

Evaluation of Asthma Control in Patients with and without Sinonasal Polyps following Treatment with Biologic Agents

Prachi Patel, BA, Chandala Chitguppi, MD, Alan Gandler, MD, Kira Murphy, MD, Tawfiq Khoury, MD, Stephanie Bork, CRNP, Pamela Monostra, PA, Elina Toskala, MD, PhD, Mindy Rabinowitz, MD, Marc Rosen, MD, Gurston Nyquist, MD, Jessica Most, MD

Short Title: Implications of Biologic Therapy on Asthma Control in Patients with Sinonasal Polyps

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ABSTRACT

Background: The effects of biologics on severe asthmatics with chronic rhinosinusitis with sinonasal polyposis (CRSwNP) have not been well established. This study evaluates overall control of asthma in patients with and without sinonasal polyps following initiation of biologics therapy.

Methods: Retrospective review of patients with asthma treated with a biologic agent (benralizumab, omalizumab, dupilumab, mepolizumab) and CRSwNP. Charts were assessed for ACT scores at time of biologic enrollment and at 4-7 months.

Results: 82 patients met inclusion criteria; 42 (52.5%) patients with asthma and 40 (47.5%) with concurrent sinonasal polyps. The average ACT score for the non-polyp cohort was 13.16 + 4.12 at baseline, and 16.45 + 4.79 at long term follow-up; 15.85 + 3.13 and 20.19 + 1.68 in patients with polyps at both time points respectively. Patients with polyps had better control of their asthma at baseline ($p=0.001$), however both cohorts had overall poor baseline asthma control ($ACT < 19$). Patients with polyps continued to have significantly better overall control of their asthma at long term follow up ($p < 0.001$) and, on average, were able to achieve sustained asthma control (mean ACT = 20.19), after initiation of biologic therapy.

Conclusions: Patients with and without sinonasal polyps who begin biologic therapy are shown to have significant improvements in their ACT score at follow-up. In addition, patients with polyps are shown to have significantly better control of their asthma while on biologics than patients with no polyps. Comorbid CRSwNP may predict response to biologic therapy in those with severe asthma (SA).

INTRODUCTION

Asthma is a common condition affecting 25 million people in the US including 6 million children. It accounts for nearly 1.8 million emergency room visits per year and 13.8 million missed school days per year. Despite many pharmacologic advances in the past two decades, over 45 percent of asthmatics reported an asthma attack in the past year.¹ Furthermore, 5-20 percent of asthmatics are considered to be refractory despite adequate maintenance inhaled therapy with frequent exacerbations and poor symptom control.²

The complex biologic mechanism of airway inflammation associated with asthma has been elucidated over the last 30 years. This has led to a revolution of pharmacologic targets and the recognition of several biomarkers that have allowed for a more personalized approach to asthma. Up to 70% of patients with asthma have evidence of type 2 inflammation, which can be modulated by biologic therapies³. These biologic therapies include antibodies against immunoglobulin E, interleukin (IL)-5, the IL-5 receptor, IL-13, and IL-4. Unfortunately, many of these therapies have overlapping clinical criteria for use, and to date there is not a standardized approach to choosing biologics.

Many patients with severe asthma (SA) have other comorbid conditions including sinonasal polyps, allergic rhinitis, and chronic idiopathic urticaria. Since some of these biologic agents have been shown to have efficacy in these other disease states, they may serve to identify patients who would benefit from a particular agent. We aim to evaluate whether having sinonasal polyps in severe asthma predicted response to biologic therapy.

METHODOLOGY

Case Selection

All patients with asthma and sinonasal polyposis who underwent therapy with a biologic agent were evaluated in a retrospective manner from 2017 to 2019. A cohort of patients with asthma without sinonasal polyps were also evaluated for comparative analysis. The biologic therapies investigated in this study were omalizumab, mepolizumab, benralizumab, and dupilumab. It is important to note that each of these therapies has a different mechanism of action, but all are approved for patients with severe asthma that is driven by type 2 inflammation. Chart abstraction included asthma control test (ACT) scores, forced expiratory volume at one second (FEV1) pre and post therapy, demographic data, comorbid conditions, fractional exhaled nitric oxide (FENO), absolute eosinophils, respiratory related complications, and progression of symptoms from initial presentation. The ACT is a validated measure for asthma control with a score of >19 considered well-controlled. This along with FEV1 was followed to determine treatment success. Patients with incomplete records, inconsistent data and absence of definitive diagnosis for either asthma or sinonasal polyposis were grounds for exclusion.

