Rhinology, 45, 112-121, 2007

Does rhinitis lead to asthma?

Paul Van Cauwenberge[1], Jean-Baptiste Watelet[1], Thibaut Van Zele[1], De-Yun Wang[2], Elina Toskala[3], Stephen Durham[4], Wytske Fokkens[5], Susanne Lau[6], Benedicte Leynaert[7], Magnus Wickman[8], Marianella Salapatas[9], Peter Burney[10], Joaquim Mullol[11] and members of GA^{2}LEN workpackages 3.2. and 3.3.

[1] Department of Otorhinolaryngology, Ghent University, Belgium
[2] Department of Otolaryngology, National University of Singapore, Singapore
[3] Department of Otorhinolaryngology, Helsinki University Central Hospital, Finland
[4] Allergy and Clinical Immunology, National Heart and Lung Institute, Imperial College, London, United Kingdom
[5] Department of Otorhinolaryngology, Academic Medical Center, University of Amsterdam, The Netherlands
[6] Department of Paediatric Pneumology and Immunology, Charité University Medical Center, Berlin, Germany
[7] INSERM Unit 700, Paris, France
[8] Occupational and Environmental Health, Stockholm County Council, Stockholm, Sweden
[9] European Federation of Allergy, Asthma Associations, Vice-President
[10] Department of Public Health Sciences, King's College London, United Kingdom
[11] Rhinology Unit, Department of Otorhinolaryngology, Hospital Clinic-IDIBAPS, Barcelona, Catalonia, Spain

SUMMARY

Rhinitis and asthma are commonly linked even if the precise pathological mechanisms explaining the relationship are not fully understood. Although there is increasing evidence that rhinitis may influence the development of asthma, there remain many gaps in our understanding of the processes involved.

The complexity of this relationship is mainly due to the multiple interactions between genetic background, environmental factors and the specific host reaction. Epidemiological surveys have highlighted significant clinical associations and identified some factors that favour the progression from rhinitis to asthma. Basic research has demonstrated numerous similarities in inflammatory and immunological mechanisms.

Key words: rhinitis, asthma, epidemiology, pathogenesis, pharmacotherapy

INTRODUCTION

Since the publication in 2001 of the Allergic Rhinitis and its Impact on Asthma (ARIA) report [(1)], the relationship between rhinitis and asthma has been the scope of recent epidemiological surveys, basic research studies, and clinical trials. Results of a recent survey suggested that comorbid asthma and allergic rhinitis substantially impact patient well-being and that the worsening of allergic rhinitis symptoms in patients with asthma can be associated with worsening asthma symptoms [(2)].

Evidence shows that rhinitis and asthma are intimately linked but that some major gaps in our knowledge remain.

I. DOES EPIDEMIOLOGICAL EVIDENCE OF SUCH A RELATIONSHIP EXIST?

Rhinitis is a risk factor for asthma independent of allergy. Epidemiological studies have consistently shown that asthma and rhinitis often co-exist in the same patients [(1,3-7)]. In an international cross-sectional study in young adults, 74-81% of subjects with asthma reported symptoms of rhinitis. Conversely, the risk of asthma increased from 2% in subjects without rhinitis to 6.7-18.8% in subjects with allergic rhinitis [(8)].

Asthma is more frequently associated with perennial allergic rhinitis (PAR). Furthermore more severe asthma was associated with PAR compared to seasonal allergic rhinitis (SAR) [(9,10)].

Recent epidemiological studies reported the prevalence of asthma in allergic rhinitis patients as 20.4% [(11)] and 24% [(12)] compared to 3.9% and 2%, respectively, in controls. In two separate epidemiological studies [(12-14)], the prevalence of asthma in intermittent and persistent allergic rhinitis was the same. In children, allergic rhinitis is often diagnosed later than asthma [(15)]. This may be due, at least in part, because rhinitis symptoms in childhood are often ignored. Some prospective longitudinal studies actually suggest the opposite, namely that rhinitis frequently precedes the development of asthma. Data from Wright and colleagues [(16)] showed that children whose allergic rhinitis began in the first year of life had more respiratory symptoms at age six and were more likely to have a diagnosis of asthma.

Other prospective and longitudinal studies supported the view that rhinitis frequently precedes the development of asthma [(17-23)]. Because rhinitis and asthma are so strongly associated in cross-sectional surveys, and because rhinitis often precedes the development of asthma, rhinitis itself might be a risk factor for

asthma [8]. Allergic rhinitis has also been found to be associated with an increased risk of bronchial hyperresponsiveness in population-based study, even in subjects without diagnosed asthma [24]. In a study of patients with persistent allergic rhinitis, 54 % showed signs of early bronchial impairment and nasal function was firmly related to bronchial calibre and bronchial hyperreactivity (BHR) grade [25].

In Europe, 18 birth cohort studies on asthma and atopic diseases have been identified with in predominately urban/metropolitan settings [26].

II. WHICH MECHANISMS ARE SUSPECTED TO LINK RHINITIS WITH ASTHMA?

Bronchial asthma and rhinitis are both manifestations of an inflammatory process within a continuous airway system [27-29]. The upper and lower airway may be considered as a unique entity, influenced by a common and probably evolving inflammatory process [1], which may be sustained and amplified by intertwined mechanisms of several risk factors.

II.a. Could anatomical similarities between upper and lower airways help explain the link between rhinitis and asthma?

The histological features of the nasal and bronchial mucosa have several similarities. Both are characterized by a pseudostratified epithelium with columnar, ciliated cells resting on a basement membrane. Underneath the epithelium, in the submucosa, vessels, and mucous glands are present with structural cells (fibroblasts), inflammatory cells (essentially monocytic cells, lymphocytes and mast cells), and nerves. There are also striking differences. In the nose, there is a large subepithelial capillary and arterial system and venous cavernous sinusoids. This high degree of vascularisation is a key feature of the nasal

Table 1. Levels of evidence for treating rhinitis and asthma: rhinitis treatment influencing the course of asthma.

