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Introduction

During the past few years the global pathogenic view of respiratory allergy has changed. The link between rhinitis and asthma – that is, upper and lower airways has been underlined by epidemiological and clinical studies. Taken together, these have led to the operative definition of “allergic rhinobronchitis” or “united airways disease (UAD)”. In recent years more evidence has been provided of the frequent co-existence of rhinitis and asthma. These relationships are particularly notable in children. Detailed knowledge of the mechanisms sustaining allergic inflammation in the respiratory tract allows a greater understanding of the functional relationships between the upper and lower sections of the tract. In this respect it is logical to assume that allergy is not a disease confined to a specific target organ, but rather a disorder of the whole respiratory tract, which has a broad spectrum of clinical manifestations. The concept of “united airways disease” also has therapeutic implications.

Galen, way back in the 2nd century AD had reported that an association existed between nasal symptoms and chest disease.

Epidemiologic Evidence

Epidemiologic evidence for the co-existence of upper and lower respiratory symptoms extends back more than 80 years.

In 1920, Keller reported that among 100 case histories of patients with chest symptoms, 86 presented with concomitant nasal pathology. Keller hypothesized that *"predominant mouth breathing secondary to persistent nasal congestion may have prevented the proper moistening, warming, and filtering of the air, thus triggering asthma symptomatology."* Since then, numerous studies have bolstered the epidemiologic link between asthma and the upper respiratory disorders, allergic rhinitis and rhinosinusitis.

The majority of patients with asthma present with symptoms of seasonal or perennial allergic rhinitis. However, it has been shown that perennial rhinitis is a risk factor for asthma independent of allergy. ***In epidemiological studies, rhinitis was found to occur in up to 80% of patients with asthma.***

In a group of 1245 subjects with documented asthma,

- 24% had seasonal allergic rhinitis only,
- 6% had perennial allergic rhinitis only,
- 22% were considered to have both.

In some large clinical studies rhinitis is present in nearly all the patients with asthma; in one study over 95% had a history of allergic rhinitis and 73% had current seasonal allergies.

Data from northern Sweden also demonstrate the association between asthma and allergic rhinitis, and show that ***an adult with a family history***

of asthma or rhinitis has a three- to four-fold increased risk for developing asthma and a two- to six-fold increased risk for developing rhinitis compared with adults without a family history.

In adults rhinitis has been prospectively shown to be a risk factor for asthma. Three studies need to be mentioned. First was the work by Settipane *et al*, who resurveyed 690 individuals 23 years after they had been originally surveyed, when they were college freshmen in Rhode Island. These 690 individuals, now in their 40s, were considered as a population at risk because, at the time of their first evaluation, they reported no diagnosis or symptoms compatible with asthma. However, 162 had a diagnosis of rhinitis. The incidence of asthma over the 23 years between the 2 surveys was 10.5% in the subjects with rhinitis and 3.6% in those without rhinitis, a highly significant difference. ***This indicates that individuals with rhinitis are about three times more likely to develop asthma than negative controls.***

Table: 23-year follow-up study

	N=1836	N=1021
	1962/63	1986/87
Asthma	5.3%	+0.7%
SAR	21.1%	+9.8%
PAR	5.2%	+4.3%
N=162 (AR with asthma) → 10.5% developed asthma		
3.6% asymptomatic people developed asthma		
Thus, patients with AR were three times more likely to subsequently develop asthma		

Another longitudinal prospective study that has assessed how much of a risk factor rhinitis is for asthma, is the Tucson Epidemiologic Study of Obstructive Lung Diseases. In that study 173 adults who had newly developed asthma over approximately 10 years in the course of the duration of the study were compared with 2177 control subjects who, during approximately the same period, did not have any chronic lower respiratory tract symptoms.

