



A Comparative Study of Symptoms, Nasal Eosinophilia and Pulmonary Function Tests Before and After Short Term Treatment with Corticosteroid Nasal Spray in Patients with Allergic Rhinitis

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Abstract Allergic rhinitis has been on the rise because of urbanization and major population shift in addition to changes in the particulate matter in the atmosphere. Intranasal corticosteroid sprays are recommended as first-line prescription treatment in all cases of allergic rhinitis. The propensity of co-existing non-apparent lower airway hyper-responsiveness is also on the rise and must be evaluated. The aim of this study is to compare the symptomatic improvement, changes in nasal eosinophilia and asymptomatic airway hyper responsiveness before and after short term treatment with steroid nasal spray. Fifty patients meeting the inclusion criteria for allergic rhinitis with no symptoms of asthma underwent pulmonary function tests and assessment of symptoms before and after one-month treatment with inhalational steroid nasal spray (Fluticasone Furoate), in the standard adult dosage. Based on TNSS (Total nasal symptom score) and TOSS (Total ocular symptom score), all 50 patients showed significant improvement after treatment. Among 20 patients with > 50 eosinophils per high power field, 80% had 0–10 eosinophils per high power field on nasal smear after treatment. Among 40 patients with mild large airway obstruction, 37 showed significant improvement in FEV₁ data. Also FEV₁/FVC data showed significant improvement. Significant improvement (FEF_{25–75} > 50%) was also noticed in small airway disease after treatment among the 5 patients. The

study showed that lower airway hyper responsiveness coexists with allergic rhinitis and treating allergic rhinitis with just steroid nasal spray assists in reducing the former, supporting the concept of Unified Airway Disease (UAD).

Keywords Allergic rhinitis · Pulmonary function tests · Unified airway disease · Nasal eosinophilia · Intranasal corticosteroid · Fluticasone furoate

Introduction

Allergic rhinitis (AR), a global health problem, is a chronic inflammatory respiratory disease, typically IgE-mediated and is characterized by one or more symptoms, including sneezing, itching, nasal congestion and rhinorrhea affecting 5–50% of the worldwide population and its prevalence is increasing [1, 2]. In accordance with ARIA guidelines (ARIA 2019), therapy with intranasal corticosteroid is recommended as first-line prescription treatment in all cases of AR with the exception of mild intermittent type [3].

During the second century, Claudius Galenus in his work “De usu partium,” identified the effect of the upper airway on the lower airway and defined the nose as a “respiratory instrument”. Only over the last 10–15 years, after Allergic Rhinitis and its Impact on Asthma (ARIA), World Health Organization workshop, the concept of a single unified airway had been given importance [4–6].

Atopy and bronchial hyperresponsiveness in asthma are closely related. Patients suffering from allergic rhinitis have distressing symptoms and experience significant morbidity along with loss of productivity. Recent studies have highlighted lower airway responsiveness to nasal allergy which was not documented earlier. Previous studies

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showed that nasal allergen challenge induces eosinophilic inflammation in the upper and lower airways, and causes airflow limitation in patients with allergic rhinitis [7].

Bronchial allergen provocation can induce nasal and bronchial symptoms as well as reductions in pulmonary and nasal function [8].

In this study, we assess the symptomatic improvement, change in nasal eosinophilia and asymptomatic airway hyper responsiveness before and after short term treatment with steroid nasal spray in patients diagnosed with allergic rhinitis. The steroid nasal spray used in this study was fluticasone furoate (Avamys; GlaxoSmithKline, County Durham, UK) in the standard adult daily dosage.

We also uncover the presence of asymptomatic lower airway hyperresponsiveness which can co-exist in patients with symptoms of allergic rhinitis which supports the concept of Unified airway disease.

Materials and Methods

This was a prospective study conducted on 50 patients who visited the department of Otorhinolaryngology-Head and neck surgery of a tertiary care hospital and teaching institution from January 2013 to January 2014. Adult patients of both sexes diagnosed with allergic rhinitis based on history, symptomatic score and confirmed by skin prick allergy test were selected. Patients with acute bacterial sinusitis, lower respiratory tract infection, asthma, nasal polyps, deviated nasal septum, past history of nasal surgery, any other forms of rhinitis, smokers and known cases of chronic obstructive pulmonary disease were excluded from the study. We also excluded patients who were already on treatment for allergic rhinitis.