Class	Evidence	Drug	Reference	Type of study	Effect
Antihistamines	Ib	Cetirizine	Grant JA, JACI 1996 [69]	Randomized, double blind, placebo controlled	+ asthma symptoms
	Ib	Terfenadine	Rafferty P, Br J Clin Pharmacol 1990 [72]	Randomized, double blind, placebo controlled, crossover	+ asthma symptoms
			Taytard A, Br J Clin Pharmacol 1987 [73]	Randomized, double blind, placebo controlled, crossover	+ asthma symptoms
	Ib	Levocetirizine	Pasquali M, Cllin Exp Allergy 2006 [84]	Randomized, placebo controlled,	+ QOL
	Ib	Desloratadine	Reinartz SM, Allergy 2005 [80]	Randomized, placebo controlled,	+ allergic inflammation
			Berger WE, Ann Allergy Asthma Immunol 2002 [81]	Randomized, double blind, placebo controlled	+ asthma symptoms
			Baena-Cagnani Int Arch Allergy 2003 [82]	Randomized, double blind, placebo controlled	+ asthma symptoms and beta-agonist use
Cromones	Ib	Cromolyn	Welsh PW, Mayo clin Proc 1987 [111]	Randomized, placebo controlled	+ asthma symptoms
Nasal steroids	Ia	Nasal steroids	Taramarcaz, Cochrane Rev 2003 [93, 94]	Meta-analysis	+ but no significant effect on asthma symtpoms
Immunotherapy	Ib	Subcutaneous immunotherapy	Bahceciler NN, Pediatr Pulmonol 2001 [107]	Randomized, double blind, placebo controlled	+ asthma exacerbations and PEF
	IIa	Sublingual immunotherapy	Marogna M, Allergy 2004 [105]	Randomized controlled open study	+ BHR and asthma symptoms
Leukotriene modifiers	Ib	Montelukast	Baena-Cagnani Int Arch Allergy 2003 [83]	Randomized, double blind, placebo controlled	+ asthma symptoms and beta-agonist use
			Perry T, Ann Allergy Asthma Immunol 2004 [102]	Randomized, double blind, placebo controlled	+ lower and upper airway responses
Anti-IgE	Ib	Omalizumab	Vignola M, Allergy 2004 [110]	Randomized, double blind, placebo controlled	+ asthma exacerbations and QoL

Table 2. Levels of evidence for treating rhinitis and asthma: asthma treatment influencing the course of rhinitis.

Class	Evidence	Drug	Reference	Type of study	Effect
Inhaled steroids	IIa	Budesonide	Greiff L, Eur Respir J 1998 [112]	Not randomized, placebo controlled	+ nasal symptoms and inflammation

mucosa and changes in vasculature may lead to severe nasal obstruction. On the other hand, in the nose, there is no airway smooth muscle, whereas in the lower respiratory tract, smooth muscle is present from the trachea down to the bronchioles which accounts for bronchoconstriction as a cardinal feature of asthma. Although both diseases are caused by similar environmental risk factors, these structural end-organ differences may account, at least in part, for the differences in the clinical manifestations and severity of allergic rhinitis compared to bronchial asthma.

II.b. What are the physiological links between the nose and the lung?

The nose is a natural airway, and breathing through the nose rather than the mouth is essential for protection of the lower airway against contaminants in inhaled air [30]. The two major functions of the nose are to maintain normal airway function and to filter and condition inspired air, which contains potentially harmful particles, such as pollen grains or other allergens, inorganic dust particles or microbes, all of which could damage the bronchial mucosa if they reached the lungs. During its passage in the nasal cavity, particles larger than 5 - 10 μm are filtered out. Another important function of the nose is to warm and humidify incoming air.

Many patients with seasonal allergic rhinitis also have lower respiratory symptoms such as cough and wheeze, and many experience lower respiratory tract symptoms, particularly when the pollen count is high. Allergic rhinitis with associated nasal obstruction may result in pollen grains reaching the bronchial mucosa and resulting in symptoms of bronchial asthma. Although there is evidence of inflammation in the bronchial mucosa in seasonal rhinitis, remodelling of the bronchi, which characterises perennial asthma, is usually absent and bronchial symptoms subside at the end of the pollen season [1].

II.c. What can we learn from the immunological and pathophysiological relationships between rhinitis and asthma?

Allergic rhinitis and asthma are characterized by similar inflammatory processes in which mast cells, basophils and eosinophils play a defining role [31].

Imbalance between Th2 and Th1 cells, in favour of Th2 plays an important role in the regulation of IgE synthesis and cell recruitment at sites of allergic inflammation. In allergic rhinitis, many studies have demonstrated that mucosal inflammation is characterized by the tissue infiltration of T-lymphocytes (CD4+ T-cells and CD25+ T-cells) in the submucosa and epithelium [32,33]. These pathophysiological characteristics are found in both allergic rhinitis and asthma.

Synthesis of allergen-specific IgE is required for the development of allergic diseases including allergic rhinitis and allergic asthma but many individuals with allergen-specific IgE do not develop symptoms [34].

It is likely that inflammation in the nasal mucosa may contribute to worsening of bronchial asthma through several putative mechanisms [35]. The same inflammatory cells (T cells, eosinophils) and Th2-like cytokines have been found in nasal and bronchial biopsy specimens [36]. The number of eosinophils in nasal smears correlates well with abnormalities of pulmonary function tests and the level of non-specific bronchial responsiveness as measured by methacholine inhalation challenge [37]. In a study of patients with allergic rhinitis without bronchial asthma, segmental bronchial allergen provocation resulted in nasal inflammation characterised by tissue eosinophilia and upregulation of the eosinophil-specific adhesion molecule VCAM-1. Conversely, nasal allergen provocation resulted in allergic inflammation detectable in both the nasal and bronchial mucosa [38]. Several mechanisms have been proposed to explain the link between uncontrolled allergic rhinitis and the occurrence or worsening of bronchial asthma. These include: (a) the existence of a neural (naso-bronchial) reflex, (b) possible post-nasal drip of inflammatory cells and/or mediators from the nose into the lower airway, an event that is most unlikely (c) absorption of inflammatory cells and/or mediators from the nose into the systemic circulation and ultimately ending up in the bronchi, and (d) nasal obstruction resulting in a reduction in filtration, humidification, and warming of incoming air [35,39].