- ***The odds ratio for developing asthma if rhinitis was present was 2.59 (95% CI, 1.54-4.34);***
- ***If rhinitis plus sinusitis was present, the odds ratio was even higher at 6.28 (95% CI, 4.01-9.82).***

The Tucson study produced an additional and very important observation: ***the risk for asthma increased with increasing severity of rhinitis.***

The Copenhagen Allergy Study reported that the frequency of allergic asthma among subjects with AR was 40-50%, whereas the frequency of allergic asthma among subjects without AR was 1% or less. Consequently ***the risk of asthma among subjects with allergic rhinitis was calculated to be up to 300 times that among subjects without allergic rhinitis.***

Pathophysiologic Mechanisms

In normal subjects, the structure of the airway mucosa shows similarities between the nose and the bronchi.

- Both nasal and bronchial mucosa are characterized by a pseudostratified epithelium with columnar, ciliated cells resting on a basement membrane.
- In the submucosa, vessels, mucous glands, structural cells (fibroblasts), some inflammatory cells (essentially monocytic cells, lymphocytes, and mast cells) and nerves are present.

There are also differences between the nose and the bronchi.

- The nose is richly supplied with a subepithelial capillary and arterial system and venous cavernous sinusoids. This rich vascularization is a key feature of the nasal mucosa and changes in the vasculature may lead to severe nasal obstruction.
- On the contrary, the bronchi are characterized by the presence of smooth muscle from the trachea to the bronchioles, accounting for the bronchoconstriction of asthma.

Recent advances in the understanding of the cellular and molecular biology of airway diseases have clearly shown that inflammation plays a critical role in the pathogenesis of asthma and rhinitis. The same inflammatory cells appear to be present in the nasal and bronchial mucosa. A growing number of studies show that ***the inflammation of nasal and bronchial mucosa is sustained by a similar inflammatory infiltrate, comprising eosinophils, mast cells, T-lymphocytes, and cells of***

the monocytic lineage. In addition, the same pro-inflammatory mediators (histamine and cysteinyl leukotrienes), Th₂ cytokines (IL-4, IL-5, IL-13, GM-CSF), chemokines (RANTES and eotaxin) and adhesion molecules appear to be involved in both nasal and bronchial inflammation in patients with rhinitis and asthma.

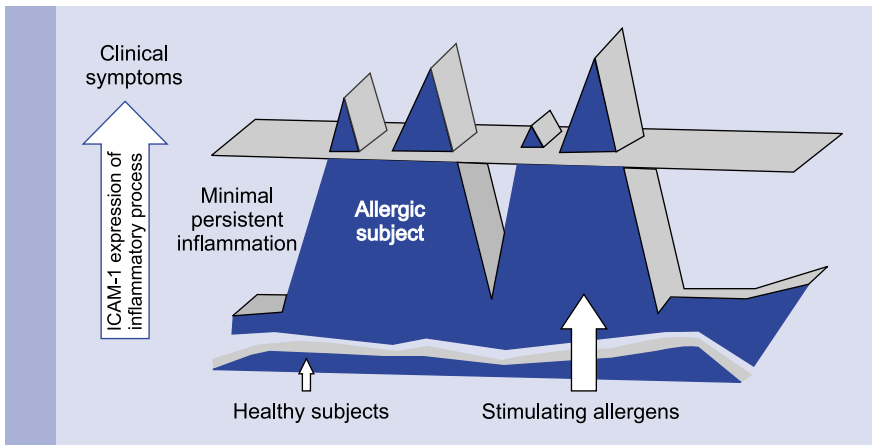
However, there are major differences between the two sites.

- Although the bronchial and, especially, the nasal mucosa are exposed to the same environmental insults, epithelial shedding is more pronounced in the bronchi than in the nasal mucosa of patients suffering from both asthma and rhinitis.
- The intensity of the inflammation may not be identical. In patients with moderate-severe asthma, eosinophilic inflammation is more pronounced in the bronchi than in the nasal mucosa whereas in patients with mild asthma inflammation appears to be similar in both sites.
- Moreover, eosinophilic inflammation of the nasal mucosa exists in asthma patients without any symptoms.
- However, the remodeling of the airways that can be found in the bronchial mucosa appears to feature less extensively in the nasal mucosa.