For nasal symptoms, Total Nasal Symptom Scoring (TNSS) and for ocular symptoms, Total Ocular Symptom Scoring (TOSS) were used to score symptoms. Nasal symptoms (rhinorrhea, nasal itching, nasal obstruction, and sneezing), were rated using a 4-point Likert scale from 0 to 3 (0 = no symptom, 1 = mild, 2 = moderate, 3 = severe), with a total possible score ranging from 0 (no symptoms) to 12 (maximum symptom intensity). Ocular symptom (eye tearing and itching), severity was rated by patients on a 4-point scale (0 = none to 3 = severe), with a total possible score ranging from 0 (no symptoms) to 6 (maximum symptom intensity).

The severity of symptoms of allergic rhinitis were graded as described by the patient. The number of impaired severity items (sleep, daily activities/sport/leisure, work/school performance, and troublesome symptoms) allows the grading of AR severity according to the original ARIA classification as “mild” (no affected item) or “moderate/severe” (1 or more items are affected).

The test allergens used in the skin prick test for confirmation of allergy in selected patients were chosen based on known allergens in the locality and was obtained in titrated and purified form from Creative Diagnostic Medicare Pvt. Ltd. from Mumbai, India. The skin of volar aspect of arms and forearms was cleaned with spirit swab and was coded with ink to identify the allergens to be tested. A drop of the allergen (extract) solution was placed on the skin beside the code. The skin was then pricked intradermal through the drop using the tip of a lancet. Two control samples were included to calibrate the extent of reaction, histamine and normal saline. Results were tabulated after waiting for 20 min as significant allergy or non-significant allergy. Only patients with significant allergy were included in the study group. Emergency kit was kept standby in case of anaphylaxis.

Following confirmation of significant allergy, nasal smear was collected by using a swab to collect secretions from the anterior aspect of the inferior turbinate on both sides and smearing the secretions on a glass slide. The slide was then sent to the cytological lab for analysis of eosinophil count and percentage. This was done before and after treatment for each patient who had significant allergy on skin prick test.

Eosinophilia is graded according to the following criteria:

- 0: no eosinophils seen.
- 1+: up to 10 eosinophils per high power field.
- 2+: up to 11–25 eosinophils per high power field.
- 3+: up to 26–50 eosinophils per high power field.
- 4+: > 50 eosinophils per high power field.

Pulmonary function test was performed in the department of Pulmonary Medicine before treatment in patients selected for the study. The pulmonary function test was repeated after short term treatment (1 month) with Fluticasone Furoate nasal spray two puffs in each nostril, once daily (50 micrograms per puff for a total of 200 micrograms per day). The following criteria were studied. FEV₁ (Forced Expiratory Volume in 1 s) and FEV₁/FVC (% of Forced Vital Capacity expired in 1 s) to study large airway obstruction and FEF_{25–75} (Forced Expiratory Flow over the middle one half of Forced vital capacity) to study small airway obstruction.

Statistical Analysis

Mantel–Haenszel (MH) test statistics was used for statistical evaluation and *p* value ≤ 0.001 was considered significant.

Statistical analysis was done using SPSS (software package for Statistical Analysis) version 16.

Results

Fifty patients were chosen for the study, of which 35 (70%) were males and 15 (30%) were females. Thirty-five (70%) patients belonged to age group of 18–30, 10 (20%) patients belonged to age group of 31–40 and 5 (10%) patients belonged to age group of 41–50.

Symptom wise, 26 patients included in the study had moderate and 24 patients had mild intensity of nasal obstruction. Post treatment with steroid nasal spray, 20 patients continued to have mild nasal obstruction out of 26 patients with moderate nasal obstruction and rest had complete resolution of nasal obstruction.

Patients (40) with severe rhinorrhea prior to treatment, had either mild (20) and rest had no rhinorrhea after treatment. Patients with severe sneezing (40) also showed absolute reduction in their symptoms. Patients with

moderate to severe nasal itching (40) showed mild itching in 20 patients and others had no itching after treatment.

Similarly, patients observed significant reductions in their ocular symptoms (itching and eye watering), even with short term treatment. A total of 19 patients, who had severe eye itching, had reverted to either mild (5,) or no nasal itching (14). And 26 patients who had moderate eye itching prior to treatment had no symptoms after therapy. In case of 5 patients, who had severe eye watering, showed absolute reduction and of 34 patients with moderate eye watering, 29 had no symptoms.