However, these mechanisms are unlikely singley to explain the entire pathological link between allergic rhinitis and asthma, as both diseases can be clinical manifestations of a systemic inflammatory process within the respiratory tract. In a nasal challenge study with house dust mites in adult patients with persistent allergic rhinitis, all patients (n=20) produced a similar early- and late-phase response by presenting nasal symptoms, inflammatory cell infiltration and mediator release in nasal secretions after challenge. Only three patients (3/5) with a history of asthma showed a fall in FEV1 readings (33%, 22% and 11% from the baseline) at seven hours post challenge and concomitant mild wheezing at night [40]. This study showed that nasal provocation may elicit concomitant asthmatic symptoms during the late phase reaction, especially in patients with a history of asthma.

II.d. Can genetic research solve the problem?

Atopy, the predisposition to develop IgE to common inhaled allergens, is a key underlying pathogenic mechanism in both allergic rhinitis and asthma. Atopy has a strong familial tendency, starting usually in childhood or adolescence [41]. Many candidate genes have been identified both by positional cloning and by linkage analysis [42-44]. A genome wide search has shown associations between certain phenotypes of allergic disease with markers on more than 14 pairs of chromosomes (chromosomes 1, 2, 3, 5, 6, 7, 9, 11, 12, 13, 14, 16, 17, 19). The complex mechanisms of inheritance of atopy and their relation to the development of clinical manifestations of atopy (allergic diseases), remain incompletely understood.

II.e. Could other environmental factors play a role?

The gene/environment interface is critical in the expression of

Table 3. Levels of evidence for treating rhinitis and asthma: rhinitis treatment preventing the allergy march.

Class	Evidence	Therapies	Reference	Type of study	Effect
Immunotherapy	Ib	Subcutaneous immunotherapy in children	Moller C, J Allergy Clin Immunol 2002 [123]	Randomized	Reduction in development of asthma
		Sucutaneous immunotherapy in children	Niggeman B. Allergy 2006 [108]	Randomized	Reduction in development of asthma
		Subcutaneous immunotherapy in adults	Polosa R, Allergy 2004 [121]	Randomized, placebo controlled	Prevention of natural progression to asthma
	Ia	Sublingual immunotherapy in children	Calamita Z et al. Allergy [109]	Meta-analysis	Beneficial but effect not large
	II	Nasal immunotherapy	Olivieri M, J Investig Allergol Clin Immunol 2000 [125]	Randomized, not placebo controlled	Onset of bronchial asthma
Antihistamines	Ib	Terfenadine	Ciprandi G, Allergy 1999 [71]	Randomized, double-blind, placebo controlled	Decrease respiratory symptoms and allergic inflammation
	Ib	Cetirizine	ETAC study group, Ped Allergy Immunol 1998 [116]	Randomised, double blind, placebo controlled	Reduction in development of asthma

Table 4. Levels of evidence for treating rhinitis and asthma. Combination therapies are better than single therapies.

Class	Evidence	Reference	Type of study	Effect
Becomethasone dipropionate inhaled and intranasal	IIa	Stelmach R, Chest 2005 [100]	Not randomized, double blind	No difference between nasal or combined therapy
Fluticasone/salmeterol with or without montelukast or fluticasone nasal spray	Ib	Nathan RA, Chest 2005 [127]	Randomized, not blinded, placebo controlled	No difference between nasal or combined therapy
Zafirlukast with nasal budesonide	Ib	Benitez HH, Rev Alergol Mex 2005 [128]	Randomized, double blind	Combination more effective
Intranasal and inhaled fluticasone	Ib	Dahl R, Allergy 2005 [129]	Randomized, double-blind, placebo controlled	Combination more effective
Loratadine and montelukast	IV	Currie GP, Q J Med 2005 [133]	Review	Combination more effective
Loratadine and zafirlukast	IIb	Roquet A, Am J Respir Crit Care Med 1997 [131]	Quasi experimental study	Combination more effective
Budesonide and montelukast	Ib	Price DB, Allergy 2006 [132]	Randomized, double-blind	Combination more effective

clinical manifestations of allergy and, most likely, in the influence of rhinitis on asthma. There are insufficient epidemiological data on the interaction between pollutants and rhinitis. Furthermore, no clear differentiation can be made between the allergens that provoke asthma and those inducing rhinitis. It seems that, probably based on the nose's poor filtration ability with respect to low molecular weight compounds [45,46], rhinitis is less common than asthma in occupational-type allergic reactions against these agents [47,48].

There is only scanty evidence on the mechanisms of occupational-type respiratory allergies.

Natural exposure studies and provocation challenges are usually poorly designed for demonstrating the mechanisms supporting the relationship between rhinitis and asthma.

Finally, the direct or indirect influence of pollution or early life infections on rhinitis and/or asthma remains unclear. At present there is little evidence to support the routine recommendation of physical or chemical methods to control indoor allergen levels, in particular allergens from furry pets [49]. Although interventional studies in adults have shown little benefit, the majority of the studies in children suggest that environmental control measures may be of benefit [50].

II.f. Which questions are remaining to explain the link between rhinitis and asthma?

Although rhinitis and asthma frequently coexist, there exist

patients that are affected by only one of these disorders. Until now, these patients are clinically classified independently of each other and a possible evolution from one disease to the other is usually neglected. There is much heterogeneity in the definitions of rhinitis employed by epidemiologists, physicians and researchers. Standardization of definitions and methods of classification are urgently needed.

The natural history of rhinitis and asthma, the chronology of events, the parameters that favour the development of rhinitis, asthma or both is poorly explored, making the categorization of patients highly variable between studies. No guidelines are available for the systematic evaluation and comparison of different studies of the link between rhinitis and asthma.

For effective diagnosis and management of rhinitis, even if specific IgE antibody determination is a necessary step for diagnosis [51], there is a clear need to develop new diagnostic tools for early categorization of airway allergic patients. Development and validation of novel in vitro testing methods [52] and measurements of new inflammatory parameters or markers of remodelling are needed to allow better labelling of patients with only rhinitis, only asthma and subjects with both rhinitis and asthma. Such precise classification will permit testing of novel hypotheses concerning the relationship between rhinitis and asthma.