Minimal Persistent Inflammation

When exposure to allergen is too low to provoke symptoms, a weak inflammatory infiltration occurs in the mucosa. This process is called **'minimal persistent inflammation'** (MPI) and it has been demonstrated in both mite-induced and pollen-induced rhinitis. MPI also involves a weak and persistent expression of intracellular adhesion molecule-1 (ICAM-1) the major receptor molecule for human rhinoviruses. MPI and ICAM-1 expression in asymptomatic allergic subjects are important because asthma exacerbations in children are frequently related to upper respiratory viral infections, primarily due to rhinoviruses. MPI and ICAM-1 expression in asymptomatic allergic subjects are important because asthma exacerbations in children are frequently related to upper respiratory viral infections, primarily due to rhinoviruses. Another functional systemic link between the nose and bronchi has recently been hypothesized, based on the observation that bone marrow can promptly and specifically respond to nasal challenge by increasing the rates of production and maturation of eosinophilic precursors.

Fig: Inflammation: An underlying cause of chronicity of the airways



Possible mechanisms for the link

1. *Nasal-bronchial Reflex*

More than 30 years ago, the existence of a nasal-bronchial reflex was proposed as a possible basis for a physiologic connection between upper and lower respiratory tract disorders.

In this paradigm, nasal stimulation promotes bronchoconstriction through a reflex arc with the afferent arm located in the pharyngolaryngeal area, a central locus possibly in the hypothalamic area and vagal efferents.

2. *Shared Inflammation*

One such study that illustrated the association between inflammation in the nose and in the airways, evaluated whether cellular infiltration was present in the nasal mucosa of asthmatic patients even in the absence of rhinitis symptomatology. It measured nasal and lung eosinophil counts in asthmatic patients with and without allergic rhinitis and in healthy control subjects. The results showed that activated eosinophil counts, in the lung, were significantly ($p < 0.01$) higher in both asthma groups when compared with the control group. Asthmatic patients, with or without rhinitis, also have elevated positive eosinophils in the nasal mucosa compared with controls. Further, there was a significant correlation ($r = 0.85$, $p = 0.001$) between elevations in both nasal and lung eosinophil counts. *This demonstrates that inflammatory cells are present in the nasal mucosa of asthmatic patients even in the absence of rhinitis symptoms.*

3. *Post-nasal drip of inflammatory material*

Patients frequently complain that post-nasal drip triggers episodes of coughing and wheezing. Early studies investigating the possibility of aspiration of nasal secretions demonstrated that substances placed in the upper respiratory tract could later be recovered from the tracheobronchial tree.

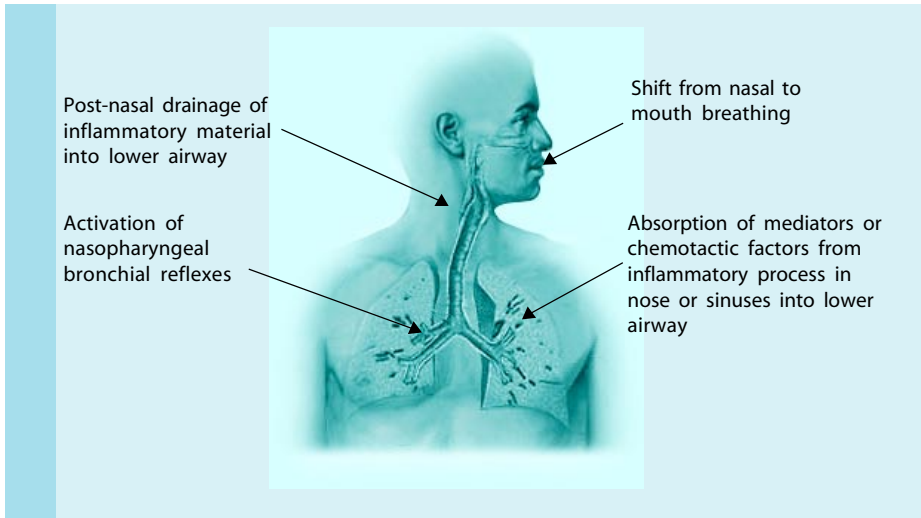
4. *Mouth breathing caused by nasal obstruction*