Statistical Analysis

Patients with a physician diagnosis of asthma, were divided into two subgroups – those with and without sinonasal polyposis on endoscopic examination by an otolaryngologist. Descriptive statistics (mean, median, standard deviation and confidence intervals (CI)) were calculated wherever relevant to summarize overall patient characteristics and outcomes. Statistical t test (compare continuous variables) and Fisher exact test (compare categorical variables) were used to compare asthma control and complication rates between the two subgroups. Further statistical analysis was done to identify patient, polyp and treatment related variables associated with control of asthma on biologics therapy. A two-tailed *P* value of 0.05 was considered statistically significant and all limits reported are provided for 95% confidence intervals. Institutional review board approval was obtained from Thomas Jefferson University Hospital.

RESULTS

Overall patient characteristics

A total of 82 patients met inclusion criteria with a diagnosis of moderate to severe asthma receiving treatment with an approved biologic agent: omalizumab, mepolizumab, benralizumab, dupilumab. Forty (47.5%) patients from this cohort suffered from concurrent sinonasal polyposis. For patients with asthma without sinonasal polyps (n=42), five were managed with omalizumab, fourteen with

mepolizumab, nineteen with benralizumab, and four with dupilumab. Likewise, for patients with concurrent sinonasal polyps, three were managed with omalizumab, ten with mepolizumab, twenty four with benralizumab, and three with dupilumab. **Table 1** summarizes the relevant phenotypic variables for each subgroup of patients. Overall, the mean age at time of treatment was 49.65 ± 15.96 years (range 14-81 years) and the mean preoperative body mass index (BMI) was 29.73 ± 6.69 kg/m² with a median BMI of 28.53 kg/m² (range, 16.21-42.40). The majority of the patients were females (64.6%, n=52). In addition, approximately a quarter of the study population were either past or current smokers (25.6%, n=21) while the rest had no history of smoking at the time during treatment. For patients with sinonasal polyps, 95% (n=38) had history of prior nasal surgery.

	Asthma & Sinonasal Polyposis	Asthma Only	p-value
Total	40	42	
Age (mean years)	50.6 ± 16.3	48.7 ± 16.2	0.59
Male	52.50%	18.80%	0.001
Smoking Hx	20.00%	31.30%	0.25
Serum IgE (IU/L)	723.8 ± 275.4	800.6 ± 583.0	0.45
Absolute eosinophil count	896.3 ± 306.4	563.4 ± 258.4	0.001
Omalizumab	7.50%	12.00%	0.50
Mepolizumab	25.00%	33.30%	0.41
Benralizumab	60.00%	45.20%	0.18
Dupilumab	7.50%	9.50%	0.75

Table 1. Summary of descriptive variables for patients with asthma on biologic therapy

Comparison of pulmonary function in patients with and without sinonasal polyps

Of the 82 patients, 40 (48.8%) had documented sinonasal polyps by an otolaryngologist. Patients with and without sinonasal polyposis were found to be comparable in terms of age, pre-treatment BMI, and smoking status. Interestingly, there were significantly more females in the subgroup of patients with asthma without sinonasal polyps. Furthermore, patients with asthma and concurrent sinonasal polyps were found to have significantly higher baseline absolute eosinophil counts, 896.3 + 306.4 versus 563.4 + 258.4 in patients without sinonasal polyps. At baseline (time of biologic enrollment), the overall average ACT score for the patients without polyps was 13.16 + 4.12. At approximately 4 months following initiation of biologic therapy, the overall average ACT score for patients without polyps was 16.45 + 4.79. As summarized by **Table 2**, the average ACT scores for patients within each individual biologic subgroup ranged from 11.33 to 17.00. There was an overall 25% percent increase in ACT scores from baseline to long term follow-up, and this was found to be statistically significant