III. TREATMENT OF RHINITIS AND ASTHMA

Finally, there is evidence suggesting that co-morbid allergic rhinitis is a marker for asthma resistant to treatment and worsened asthma outcomes [53]. It highlights the potential for improving asthma outcomes by following a combined therapeutic approach to co-morbid allergic rhinitis and asthma rather than targeting each condition separately.

Clinical trials represent an important source of information for investigating the impact of rhinitis on asthma. By targeting one organ and acting on one specific phase of the pathomechanism, some important information could be collected.

III.a. Does rhinitis treatment influence the course of asthma?

An adequate treatment of allergic rhinitis in asthmatics has been shown to improve asthma symptoms [54-57], pulmonary function tests [55] and to reduce costs [58]. The risk of emergency room treatment or hospitalisations [59], exercise-induced asthma [60] or bronchial hyperesponsiveness [61,62] were also shown to have reduced.

Furthermore, inadequately controlled allergic rhinitis in asthmatic patients can contribute towards increasing asthma exacerbations and poorer symptom control, which may increase medical resource use [63]. The treatment of allergic rhinitis reduces the number of asthma-related hospitalisations and emergency department visits [64-66].

III.a.1. Antihistamines

Oral H1-antihistamines represent the first-line treatment of allergic rhinitis and must not be considered as first-line treatment in asthma. However, some studies with antihistamines have found a modest effect on asthma symptoms [67-71]. In most of the studies evaluated, antihistamines were administrated at higher than recommended doses and whereas symptoms improved, objective measures including pulmonary function tests and/or peak flow rates were often unchanged [72-76]. In general, whereas antihistamines may reduce peak seasonal wheezing associated with associated severe rhinitis symptoms, these drugs are not recommended for the treatment of asthma [77-79] and inhaled corticosteroids and long-acting bronchodilators must be preferred.

In patients with allergic rhinitis and concomitant asthma, cetirizine relieves upper and lower respiratory tract symptoms [77]. Desloratadine therapy improved allergic rhinitis, and the early bronchial response [80], asthma symptoms and reduced the need for beta-agonists [81] whilst not altering pulmonary function in patients with concomitant seasonal allergic rhinitis and asthma [82]. In addition, desloratadine was as effective as montelukast in reducing symptoms associated with asthma [83]. Finally, treatment with levocetirizine decreased both symptoms and improved quality of life (Rhinasthma questionnaire) in patients with persistent allergic rhinitis and asthma [84]. Prolonged therapy over 6 months with levocetirizine reduced co-morbidities including asthma in patients with persistent allergic rhinitis and improved rhinitis-specific quality of life [85]. The effects of the novel agents ebastine and rupatadine have yet to be tested in bronchial asthma in double-blind, placebo-controlled studies.

III.a.2. Intranasal glucocorticosteroids

Intranasal treatment with glucocorticosteroids (GCS) has been found to moderately improve asthma in some but not all studies [86-92].

A recent review identified a trend for a beneficial effect in asthma but no firm conclusions could be drawn [93]. Importantly, a recent Cochrane Airways review concluded that since AR and asthma patients treated with intranasal GCS did not show appreciable differences compared with patients who were not treated, the combination of intranasal plus intrabronchial corticosteroids should remain the current clinical practice pending more research [94].

Nasal beclomethasone prevented a seasonal increase in bronchial responsiveness in patients with allergic rhinitis and asthma [95,96]. A number of aspects, such as the extent to which the pathophysiology of the two diseases overlap, and whether treating one will affect the other, remains to be clarified. Triamcinolone acetonide nasal spray blocked the increase in bronchial hyperreactivity to metacholine after high-load natural pollen exposure in children with seasonal allergic rhinitis [97] and markers of lower airways inflammation [98]. Treatment of allergic rhinitis with intranasal glucocorticosteroids significantly reduced the level of cys-LTs, a major marker of lower airway inflammation, in exhaled breath condensate [99].

Although it has been suggested that some patients with asth-

ma and rhinitis can be controlled by use of nasal medication [100], cross-sectional analysis of the effectiveness of nasal corticosteroids on asthma outcomes may result in considerable exaggeration of the protective effect of these medications in preventing severe asthma exacerbations [101].

III.a.3. Oral glucocorticosteroids

Oral glucocorticosteroids are highly effective in the treatment of rhinitis and asthma but their long-term use for this indication is restricted by severe side effects.

III.a.4. Leukotriene modifiers

Leukotriene modifiers were shown to be effective in controlling the symptoms of mild to moderate asthma and the symptoms of rhinitis [102], and the use of asthma and rhinitis medication is reduced [103]. However, a large number of patients from 2-3 studies was needed to show a 5% difference from placebo that is clinically of limited value.

III.a.5. Immunotherapy

Specific immunotherapy is effective for patients with perennial allergic rhinitis with asthma, and improves significantly their lung function [104]. It can halve the clinical score and reduces bronchial hyperreactivity [105-107]. Immunotherapy for 3 years with standardized allergen extracts of grass and/or birch showed long-term clinical effect and had a preventive effect on development of asthma in children with seasonal rhinoconjunctivitis [108]. Finally, a recent Cochrane analysis concluded that sublingual immunotherapy is beneficial for asthma treatment, albeit the magnitude of the effect is not very large [109].

III.a.6. Other therapies

Omalizumab, an anti-IgE medication, was shown to be effective in preventing asthma exacerbations in patients with concomitant asthma and persistent allergic rhinitis [110]. However, clinical applications are limited by the high cost of this medication and nowadays, it cannot be considered as first-line therapy.

III.b. Does asthma treatment influence the course of rhinitis?

Less is known about the effects on nasal disease from inhaled (intra-bronchial) treatment with glucocorticosteroids. A study examined the effects on nasal allergic disease of inhaled budesonide (avoiding nasal deposition of the drug) in patients with seasonal allergic rhinitis but without asthma [111]. During the birch pollen season, budesonide reduced the seasonal eosinophilia both in the circulation and in the nose and produced an attenuation of seasonal nasal symptoms. Nasal and systemic anti-eosinophil actions are produced at commonly employed dose levels of orally inhaled budesonide.

Theophylline was found to reduce nasal inflammation [112]. It was also observed that theophylline can reduce bronchial hyperresponsiveness in patients with allergic rhinitis [113]. However, no controlled data exist concerning the therapeutic effect of this drug on nasal symptoms.