Based on TNSS and TOSS, there was significant improvement in symptom scores after 1 month of treatment with intranasal corticosteroid spray (Figs. 1, 2).

With regard to eosinophilia, there was significant reduction in eosinophil count from nasal smear. Prior therapy, 20 patients had counts > 50%. After therapy 80%

Fig. 1 Pretreatment Total Nasal Symptom Score (TNSS) versus Post treatment Total Nasal Symptom Score (TNSS)

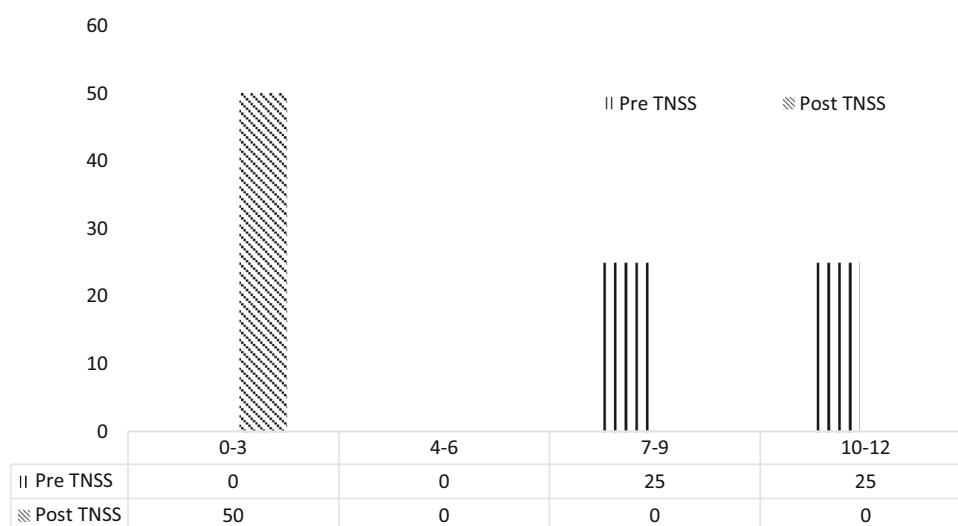


Fig. 2 Pretreatment Total Ocular Symptom Score (TOSS) versus Post treatment Total Ocular Symptom Score (TOSS)

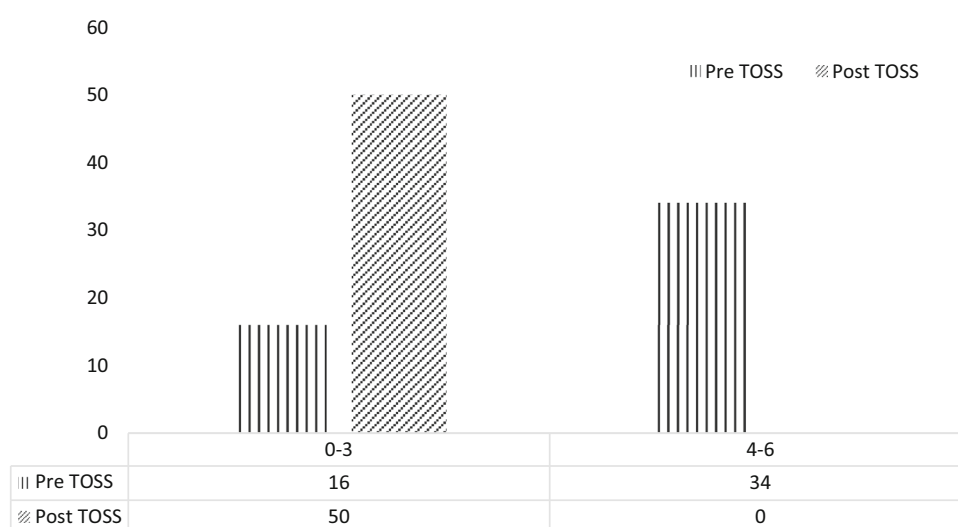


Table 1 Pretreatment nasal eosinophil versus Post treatment nasal eosinophil Crosstabulation

	Post treatment eosinophil		Total
	0–10%	11–25%	
Pretreatment eosinophil			
0–10%	10 (100%)	0	10 (100%)
11–25%	5 (100%)	0	5 (100%)
26–50%	15 (100%)	0	15 (100%)
> 50%	10 (50%)	10 (50%)	20 (100%)
Total	40 (80%)	10 (20%)	50 (100%)

had 0–10% and 20% had 11–25% eosinophils on nasal smear (Table 1).