Nasal blockage resulting from tissue swelling and secretions may cause a shift from the normal pattern of nasal breathing to predominantly mouth breathing. Previous work has shown that mouth breathing associated with nasal obstruction resulted in worsening of exercise-induced bronchospasm, whereas exclusive nasal breathing significantly reduced asthma after exercise. Improvements in asthma associated with nasal breathing may be the result of superior humidification and warming of inspired air before it reaches the lower airways. Similarly, it would be expected that airborne allergens and pollutants would also be less likely to enter the lungs during periods of normal nasal function.

Table: Possible mechanisms linking rhinitis to asthma

- Neural (nasal bronchial reflex)
- Post-nasal drip of inflammatory cells and/or mediators from the nose into the lower airways which leads to absorption of inflammatory cells and/or mediators from the nose into the systemic circulation and ultimately the lung
- Shared Inflammation
- Nasal obstruction causing reduction in filtration, humidification and warming function of the nose.

Fig: Proposed mechanisms for the pathologic link between the upper and lower airway diseases



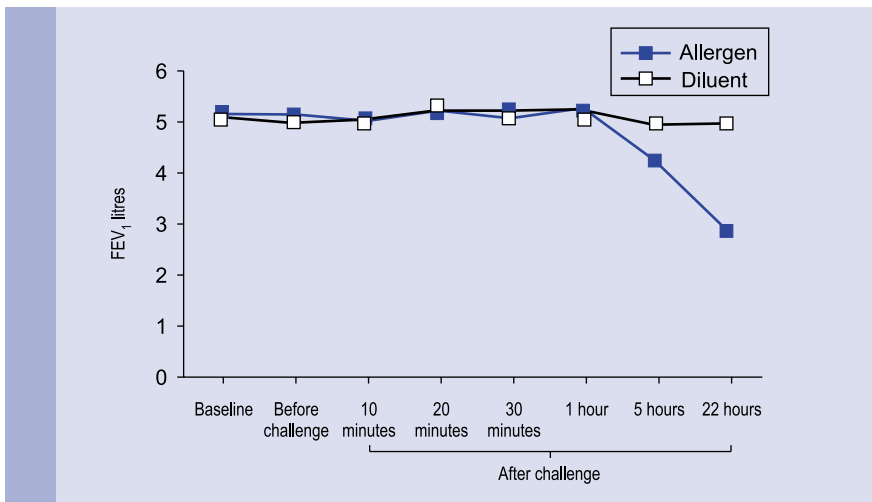
Clinical Evidence

A number of clinical and experimental observations that indicate a complicated relationship, have been made. These observations centre around the concept that changes in the nasal airways might affect the lower airways.

In 1992, Corren *et al* suggested that nasal provocation with allergen could lead to increased lower airways responsiveness in subjects with allergic rhinitis and asthma.

It has also been shown that, although lung function does not change immediately after nasal allergen challenge, 6 hours later, a significant reduction in FEV₁ and FVC can be seen.

Fig: Evaluation of FEV₁ in a subject with allergic rhinitis and asthma who underwent nasal provocations (1 with allergen and 1 with its diluent) on 2 occasions that were separated by approximately 2 weeks. The depicted subject's response represents an extreme in a wide spectrum. On average, about 25% to 30% of asthmatic patients who undergo a single nasal-allergen provocation demonstrate meaningful reductions in lung function. These reductions peak after 5 to 6 hours.