A high percentage of asthmatics have coincidental rhinitis and so treatment for asthma that is also beneficial for rhinitis would be applicable to many patients with asthma. Such approaches include humanized monoclonal antibodies against IgE, drugs inhibiting eosinophilic inflammation or inhibiting allergic inflammation.

III.c. Can an adequate treatment of rhinitis prevent the allergic march?

The prevention effect of pharmacological treatment of allergic rhinitis on seasonal asthma is highly controversial [114] and more data are needed to fully appreciate this effect.

In infants with house dust mite or grass pollen sensitisation, treatment with antihistamines may exert a prophylactic effect on asthma onset. In the ETAC® (Early treatment of the atopic child) trial, a multi-country, double-blind, randomised, placebo-controlled trial, when considering the total group of children, no significant difference was visible but cetirizine halved the number of patients developing asthma in the subgroups sensitised to grass pollen or to house dust mite [115].

Children with pollen allergy were treated for allergic rhinitis in an open trial of three-year specific immunotherapy or allergy vaccination. Results indicate that allergen vaccination with grass or tree pollen may reduce the development of asthma in children with allergic rhinitis [116,117]. Treatment with allergen immunotherapy could lower the risk of the development of new asthma cases in adults with allergic rhinitis [118]. In routine clinical practice, specific immunotherapy could, in some way, slow the march of allergy [119-122]. This should also be the case for sublingual immunotherapy in children [123] or adults [124] with allergic rhinoconjunctivitis. The working mechanisms leading to this remain unclear including the characteristics of patients susceptible to be good responders.

III.d. In asthmatics with allergic rhinitis, is a combination of therapies more effective than a single therapy?

It has been shown that loratadine plus pseudo-ephedrine improved nasal and asthma symptoms, pulmonary function and quality of life in patients with seasonal allergic rhinitis and concomitant mild asthma [125].

In patients with persistent asthma treated with fluticasone proprionate/salmeterol, the addition of montelukast or fluticasone proprionate aqueous nasal spray for the treatment of seasonal allergic rhinitis resulted in no additional improvements in overall asthma control compared with fluticasone proprionate/salmeterol alone [126]. The association of a nasal steroid (budesonide) with a leukotriene modifier (zafirlukast) was more effective for controlling nasal symptoms and especially bronchial symptoms than the association of a nasal steroid (budesonide) with antihistamines (loratadine) with pseudoephedrine [127]. In patients with pollen-induced rhinitis and asthma, the combination of intranasal and inhaled glucocorticosteroids (fluticasone) is needed to control the seasonal increase in nasal and asthmatic symptoms [128].

Several controlled studies suggest that combination therapy with antihistamines and antileukotrienes may be as effective as corticosteroid use in patients with allergic asthma and seasonal allergic rhinitis [129,130]. There is evidence in favour of the use of anti-leukotrienes to treat asthma and also rhinitis but more data are needed to fully evaluate their full potential. Moreover, the combination of anti-leukotriene and H1-antihistamine produces a predominant inhibition of allergen-induced allergy and late-phase airway obstruction in asthmatics [131]. In asthmatics with allergic rhinitis, a combined treatment approach that included montelukast and budesonide provided significantly greater, but limited efficacy in reducing airflow obstruction when compared with doubling the dose of budesonide [132]. However, complementary cost analyses are needed before supporting such a strategy and also direct comparisons with alternative strategies such as the addition of a theophylline or a long acting inhaled bronchodilator in terms of effect size and cost.

III.e. What questions remain?

As reported above, the major studies have focused on the possible influence of rhinitis treatment on the future course and outcome of bronchial asthma. Data analysing the inverse relationship are more fragmented. Furthermore, no specific treatment is proposed for patients combining rhinitis and asthma. They are usually treated for both conditions independently with the exception of allergen immunotherapy which has been shown to be effective for both conditions and no general therapy is usually prescribed. The duration of treatment also requires further evaluation.

The possible interaction between local treatments for upper and lower airways is poorly explored and no clear guidelines are available for adapting treatment options in concomitant rhinitis and asthma. Whether or not treating rhinitis improves asthma *per se*, it is important to recognise and treat rhinitis in patients with bronchial asthma because this improves their symptoms and quality of life, whether or not the asthma improves. Finally, only limited data exists for the possible preventive role of early treatment of atopic children in the development of clinical rhinitis and asthma, whereas the early indications from long term studies of allergen immunotherapy in children with rhinitis are encouraging.

CONCLUSIONS

Epidemiological surveys have highlighted important clinical associations between rhinitis and asthma and have also identified both genetic and environmental factors that may influence disease development. Basic research has demonstrated the numerous similarities in inflammatory and remodelling pathomechanisms. New models are required to enable better differentiation of patients suffering from rhinitis and asthma. Clinical trials with current medications for rhinitis and asthma have provided new insights on the complex link between rhinitis and asthma.

ACKNOWLEDGEMENTS

GA^{2}LEN (Global Allergy and Asthma European Network) is a European Commission funded network of excellence dedicated to allergy and asthma. Supported by EU framework programme for research, contract n° Food-CT-2004-506378.