Regarding large airway obstruction, as we chose patients who had no history of wheezing or asthma, we discovered that a significant number of test subjects (40 out of 50), had mild large airway obstruction which was not apparent clinically. Following treatment, FEV₁ improved significantly, with only 3 patients continuing to have mild large airway obstruction suggesting that large airway obstruction is obviously present and treatable with the use of steroid nasal spray (Table 2).

Data for FEV₁/FVC showed that out of 14 patients who had airway obstruction, 11 patients showed improvement after treatment (Table 3).

Significant improvement (FEF_{25–75} > 50%), was also noticed in small airway disease after treatment among the 5

Table 2 Pretreatment FEV1 versus Post treatment FEV1 Crosstabulation

	Post FEV1		Total
	> 80%	50–79%	
Pre FEV1			
> 80%	10 (100%)	0	10 (100%)
50–79%	37 (92.5%)	3 (7.5%)	40 (100%)
Total	47 (94%)	3 (6%)	50 (100%)

Table 3 Pretreatment FEV1/FVC versus Post treatment FEV1/FVC Crosstabulation: Ratio of less than 0.7 was considered as high for airway obstruction and ratio higher than 0.7 was considered low for airway obstruction

	Post FEV1/FVC		Total
	< 0.7	> 0.7	
Pre FEV1/FVC			
< 0.7	3 (21.4%)	11 (78.6%)	14 (100%)
> 0.7	0	36 (100%)	36 (100%)
Total	3 (6%)	47 (94%)	50 (100%)

Table 4 Pretreatment FEF25–75 versus Post treatment FEF25–75 Crosstabulation

	Post FEF25–75		Total
	< 50%	> 50%	
Pre FEF25–75			
< 50%	1 (4%)	4 (96%)	5 (100%)
> 50%	0	45 (100%)	45 (100%)
Total	1 (2%)	49 (98%)	50 (100%)

FEF_{25–75} less than 50% considered as significant small airway obstruction

patients who had (FEF_{25–75} < 50%), before treatment (Table 4).

Mantel–Haenszel (MH) test statistics was used as we were analyzing a set of stratified categorical data of symptoms and eosinophil percentage before and after short term treatment. The MH statistic values were obtained, and the p values obtained for the analysis was < 0.001. The same test statistics was used as we were analyzing a set of stratified categorical data for the pulmonary function tests as well. The MH statistic values were obtained, and the p value obtained for the analysis was ≤ 0.001 (Tables 5, 6).

Discussion

Allergic rhinitis is a common problem with considerable morbidity and it has shown a rising trend in recent years. Urbanization, globalization and increase in population migration to urban areas along with atmospheric pollution are some of the reasons implicated for the increased incidence. A similar rise is seen in smaller towns and cities on account of increase in atmospheric pollution. The patient may have coexisting lower airway hyper-responsiveness which may only become evident once the patient develops full blown asthma as a significant number of patients with allergic rhinitis often do. Therefore, this must be kept in mind during clinical examination, and the sensation of feeling of breathlessness during an attack of allergic rhinitis must include an examination of the lower airway also. Since it may not be feasible to do a pulmonary function test on every patient with allergic rhinitis, treating the patient with a steroid nasal spray may alleviate lower airway hyper-responsiveness.

Dating back to 1919, Sluder hypothesized the existence of a nasal-bronchial reflex [9], supported by the evidence of a similar innervation of both upper and lower airways [10]. More recent studies have demonstrated the role of localized inflammatory changes in the upper and lower airways, which lead to a systemic response [11–13].

Table 5 Mantel–Haenszel (MH) test- Analyzing a set of stratified categorical data of symptoms and eosinophil count before and after short term treatment

	Pre obstruction and post obstruction	Pre rhinorrhoea and post rhinorrhoea	Pre sneezing and post sneezing	Pre itching and post itching	Pre eye irritation and post eye irritation	Pre eye watering and post eye watering	Pre eosinophil and post eosinophil
Mantel Haenszel (MH) test							
Distinct values	3	4	4	4	4	4	4
Off-diagonal cases	45	50	50	50	50	40	40
Observed MH statistic	115.000	190.000	190.000	145.000	164.000	124.000	135.000
Mean MH statistic	90.000	130.000	122.500	110.000	112.000	84.500	92.500
SD of MH statistic	3.873	8.660	9.811	5.244	7.746	6.461	6.982
Std. MH statistic	6.455	6.928	6.880	6.674	6.713	6.113	6.087
Asymp. sig. (2-tailed)	0.000	0.000	0.000	0.000	0.000	0.000	0.000