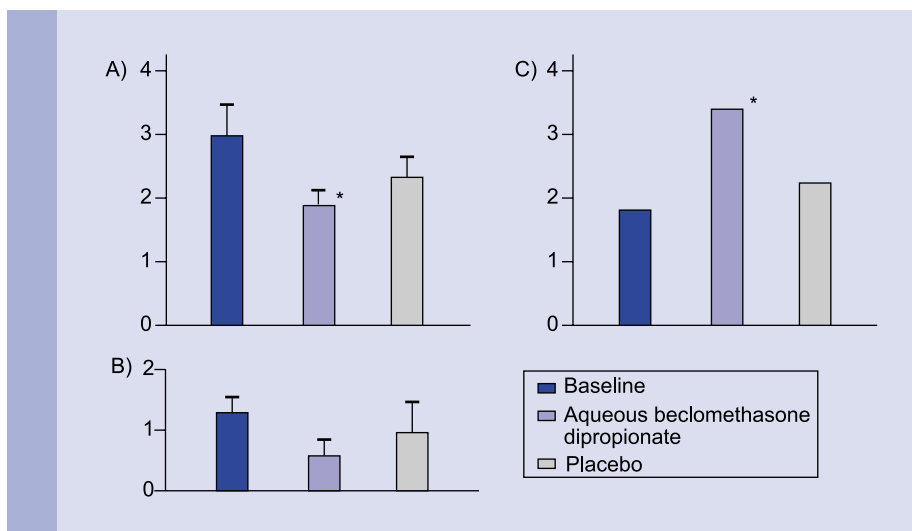
The connection between the upper and lower respiratory tracts can also be studied in terms of response to therapy. Various studies have shown that patients with allergic rhinitis and asthma had lower airway responsiveness after use of intranasal corticosteroids. This decrease in responsiveness may be associated with decreased symptoms on exposure to other stimuli such as allergens, physical exercise, or cold, dry air inhalation. Ignoring inflammation in the upper airway may lead to suboptimal results in asthma treatment.

In this particular study the effects of intranasal aqueous beclomethasone (IN aq BDP) with intranasal placebo on changes in lower airway responsiveness in patients with AR and asthma was studied. Twenty-one patients with PAR or asthma, with documented lower airway hyperresponsiveness (PC_{20} methacholine < 8 mg/ml), were treated with IN aq BDP (100 mcg) & placebo, in each nostril bid in a double-blind, crossover manner for 4 weeks. Patients recorded rhinitis and asthma symptom scores and monitored peak expiratory flow rates every morning and evening. Patients recorded global assessment of rhinitis and global asthma symptom scores at the beginning and end of each treatment. PC_{20} methacholine was performed at baseline and at the end of each treatment period. There was significant improvement in the daily rhinitis symptom scores (nasal stuffiness, nasal itching, sneezing, post-nasal drip and nasal discharge) and also the global assessment of rhinitis. Improvement was seen in the asthma symptoms also but these were not statistically significant.

However, the geometric mean of PC_{20} methacholine improved significantly after 4 weeks of IN aq BDP, but not after placebo ($p = 0.04$). Nine of the 21 patients had more than a doubling dose increase in PC_{20} methacholine after active treatment. The study therefore shows that

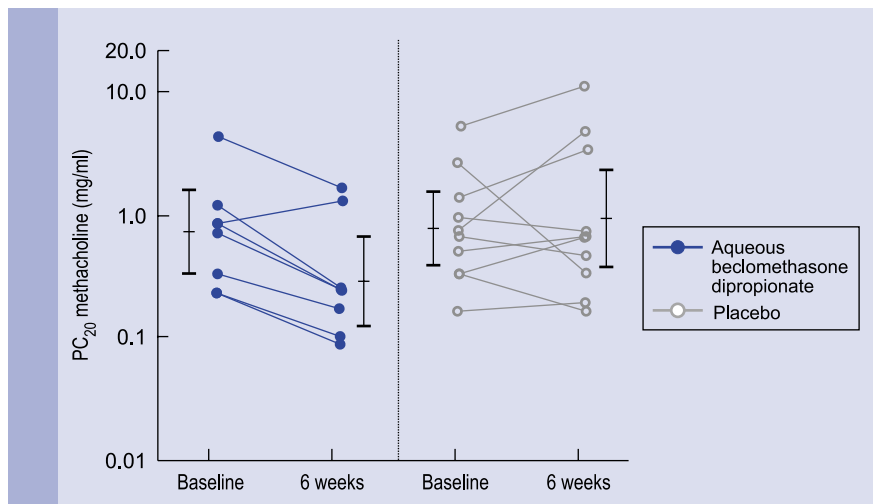
treatment of AR with IN aq BDP improved rhinitis and asthma symptoms and airway responsiveness. This decrease in responsiveness may be associated with decreased symptoms on exposure to other stimuli such as allergens, physical exercise, or cold, dry air inhalation.