REFERENCES

1. Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic rhinitis and its Impact on Asthma (ARIA) (ARIA Workshop Report). J Allergy Clin Immunol 2001; 108 (5 Suppl): S147-334.
2. Valovirta E, Pawankar R. Survey on the impact of comorbid allergic rhinitis in patients with asthma. BMC Pulmonary Medicine 2006; 6 (suppl 1): S3.
3. Yawn BP, Yunginger JW, Wollan PC, Reed CE, Silverstein MD, Harris AG. Allergic rhinitis in Rochester, Minnesota residents with asthma: frequency and impact on health care charges. J Allergy Clin Immunol 1999; 103: 54-59.
4. Sibbald B, Rink E. Epidemiology of seasonal and perennial rhinitis: clinical presentation and medical history. Thorax 1991; 46: 895-901.
5. Neukirch F, Pin I, Knani J, Henry C, Pison C, Liard R et al. Prevalence of asthma and asthma-like symptoms in three French cities. Respir Med 1995; 89: 685-692.
6. Huovinen E, Kaprio J, Laitinen LA, Koskenvuo M. Incidence and prevalence of asthma among adult Finnish men and women of the Finnish Twin Cohort from 1975 to 1990, and their relation to hay fever and chronic bronchitis. Chest 1999; 115: 928-936.
7. Matsuno O, Miyazaki E, Takenaka R, Ando M, Ito T, Sawabe T, et al. Links between bronchial asthma and allergic rhinitis in the Oita Prefecture, Japan. J Asthma. 2006; 43: 165-167.
8. Leynaert B, Neukirch C, Kony S, Guenegou A, Bousquet J, Aubier M, et al. Association between asthma and rhinitis according to atopic sensitization in a population-based study. J Allergy Clin Immunol. 2004; 113: 86-93.
9. Boulet LP, Turcotte H, Boutet M, Montminy L, Laviolette M. Influence of natural antigenic exposure on expiratory flows, methacholine responsiveness, and airway inflammation in mild allergic asthma. J Allergy Clin Immunol 1993; 91: 883-893.
10. Verdiani P, Di Carlo S, Baronti A. Different prevalence and degree of nonspecific bronchial hyperreactivity between seasonal and perennial rhinitis. J Allergy Clin Immunol 1990; 86: 576-582.
11. Bauchau V, Durham SR. Prevalence and rate of diagnosis of allergic rhinitis in Europe. Eur Resp J 2004; 24: 758-764.
12. Bousquet J, Annesi-Maesano I, Carat F, Leger D, Rugina M, Pribil C et al. Characteristics of intermittent and persistent allergic rhinitis: DREAMS study group. Clin Exp Allergy 2005; 35: 728-732.
13. Bachau V, Durham SR. Epidemiological characterization of the intermittent and persistent types of allergic rhinitis. Allergy 2005; 60: 350-353.
14. Van Hoecke H, Vastesaeger N, Dewulf L, De Bacquer D, van Cauwenberge P. Is the allergic rhinitis and its impact on asthma classification useful in daily primary care practice? J Allergy Clin Immunol 2006; 118: 758-759.
15. Sherman CB, Tosteson TD, Tager IB, Speizer FE, Weiss ST. Early childhood predictors of asthma. Am J Epidemiol 1990; 132: 83–95.
16. Wright AL, Holberg CJ, Martinez FD, Halonen M, Morgan W, Taussig LM. Epidemiology of physician-diagnosed allergic rhinitis in childhood. Pediatrics 1994; 94: 895-901.
17. Leynaert B, Bousquet J, Neukirch C, Korobaeff M, Liard R, Neukirch F. Perennial rhinitis: an independent risk factor for asthma in nonatopic subjects. Results from the European Community Respiratory Health Survey. J Allergy Clin Immunol 1999; 104: 301–304.
18. Jenkins MA, Hopper JL, Bowes G, Carlin JB, Flander LB, Giles GG. Factors in childhood as predictors of asthma in adult life. BMJ 1994; 309: 90-93.
19. Huovinen E, Kaprio J, Laitinen LA, Koskenvuo M. Incidence and prevalence of asthma among adults Finnish men and women of