	Therapeutic Biologic	Baseline ACT	Follow Up ACT
Asthma	omalizumab	11.33 ± 5.77	17.67 ± 5.86
	mepolizumab	11.45 ± 4.55	12.55 ± 4.31
	benralizumab	13.20 ± 4.79	16.11 ± 4.99
	dupilumab	17.00 ± 4.98	19.50 ± 3.56
Asthma + Sinonasal Polyps	omalizumab	18.50 ± 0.71	22.00 ± 0.01
	mepolizumab	15.71 ± 7.52	20.00 ± 6.79
	benralizumab	17.68 ± 6.12	20.75 ± 5.87
	dupilumab	11.50 ± 3.53	18.00 ± 2.12

Table 2. ACT scores at time of therapy enrollment and on long term follow-up for individual biologic regimens

($p=0.001$). However, on average, scores stayed below 19 (poorly controlled asthma) following initiation of biologic therapy. For patients with concurrent polyps, the average ACT score at baseline was $15.85 + 3.13$. Following initiation

of biologics therapy, at approximately 4 months, the average ACT score increased to $20.19 + 1.68$. ACT scores for individual biologic regimens are further summarized in **Table 2**. The subgroup of patients without sinonasal polyps had, an overall 27.4% increase in ACT scores from baseline to long term follow-up ($p<0.001$). Patients with polyps had significantly better control of their asthma at baseline than patients with no polyps ($p=0.001$). However, both groups of patients had poor average baseline asthma control ($ACT < 19$). Patients with polyps continued to have significantly better control of their asthma at long term follow-up ($p < 0.001$). By 4-7 months patients with polyps were, on average, were able to achieve an overall ACT score of greater than 19 (mean= 20.19), demonstrating the ability to achieve well controlled asthma after initiation of biologic therapy (**Figure 1a-d**). Furthermore, the subgroup with asthma and concurrent sinonasal polyps had a significantly greater number of total ACT scores greater than 19 at long term follow up than patients without sinonasal polyps ($p < 0.05$).

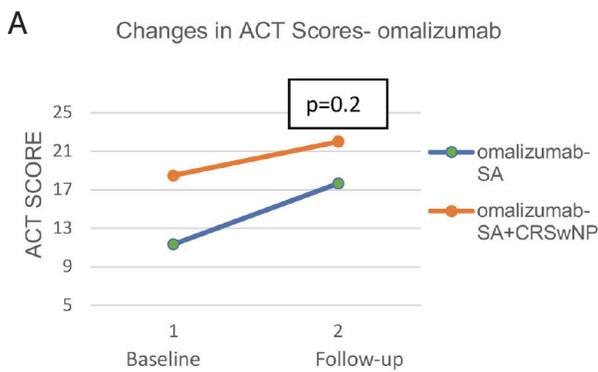


Figure 1A. Comparison of ACT scores for patients with asthma and comorbid upper airway disease on omalizumab. p-values evaluate significant differences between endpoint ACT scores.

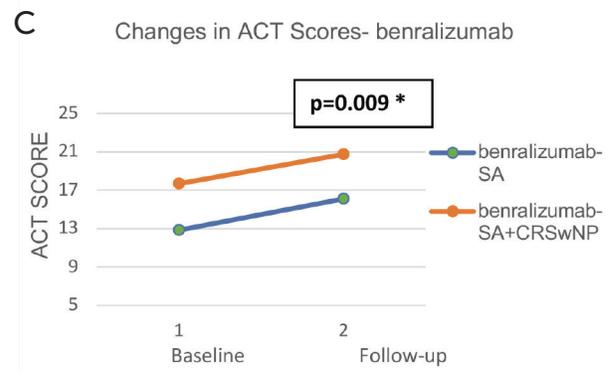


Figure 1C. Comparison of ACT scores for patients with asthma and comorbid upper airway disease on benralizumab. p-values evaluate significant differences between endpoint ACT scores.