Fig: Effects of treatment on global assessments; (a) Rhinitis scores decreased significantly after beclomethasone treatment ($p=0.05$). (b) Asthma symptom scores: no significant differences were seen between the two treatments. (c) Geometric mean PC_{20} methacholine increased significantly after intranasal beclomethasone ($p=0.04$)



Another study confirmed that intranasal corticosteroids can prevent the seasonal increase in bronchial hyperresponsiveness in patients with both seasonal allergic rhinitis and asthma. In this study, 18 patients with a history of seasonal allergic rhinitis and asthma, who had a positive skin test to ragweed and bronchial hyperresponsiveness to inhaled methacholine, were randomized to treatment with BDP (two sprays twice daily, 336 $\mu\text{g}/\text{day}$) or placebo.

Fig: Concentration of methacholine producing a 20% reduction in FEV₁ (PC₂₀) for patients at baseline and after 6 weeks treatment with BDP or placebo. Intergroup difference (v/s baseline) p=0.022



Once again, intranasal treatment with the corticosteroid prevented the increase in lower hyperresponsiveness, as characterized by the significant ($P = 0.22$) decrease in PD₂₀ to methacholine compared with placebo.

Other treatments for seasonal allergic rhinitis, such as antihistamines, have also been shown to be effective in reducing the symptoms of asthma.

In a 6-week, double-blind, randomized study in 93 subjects (aged 12–70 years) with a history of SAR and asthma, loratadine (5 mg) plus pseudoephedrine (120 mg) (L/P) twice daily was significantly more effective than placebo in reducing total rhinitis and asthma severity scores. Peak expiratory flow rates improved significantly in patients treated with L/P as did FEV₁ vs placebo. In addition, select measures of the asthma – specific quality of life improved significantly relative to placebo.

Fig: PEFs in morning (A.M.) and evening (P.M.), expressed as mean changes from baseline. *p<0.05

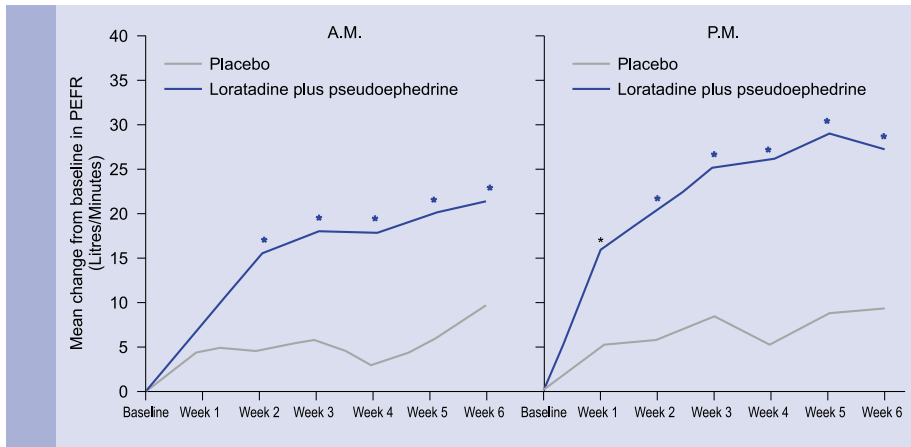
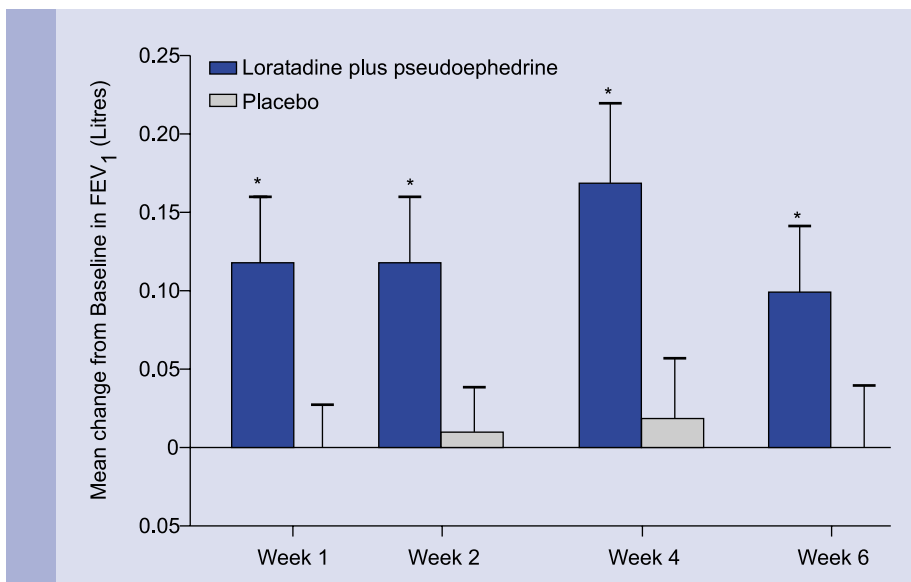