the Finnish Twin Cohort from 1975 to 1990, and their relation to hay fever and chronic bronchitis. Chest 1999; 115: 928-936.
20. Anderson HR, Pottier AC, Strachan DP. Asthma from birth to age 23: incidence and relation to prior and concurrent atopic disease. Thorax 1992; 47: 537-542.
21. Settipane RJ, Hagy GW, Settipane GA. Long-term risk factors for developing asthma and allergic rhinitis: a 23-year follow up study of college students. Allergy Proc 1994; 15: 21-25.
22. Plaschke PP, Janson C, Norrman E, Björnsson E, Ellbjär S, Järvholm B. Onset and remission of allergic rhinitis and asthma and the relationship with atopic sensitization and smoking. Am J Respir Crit Care Med 2000; 162: 920-924.
23. Guerra S, Sherrill DL, Martinez FD, Barbee RA. Rhinitis as an independent risk factor for adult-onset asthma. J Allergy Clin Immunol 2002; 109: 419-425.
24. Leynaert B, Bousquet J, Neukirch C, Korobaeff M, Liard R, Neukirch F. Perennial rhinitis: an independent risk factor for asthma in nonatopic subjects. Results from the European Community Respiratory Health Survey. J Allergy Clin Immunol 1999; 104: 301–304.
25. Ciprandi G, Cirillo I, Vizzaccaro A, Monardo M, Tosca MA. Early bronchial airflow impairment in patients with persistent allergic rhinitis and bronchial hyperreactivity. Med Respir 2005; 99: 1606-1612.
26. Keil T, Kulig M, Simpson A, Custovic A, Wickman M, Kull I et al. European birth cohort studies on asthma and atopic diseases: I. Comparison of study designs: a GA^2LEN initiative. Allergy 2006; 61: 221-228.
27. Meltzer EO. The relationships of rhinitis and asthma. Allergy Asthma Proc 2005; 26: 336-340.
28. Chakir J, Laviolette M, Turcotte H, Boutet M, Boulet LP. Cytokine expression in the lower airways of nonasthmatic subjects with allergic rhinitis : influence of natural allergen exposure. J Allergy Clin Immunol 2000; 106: 904-910.
29. Braunstahl GJ, Kleinjan A, Overbeek SE, Prins JB, Hoogsteden HC, Fokkens WJ. Segmental bronchial provocation induces nasal inflammation in allergic rhinitis patients. Am J Respir Crit Care Med 2000; 161: 2051-2057.
30. Togias A. Rhinitis and asthma: evidence for respiratory system integration. J Allergy Clin Immunol 2003; 111: 1171-1183.
31. Gillissen A, Hoffken G, Juergens UR. A connection between allergic rhinitis and allergic asthma? The "one-airway-one-disease"-hypothesis. Pneumologie 2005; 59: 112-119.
32. Varney VA, Jacobson MR, Sudderick RM, Robinson DS, Irani AM, Schwartz LB et al. Immunohistology of the nasal mucosa following allergen-induced rhinitis. Identification of activated T lymphocytes, eosinophils, and neutrophils. Am Rev Respir Dis 1992; 146: 170-176.
33. Durham SR, Ying S, Varney VA, Jacobson MR, Sudderick RM, Mackay IS et al. Cytokine messenger RNA expression for IL-3, IL-4, IL-5, and granulocyte/macrophage-colony-stimulating factor in the nasal mucosa after local allergen provocation: relationship to tissue eosinophilia. J Immunol 1992; 148: 2390-2394.
34. Bousquet J, Anto JM, Bachert C, Bousquet PJ, Colombo P, Crameri R et al. Factors responsibles for differences between asymptomatic subjects and patients presenting an IgE sensitization to allergens. A GA^2LEN project. Allergy 2006; 61: 671-680.
35. Corren J. The impact of allergic rhinitis on bronchial asthma. J Allergy Clin Immunol 1998; 101: S352-S356.
36. Bousquet J, Vignola AM, Demoly P. Links between rhinitis and asthma. Allergy 2003; 58: 691–706.
37. Ciprandi G, Vizzaccaro A, Cirillo I, Tosca M, Massolo A, Passalacqua G. Nasal eosinophils display the best correlation with symptoms, pulmonary function and inflammation in allergic rhinitis. Int Arch Allergy Immunol 2005; 136: 266-272.
38. Braunstahl GJ, Overbeek SE, KleinJan A, Prins JB, Hoogsteden HC, Fokkens WJ. Nasal allergen provocation induces adhesion molecule expression and tissue eosinophilia in upper and lower airways. J Allergy Clin Immunol 2001; 107: 469–476.
39. Aubier M, Levy J, Clerici C, Neukirch F, Cabrieres F, Herman D. Protective effect of theophylline on bronchial hyperresponsiveness in patients with allergic rhinitis. Am Rev Respir Dis 1991; 143: 346-350.
40. Wang DY, Goh DYT, Ho AKL, Chew FT, Yeoh KH, Lee BW. The upper and lower airway responses to nasal challenge with house dust mite Blomia tropicalis. Allergy 2003; 58: 78-82.
41. Johansson SGO, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, et al. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. J Allergy Clin Immunol 2004; 113: 832-836.
42. Toda M, Ono SJ. Genomics and proteomics of allergic disease. Immunology 2002; 106: 1-10.
43. Moffatt MF, Cookson WO. Genetics of asthma and inflammation: the status. Curr Opin Immunol 1999; 11: 606-609.
44. Peden DB. Influences on the development of allergy and asthma. Toxicology 2002; 181-182: 323-328.
45. Watelet JB, Van Cauwenberge P. Applied anatomy and physiology of the nose and paranasal sinuses. Allergy 1999; 54 Suppl 57: 14-25.
46. Seaton A, MacNee W, Donaldson K, Godden D. Particulate air pollution and acute health effects. Lancet 1995; 345: 176-178.
47. Malo JL, Lemiere C, Desjardins A, Cartier A. Prevalence and intensity of rhinoconjunctivitis in subjects with occupational asthma. Eur Respir J 1997; 10: 1513-1515.
48. Hytonen M, Kanerva L, Malmberg H, Martikainen R, Mutanen P, Toikkanen J. The risk of occupational rhinitis. Int Arch Occup Environ Health 1997; 69: 487-490.
49. Terreehorst I, Hak E, Oosting AJ, Tempels-Pavlica Z, de Monchy JG, Bruijnseel-Koomen CA, Aalberse RC, Gerth van Wijk R. Evaluation of impermeable covers or bedding in patients with allergic rhinitis. N Engl J Med 2003; 349: 237-246.
50. Custovic A, Gerth van Wijk R. The effectiveness of measures to change the indoor environment in the treatment of allergic rhinitis and asthma: ARIA update (in collaboration with GA^2LEN). Allergy 2005; 60: 1112-1115.
51. Duran-Tauteria E, Vignati G, Guedan MJA, Petersson CJ. The utility of specific immunoglobulin E measurements in primary care. Allergy 2004; 59 (suppl 78): 35-41.
52. Host A, Andrae S, Charkin S, Diaz-Vazquez C, Dreborg S, Eigenmann PA et al. Allergy testing in children: why, who, when and how? Allergy 2003; 58: 1-11.
53. Thomas M. Allergic rhinitis: evidence for impact on asthma. BMC Pulmonary Medicine 2006; 6 (suppl 1): S4
54. Foresi A, Pelucchi A, Gherson G, Mastropasqua B, Chiapparino A, Testi R. Once daily intranasal fluticasone proprionate (200 micrograms) reduces nasal symptoms and inflammation but also attenuates the increase in bronchial responsiveness during the pollen season in allergic rhinitis. J Allergy Clin Immunol 1996; 98: 274-282.
55. Pedersen B, Dahl R, Lindqvist N, Mygind N. Nasal inhalation of the glucocorticoid budesonide from a spacer for the treatment of patients with pollen rhinitis and asthma. Allergy 1990; 45: 451-456.
56. Hayden ML. Allergic rhinitis: proper management benefits concomitant diseases. Nurse Pract 2004; 29: 26-30.
57. Meltzer EO. The relationships of rhinitis and asthma. Allergy Asthma Proc. 2005; 26: 336-340.
58. Price D, Zhang Q, Kocevar VS, Yin DD, Thomas M. Effect of concomitant diagnosis of allergic rhinitis on asthma related health care use by adults. Clin Exp Allergy 2005; 35: 282-287.
59. Corren J, Manning BE, Thompson SF, Hennessy S, Strom BL. Rhinitis therapy and the prevention of hospital care for asthma: a case-control study. J Allergy Clin Immunol 2004; 113: 415-419.
60. Henriksen JM, Wenzel A. Effect of an intranasal administered corticosteroid (budesonide) on nasal obstruction, mouth breathing, and asthma. Am Rev Respir Dis 1984; 130: 1014-1018.
61. Corren J, Adinoff AD, Irvin CG. Changes in bronchial responsiveness following nasal provocation with allergen. J Allergy Clin Immunol 1992; 89: 611-618.
62. Aubier M, Levy J, Clerici C, Neukirch F, Herman D. Different effects of nasal and bronchial glucocorticosteroid administration on bronchial hyperresponsiveness in patients with allergic rhinitis. Am Rev Respir Dis 1992; 146: 122-126.