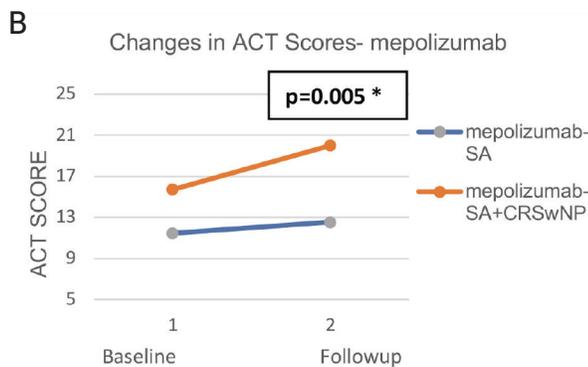


Figure 1B. Comparison of ACT scores for patients with asthma and comorbid upper airway disease on mepolizumab. p-values evaluate significant differences between endpoint ACT scores.

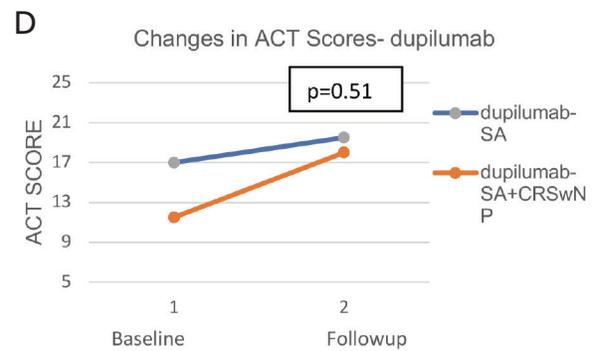


Figure 1D. Comparison of ACT scores for patients with asthma and comorbid upper airway disease on dupilumab. p-values evaluate significant differences between endpoint ACT scores.

When assessing pulmonary function, patients without sinonasal polyps had a baseline average FEV1 of $1.86 + 0.17$. Following 4-7 months on biologic therapy, these patients had an increase in average FEV1 to $2.10 + 0.18$, representing an improvement in pulmonary function. For patients with sinonasal polyps, the average baseline FEV1 was $1.89 + 0.46$, which was found to increase to $2.39 + 0.12$ at long term follow-up. Though both groups showed improvement in pulmonary function at 4-7 months, patients with concurrent sinonasal polyps were found to achieve significantly greater improvements from baseline FEV1 when compared to patients without sinonasal polyps ($p < 0.0001$).

Symptomatology

Patients presenting to otolaryngology with sinonasal polyps were noted to have multiple symptoms including pain, congestion, headaches, and loss of smell. Of the 40 patients with sinonasal polyps on biologic therapy, 62.5% presented with complaints of anosmia. Following 4-7 months of therapy on a biologic agent, only 15% of the patients continued to present with anosmia. Furthermore, symptoms of pain, congestion, and headaches all decreased on long term follow-up.

DISCUSSION

The pathophysiology in severe eosinophilic asthma involves type 2 inflammation characterized by signaling from IL-4, IL-5, and IL-13. Furthermore, patients with chronic rhinosinusitis with sinonasal polyps (CRSwNP), a known type 2 dominant inflammatory process characterized by extensive tissue eosinophilia and increased local IgE, may also benefit from biologic therapy.¹⁶ However, the indications for biologic therapy are imprecise and the ability to predict which biologic will render the best results has proven to be difficult. All of the approved biologic therapies for asthma have been shown to reduce asthma exacerbations and improve symptoms control.^{3,4} For patients with CRSwNP, the efficacy of biologics and their indications are more controversial due to the lack of complete clinical trials. Dupilumab, recently approved by the FDA for treatment of sinonasal polyps, has shown to reduce polyp burden in patients including reduction in polyp size and improved sinonasal symptoms. Clinical trials for omalizumab, mepolizumab, and benralizumab are currently being conducted to provide further information of their efficacy in treating sinonasal polyposis. Whether or not other comorbidities of asthma, including sinonasal polyposis, may help predict success with these medications has yet to be determined.

