chronic rhinosinusitis. *Am J Rhinol Allergy.* 2009;23(5):506–511.
9. Hoyt A, Borish L, Gurrola J, Payne S. Allergic fungal rhinosinusitis. *J Allergy Clin Immunol.* 2016;4(4):599–604.
10. Kramer M, Rasp G. Nasal polyposis: eosinophils and interleukin-5. *Allergy.* 1999;54(7):669–680.
11. Avdeeva K, Fokkens W. Precision medicine in chronic rhinosinusitis with nasal polyps. *Curr Allergy Asthma Rep.* 2018;18(4):25.
12. Nucala-GSK Canada. GSK Inc [Internet]. <https://ca.gsk.com/media/1209435/nucala.pdf>. Published 2016. Accessed August 05, 2020.
13. Dennis S, Lam K, Luong A. A review of classification schemes for chronic rhinosinusitis with nasal polyposis endotypes. *Laryngoscope Invest Otolaryngol.* 2016;1(5):130–134.
14. Wang E, Barberis N, Katial R. Chapter 3 – Management of Severe Asthma in Adults. In: Szeffler SJ, Holguin F, Wechsler M, editors. *Personalizing Asthma Management for the Clinician.* Elsevier; 2018. p. 19–32.
15. Tuttle KL, Buchheit KM, Schneider T, et al. A pragmatic analysis of mepolizumab in patients with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol.* 2018;141:AB168.
16. Bachert C, Sousa AR, Lund VJ, et al. Reduced need for surgery in severe nasal polyposis with mepolizumab: randomized trial. *J Allergy Clin Immunol.* 2017;140:1024.e14–1031.e14.
17. Lind H, Joergensen G, Lange B, Svendstrup F, Kjeldsen A. Efficacy of ESS in chronic rhinosinusitis with and without nasal polyposis: a Danish cohort study. *Eur Archiv Otorhinolaryngol.* 2015;273(4):911–919.
18. Hopkins C, Slack R, Lund V, Brown P, Copley L, Browne J. Long-term outcomes from the English national comparative audit of surgery for nasal polyposis and chronic rhinosinusitis. *Laryngoscope.* 2009;119(12):2459–2465.
19. Psaltis AJ, Li G, Vaezaefshar R, Cho KS, Hwang PH. Modification of the Lund-Kennedy endoscopic scoring system improves its reliability and correlation with patient-reported outcome measures: modified Lund-Kennedy endoscopic scoring. *Laryngoscope.* 2014;124(10):2216–2223.
20. Hopkins C, Gillett S, Slack R, Lund VJ, Browne JP. Psychometric validity of the 22-item sinonasal outcome test. *Clin Otolaryngol.* 2009;34(5):447–454.
21. Wise SK, Ghegan MD, Gorham E, Schlosser RJ. Socioeconomic factors in the diagnosis of allergic fungal rhinosinusitis. *Otolaryngol Head Neck Surg.* 2008;138(1):38–42.
22. Fala L. Nucala (mepolizumab): first IL-5 antagonist monoclonal antibody FDA approved for maintenance

- treatment of patients with severe asthma. *Am Health Drug Benefits* 2016;9:106–110.
23. Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet*. 2012;380(9842):651–659.
24. Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med*. 2014;371:1198–1207.
25. Bel EH, Wenzel SE, Thompson PJ, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med*. 2014;371(13):1189–1197.
26. Gan EC, Habib ARR, Rajwani A, Javer AR. Omalizumab therapy for refractory allergic fungal rhinosinusitis patients with moderate or severe asthma. *Am J Otolaryngol*. 2015;36(5):672–677.
27. Gevaert P, Van Bruaene N, Blomme K, et al. Mepolizumab, a humanised anti-IL-5 monoclonal antibody, as treatment of severe nasal polyposis. *J Allergy Clin Immunol*. 2008;121(3):797.
28. Gevaert P, Calus L, Van Zele T, et al. Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma. *J Allergy Clin Immunol*. 2013;131(1):110.e1–116.e1.
29. Gevaert P, Landloldolt D, Lackner A, et al. Nasal IL-5 levels determine the response to anti-IL-5 treatment in patients with nasal polyps. *J Allergy Clin Immunol*. 2006;118(5):1133–1141.