Table 6 Mantel Haenszel (MH) test -Analyzing a set of stratified categorical data for the pulmonary function tests

	Pre FEV ₁ and post FEV ₁	Pre FECV ₁ /FVC and post FEV ₁ /FVC	Pre FEF _{25–75} and post FEF _{25–75}
Distinct values	2	2	2
Off-diagonal cases	36	11	26
Observed MH statistic	36.000	11.000	22.000
Mean MH statistic	0.000	0.000	0.000
SD of MH statistic	6.000	3.317	5.099
Std. MH statistic	6.000	3.317	4.315
Asymp. sig. (2-tailed)	0.000	0.001	0.000

The mechanism put forth is that due to localized inflammatory changes in the upper and lower airway, there is systemic response with bone marrow involvement which releases the progenitor cells that are then recruited to tissue sites. The nose is usually the first site of exposure to allergens or other noxious substances but there is minimal nasal epithelial damage and a marked bronchial epithelial disruption may be present. This is because, nasal mucosa has developed protective mechanisms that minimize remodeling and enhance epithelial regeneration [14]. An important proof of the unified airway disease interplay is the presence of epithelial basement membrane thickening, the typical hallmark of lower airway remodeling, not only in asthmatic patients but also in atopic patients without asthma and patients with AR, though it is less extensive in the nasal mucosa [15].

Various studies have been performed to study what drug and treatment regimens have greatest efficacy. Intranasal corticosteroid sprays have been in the forefront in treating allergic rhinitis for the past 30 years [16, 17].

Berlin et al. [18] reported that patients treated with antihistamine nasal spray showed greater improvement in rhinorrhea, while patients treated with steroid nasal spray showed greater improvement in congestion, sneezing and nasal and ocular pruritus. Scadding et al. [19] conducted a study on fluticasone nasal spray in patients with allergic rhinitis comparing the symptom score with those on no therapy and found that post challenge nasal obstruction was decreased by 45%, sneezing, itching and rhinorrhea by 73%, 78% and 80% respectively in the group on fluticasone nasal spray.

In our study too, after 1 month use of morning once daily nasal spray, 60% had no symptoms of rhinorrhea and 40% had only mild symptoms but had significantly reduced severity ($p < 0.001$).

It was also seen that among patients who had nasal obstruction, 52% had no symptoms and remaining 48% had only mild symptom after treatment, consistent with other studies results ($p < 0.001$). Also 90% of patients were relieved from sneezing spells and remaining 5% had only mild symptoms ($p < 0.001$). Similarly, nasal and eye itching were significantly reduced after intranasal steroid spray in our study ($p < 0.001$).

Bhakshi et al. conducted a randomized study comparing the efficacy of mometasone furoate and fluticasone furoate on the ocular and nasal symptoms of allergic rhinitis by total ocular symptom score [TOSS] and total nasal symptom score [TNSS] at 2, 6 and 12 weeks interval. He randomly divided 90 patients with perennial allergic rhinitis and ocular symptoms were randomly divided into 2 groups. One group received mometasone furoate nasal spray once daily and the other group received 110 µg of fluticasone furoate nasal spray daily. There was a statistically significant reduction in both the groups in respect to the TOSS and TNSS scores [20].

There was significant improvement in TNSS and TOSS scores. 25 patients each with TNSS score of 7–9 and 10–12 respectively showed score of 0–3 after treatment. Similarly, 19 patients with TOSS score of 4–6 showed scores of 0–3 after treatment.

The recent advancement in this field of study is the question of unified airway disease. This entity is quite often overlooked when treating such patients.

Jang et al. conducted a study which involved observing nasal eosinophil in allergic rhinitis and showed that upper airway resistance was related to nasal eosinophil count. Patients with higher eosinophil in nasal smear needed lesser concentration of methacholine to decrease the FEV₁ by 20%. There were no differences of nasal eosinophils between perennial and seasonal allergic rhinitis [21].

Kamp et al. [22] studied degranulation of eosinophils in patients with allergic rhinitis and asthma and concluded that systemically activated eosinophils and neutrophils have similar patterns of degranulation after allergen exposure in allergic rhinitis and allergic asthma. Tatar et al. [23] similarly concluded that eosinophilic inflammation of lower airways and increased bronchial reactivity was present in adult patients with allergic rhinitis.