In our study, patients on biologic therapy with asthma and concurrent sinonasal polyps showed greater

symptomatic improvement at long term follow-up, as measured by ACT score (ACT= $20.19 + 1.68$), than those without sinonasal polyps (ACT= $16.45 + 4.79$). This may be that sinonasal polyps in patients with asthma represent another marker of type 2 inflammation and therefore predict better success with biologic medications. These findings are echoed in a randomized control trial conducted by Bachert et al., where lung function was found to be improved in patients with asthma and CRSwNP despite high or low baseline blood eosinophils.¹³ Furthermore, the significant improvements seen in the group with sinonasal polyposis could be due to concomitant improvement in their upper airway disease as suggested by a prior 2006 prospective study that found that an improvement in upper airway disease correlated with an improvement in asthma symptoms. Furthermore, patients with polyps managed on medical therapy were found to have prolonged asthma control when compared to those managed surgically.¹⁴

The better asthma control found in patients with asthma and sinonasal polyps in our study may also be explained by a tendency for patients to place a greater emphasis on upper airway symptoms versus lower airway as well as an improved ability to breathe through the nose. A prospective study done by Miller et al. proposed that upper airway obstruction may lead to excessive drying of the lower airways due to increased mouth breathing.¹⁶ Improvement of this obstruction may be associated with relief of more subtle lower airway symptoms. Given these findings, determining whether sinonasal polyps independently predict success from biologic therapy in asthma warrants prospective studies.

Currently there is no preferred biologic therapy in severe asthma. In our cohort, dupilumab demonstrated the greatest improvement in asthmatic patients with comorbid polyps, showing improvements from an ACT of $11.50 + 3.53$ at baseline to $18.00 + 2.12$ on long term follow-up (% increase= 56.5%). A randomized control trial completed in 2016 demonstrated that patients treated with dupilumab had improvement in sinonasal imaging scores, sinonasal symptom scores, and sense of smell, thus further emphasizing the effects of dupilumab on CRSwNP.⁹ Our study data also found mepolizumab and omalizumab to have greater improvements in polyposis population than benralizumab, for which the least evidence exists in sinonasal polyps⁹⁻¹¹. In our study cohort of asthmatics without sinonasal polyps, improvements in ACT were more modest. Aside from omalizumab, none of the others reached a clinically significant improvement of 3 on ACT at long term follow-up. Overall, the number of patients in each group are too small to draw conclusions on the correct biologic with or without sinonasal polyps, though our data reinforces the benefit of each biologic therapy in severe asthma.

The most common presenting symptom in patients with sinonasal polyps was anosmia (62.5%), and after 4-7 months of therapy on a biologic agent, only 15% of the patients had persistent anosmia. A cross sectional study completed by Vizuete et al. proved that anosmia may be a significant clinical marker for comorbid severe asthma in patients with sinonasal polyposis.¹⁸ Furthermore, because of the frequency and severity of anosmia on a patient's quality of life and function, it should be an important consideration when determining treatment regimens for patients with sinonasal polyps.¹⁹ Our data shows that biologics may play a role in ameliorating symptoms such as anosmia, and may serve as an additional consideration when deciding to start a severe asthmatic on biologics.

The major limitations of this study is the retrospective study design and small sample size. Additionally, the difference in baseline eosinophils may be a confounding variable in the outcomes. Future studies on the effects of biologics on patients with comorbid sinonasal polyposis should include larger sample sizes with matched controls in a prospective design.

Our study suggests that sinonasal polyps with comorbid asthma may represent a high type 2 high population that may benefit more from biologic therapy. Many patients with sinonasal polyps have concurrent asthma along with the shared immunologic characteristics has led to some to suggest a united airway.¹² Presence of sinonasal polyposis in the setting of severe asthma should warrant consideration of biologic therapy.

CONCLUSION

Patients with and without sinonasal polyps who begin biologic therapy are shown to have significant improvements in their asthma control at follow-up. In addition, patients with polyps are shown to have significantly better control of their asthma while on biologics than patients with no polyps. Thus, comorbid sinonasal polyposis can be considered an additional marker when considering initiation of biologic therapy for severe asthma.