Fig: FEV₁ (mean±SEM) measured at clinic visits, expressed as changes from baseline. *p<0.05



After decades of research, a new class of medication has emerged that focuses on leukotrienes, mediators of inflammation. Of the available anti-leukotrienes, Montelukast which blocks the interaction of cysteinyl leukotrienes with their receptors resulting in downstream events is the most widely studied and accepted molecule in this class. Recently, the results of the COMPACT study (Clinical Outcomes with Montelukast as a Partner to inhaled Corticosteroids Therapy) were published. According to the study the addition of Montelukast (MNK) to inhaled Budesonide (BUD) is an effective and well tolerated alternative to doubling the dose of inhaled BUD in adult asthma patients experiencing symptoms and inadequate control on BUD alone.

In a post-hoc analysis of patients with a history of AR, in the COMPACT trial, 216 received both MNK and BUD, and 184 who received double-dose BUD.

Over 12 weeks, both treatments significantly improved morning PEF. In the subgroup of patients with AR, the treatment difference significantly favoured Montelukast + Budesonide 14.2 L/min (95% CI; 1.6-26.8; $p = 0.03$) compared with 4.2 L/min ($p = 0.36$) in the full cohort.

So, it can be concluded that in a select group of patients with AR, treatment resulted in greater improvement in an asthma end point compared to the asthma improvement in patients without AR.

This trial further emphasizes on the fact that ***having allergic rhinitis, impacts on asthma.***

Implications for Therapy

The main concept is that of integration of the two conditions, allergic rhinitis and asthma, as manifestations of one syndrome, *the chronic allergic respiratory syndrome*.

In examining and treating this syndrome, we should be simultaneously considering the parallel relationship between rhinitis and asthma.

In patients with rhinitis, repetitive evaluation of the lower airways should be part of a clinical routine in an effort towards early detection of symptoms and signs of bronchial involvement. In patients with asthma, the nasal airways should become part of standard clinical assessment and follow-up, and rhinosinusitis should be managed aggressively.

In treating the chronic allergic respiratory syndrome, we should take into account its systemic inflammatory aspect and should adjust pharmacotherapy accordingly. It has been shown that treatment of AR with intranasal corticosteroids and/or antihistamines have the capacity to modulate different aspects of the inflammatory cascade leading to improvement in concomitant asthma.

Further, in those patients where rhinitis precedes asthma, future research will also need to explore how rhinitis may be a risk factor for asthma and whether timely rhinitis treatment can delay, or even prevent asthma development.

In the primary care setting, prompt recognition and diagnosis of allergic rhinitis may be the first step in the identification of a systemic inflammatory aspect that can encompass both upper and lower respiratory disorders.

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