Similarly, in our patients, non-symptomatic lower airway obstruction could be explained by release of eosinophils as seen in allergic asthma.

Di Lorenzo et al. observed that the eosinophil count was statistically significantly higher in allergic rhinitis patients. They found that eosinophil count in nasal fluid (ECNF)

presented a high accuracy as regards to severity of nasal symptoms in allergic rhinitis, but there have also been some studies which have been conducted that refute this [24].

In our study, nasal eosinophil count was higher in patients with allergic rhinitis. 30% of patients with allergic rhinitis had 26–50% eosinophil count in nasal smear, and 40% of them had > 50% eosinophil count in nasal smear.

Giorgio Ciprandi et al. studied that a relevant percentage of AR patients had bronchial hyper-responsiveness (BHR), and impaired FEF_{25–75} values might predict it. Among patients with AR, 14% of patients had severe BHR and 25.3% had mild BHR. Patients with severe BHR showed low FEF_{25–75} values ($p < 0.001$) [25].

Giorgio Ciprandi et al. in other study showed that an impairment of spirometric parameters and presence of BHR may be observed in patients with allergic rhinitis alone. Spirometry and methacholine bronchial challenge were performed on 100 patients. Five patients showed reduced values of FEV₁ without symptoms of asthma. Forty-eight patients had reduced FEF_{25–75} values. Seventy-two patients showed a positive methacholine challenge. In this group, reduced values of FVC ($p < 0.05$), FEV₁ ($p < 0.05$), and FEF_{25–75} ($p < 0.01$) were demonstrated in comparison with BHR-negative patients. There was a relationship between the degree of BHR and FEV₁ values ($p < 0.05$) and FEF_{25–75} values ($p < 0.01$) [26].

In our study, as we chose patients who had no history of asthma, we discovered that 40 of them had mild upper airway obstruction, whereas 10 had no upper airway obstruction when FEV₁ was taken as parameter. When FEV₁/FVC parameter was considered 14 had high upper airway obstruction and 36 had low upper airway obstruction. According to FEF_{25–75}, only 5 patients with allergic rhinitis had lower airway obstruction.

Fluticasone furoate (FF) is a synthetic corticosteroid with potent anti-inflammatory activity and low systemic exposure. The drug comes as an aqueous suspension of micronized fluticasone furoate for topical administration to the nasal mucosa by means of a metering, atomizing spray pump.

Vipin et al. stated that the treatment of inflammation in the upper airway using fluticasone furoate nasal spray indirectly improves the symptoms of hyperactive lower airway disorders and decreased bronchial hyperactivity.

Patients with moderate to severe allergic rhinitis were started on a fixed dose of intranasal fluticasone furoate nasal spray for a period of 2 months and the pretreatment and post treatment FEV₁ and PEFR (Peak expiratory flow rate) were compared and statistically analyzed for the effect. Approximately 50% of patients with allergic rhinitis showed associated lower airway hyper reactivity. There was statistically significant improvement in pulmonary

function test readings after 2 months therapy with intra-nasal fluticasone spray [27].

In our study, 40 patients post treatment had $FEV_1 > 80\%$, 47 patients had $FEV_1/FVC > 0.7$ and 49 patients had significant improvement in $FEF_{25-75} (> 50\%)$. All were statistically significant ($p < 0.001$).

Conclusion

In susceptible individuals, exposure of the nose and lungs to allergen elicits early phase and late phase responses. Localized inflammatory changes are the key features in both allergic rhinitis and asthma. There are potential benefits for application of anti-inflammatory strategies that target both these anatomic sites, the nasal cavity and lower airway. Both upper airway and lower airway symptoms can be treated as a unified airway disease. The “unified airway disease hypothesis” proposes that upper and lower airway diseases are both manifestations of a single inflammatory process [28]. Otolaryngologists treating patients with allergic rhinitis are beginning to identify, monitor, and manage patients with concurrent asthma. Otolaryngologists who treat chronic rhinosinusitis are beginning to incorporate allergy evaluation and treatment into their operative and non-operative management schemes. The end result is the potential for improved patient care.

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Compliance with Ethical Standard

Conflict of interest No conflicts of interest regarding submission and publication of this manuscript and its potential implications.

Ethical Statement Ethics committee approval has been obtained from Institutional ethics committee for the study.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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