REFERENCES

1. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2019. Available from: www.ginasthma.org.
2. Type 2 Inflammation and the Evolving Profile of Uncontrolled Persistent Asthma - European Medical Journal [Internet]. [cited 2020 Feb 25]. Available from: <https://www.emjreviews.com/respiratory/symposium/type-2-inflammation-and-the-evolving-profile-of-uncontrolled-persistent-asthma/>
3. Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF, et al. Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma. *N Engl J Med*. 2018 Jun 28;378(26):2486-2496.
4. Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med*. 2014 Sep 25;371(13):1198-1207.
5. Bleeker ER, FitzGerald JM, Chanez P, Papi A, Weinstein SF, Barker P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β_2 -agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet*. 2016 Oct 29;388(10056):2115-2127.
6. Hopkins C. Chronic Rhinosinusitis with Sinonasal Polyps. *N Engl J Med*. 2019 Jul 4;381(1):55-63.
7. Akdis CA, Bachert C, Cingi C, Dykewicz MS, Hellings PW, Naclerio RM, et al. Endotypes and phenotypes of chronic rhinosinusitis: a PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology. *J Allergy Clin Immunol*. 2013 Jun;131(6):1479-1490.
8. Tosun F, Arslan HH, Karslioglu Y, Deveci MS, Durmaz A. Relationship between postoperative recurrence rate and eosinophil density of sinonasal polyps. *Ann Otol Rhinol Laryngol*. 2010 Jul;119(7):455-459.
9. Bachert C, Mannent L, Naclerio RM, Mullol J, Ferguson BJ, Gevaert P, et al. Effect of subcutaneous dupilumab on sinonasal polyp burden in patients with chronic sinusitis and sinonasal polyposis: A randomized clinical trial. *JAMA*. 2016 Feb 2;315(5):469-479.
10. Gevaert P, Van Bruaene N, Cattaert T, Van Steen K, Van Zele T, Acke F, et al. Mepolizumab, a humanized anti-IL-5 mAb, as a treatment option for severe sinonasal polyposis. *J Allergy Clin Immunol*. 2011 Nov;128(5):989-95.e1.
11. Gevaert P, Calus L, Van Zele T, Blomme K, De Ruyck N, Bauters W, et al. Omalizumab is effective in allergic and nonallergic patients with sinonasal polyps and asthma. *J Allergy Clin Immunol*. 2013 Jan;131(1):110-6.e1.
12. Håkansson K, Bachert C, Konge L, Thomsen SF, Pedersen AE, Poulsen SS, et al. Airway Inflammation in Chronic Rhinosinusitis with Sinonasal Polyps and Asthma: The United Airways Concept Further Supported. *PLoS One*. 2015 Jul 1;10(7):e0127228.
13. Bachert C, Han JK, Desrosiers M, Hellings PW, Amin N, Lee SE, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with sinonasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. *Lancet*. 2019 Nov 2;394(10209):1638-1650.
14. Ragab S, Scadding GK, Lund VJ, Saleh H. Treatment of chronic rhinosinusitis and its effects on asthma. *Eur Respir J*. 2006;28(1):68-74.
15. Laidlaw TM, Buchheit KM. Review Article: Biologics in chronic rhinosinusitis with sinonasal polyposis. *Ann Allergy Asthma Immunol*. 2019; 19: 1081-1206
16. Miller EK, Hernandez JZ, Wimmenauer V, et al. A mechanistic role for type III IFN- λ 1 in asthma exacerbations mediated by human rhinoviruses. *Am J Respir Crit Care Med*. 2012;185(5):508-16.
17. Fokkens WJ, Hellings PW. Sinonasal polyposis and asthma: the otorhinolaryngologist's view. In: Bachert C, Bourdin A, Chanez P, et al. *The Nose and Sinuses in Respiratory Disorders* [ERS Monograph]. Sheffield, European Respiratory Society, 2017; 87-104.
18. Vizuete J, Picado C, Plaza V, Rodrigo G, Julia B, Fernandez C, et al. Loss of smell: a clinical marker of severe asthma. *European Respiratory Journal* 2018 52: Suppl. 62, PA3984.
19. Heffler E, Malvezzi L, Pirola F, et al. Treatable traits in chronic rhinosinusitis with sinonasal polyps. *Curr Opin Allergy Clin Immunol*. 2019;19(4):373-378.