63. Bousquet J, Gaugris S, Sazonov Kocevar V, Zhang Q, Yin DD et al. Increased risk of asthma attacks and emergency visits among asthma patients with allergic rhinitis and: a subgroup analysis of the improving asthma control trial. Clin Exp Allergy 2005; 35: 723-727.
64. Crystal-Peters J, Neslusan C, Crown WH, Torres A. Treating allergic rhinitis in patient with comorbid asthma: the risk of asthma-related hospitalizations and emergency department visits. J Allergy Clin Immunol 2002; 109: 57-62.
65. Adams RJ, Fuhlbrigge AL, Finkelstein JA, Weiss ST. Intranasal steroids and the risk of emergency department visits for asthma. J Allergy Clin Immunol 2002; 109: 636-642.
66. Fuhlbrigge AL, Adams RJ. The effect of treatment of allergic rhinitis on asthma morbidity, including emergency department visits. Curr Opin Allergy Clin Immunol 2003; 3: 29-32.
67. Prenner BM , Schenkel E. Allergic rhinitis: treatment based on patient profiles. Am J Med 2006; 119: 230-237.
68. Wilson AM. Are antihistamines useful in managing asthma? Curr Opin Allergy Clin Immunol 2002; 2: 53-59
69. Grant JA, Nicodemus CF, Findlay SR, Glovsky MM, Grossman J, Kaiser H et al. Cetirizine in patients with seasonal rhinitis and concomittant asthma: prospective, randomized, placebo-controlled trial. J Allergy Clin Immunol 1995; 95: 923-932.
70. Larsen JS. Do antihistamines have a role in asthma therapy? Pharmacotherapy 2001; 21: S 28- 33.
71. Ciprandi G, Ricca V, Tosca M, Landi M, Passalacqua G, Canonica GW. Continuous antihistamine treatment controls allergic inflammation and reduces respiratory morbidity in children with mite allergy. Allergy 1999; 54: 358-365.
72. Rafferty P, Jackson L, Smith R, Holgate S. Terfenadine, a potent histamine H1-receptor antagonist in the treatment of grass pollen sensitive asthma. Br J Clin Pharmacol 1990; 30: 229-235.
73. Taytard A, Beaumont D, Pujet JC, Sapene M, Lewis PJ. Treatment of bronchial asthma with terfenadine: a randomised controlled trial. Br J Clin Pharmacol 1987; 24: 743-746.
74. Bousquet J, Emonot A, Germouty J, Molina C, Montane F, Perrin-Fayolle M et al. Double-blind multicenter study of cetirizine in grass pollen-induced asthma. Ann Allergy 1990; 65: 504-508.
75. Nelson HS. Prospects for antihistamines in the treatment of asthma. J Allergy Clin Immunol 2003; 112: S96-100.
76. Zitt MJ. The role of nonsedating antihistamines in asthma therapy. Allergy Asthma Proc. 2003; 24: 239-252.
77. Global strategy for asthma management and prevention. WHO/NHLBI workshop report 95-3659, 1995.
78. Bousquet J, Godard P, Michel FB. Antihistamines in the treatment of asthma. Eur Respir J 1992; 5: 1137-1142.
79. Van Ganse E, Kaufman L, Derde MP, Yernault JC, Delaunois L, Vincken W. Effects of antihistamines in adult asthma: a meta-analysis of clinical trials. Eur Respir J 1997; 10: 2216-2224.
80. Reinartz SM, Overbeek SE, Kleinjan A, Drunen CM, Braunstahl GJ, Hoogsteden HC et al. Desloratadine reduces systemic allergic inflammation following nasal provocation in allergic rhinitis. Allergy 2005; 60: 1301-1307.
81. Berger WE, Schenkel EL, Mansfield LE; Desloratadine Study group. Safety and efficacy of desloratadine 5 mg in asthma patients with seasonal allergic rhinitis and nasal congestion. Ann Allergy Asthma Immunol 2002; 89: 485-491.
82. Baena-Cagnani CE. Desloratadine activity in concurrent seasonal allergic rhinitis and asthma. Allergy 2001; 56 (suppl 65): 21-27.
83. Baena-Cagnani CE, Berger WE, DuBuske LM, Gurne SE, Stryszak P, Lorber R et al. Comparative effects of desloratadine versus montelukast on asthma symptoms and use of beta-agonists in patients with seasonal allergic rhinitis and asthma. Int Arch Allergy Immunol 2003; 130: 307-313.
84. Pasquali M, Baiardini I, Rogkakou A, Riccio AM, Gamalero C, Descalzi D et al. Levocetirizine in persistent allergic rhinitis and asthma: effects on symptoms, quality of life and inflammatory parameters. Clin Exp Allergy 2006; 36: 1161-1167.
85. Bachert C, Bousquet J, Canonica GW, Durham SR, Klimek L, Mullol J et al. Levocetirizine improves quality of life and reduces costs in long-term management of persistent allergic rhinitis. J Allergy Clin Immunol 2004; 114: 838-844.
86. Watson WT, Becker AB, Simons FE. Treatment of allergic rhinitis with intranasal corticosteroids in patient with mild asthma: effect on lower airway hyperesponsiveness. J Allergy Clin Immunol 1993; 91: 97-101.
87. Reed CE, Marcoux JP, Welsh PW. Effects of topical nasal treatment on asthma symptoms. J Allergy Clin Immunol 1988; 81: 1042-1047.
88. Pedersen W, Hjuler I, Bisgaard H, Mygind N. Nasal inhalation of budesonide from a spacer in children with perennial rhinitis and asthma. Allergy 1998; 53: 383-387.
89. Thio BJ, Slingerland GL, Fredriks AM, Nagelkerke AF, Scheeren RA, Neijens HJ et al. Influence of intranasal steroids during the grass pollen season on bronchial responsiveness in children and young adults with asthma and hay fever. Thorax 2000; 55: 826-832.
90. Borish L. Allergic rhinitis: systemic inflammation and implications for management. J Allergy Clin Immunol 2003; 112: 1021-1031.
91. Vignola AM, Chanez P, Godard P, Bousquet J. Relationships between rhinitis and asthma. Allergy 1998; 53: 833-839.
92. Pauwels R. Influence of treatment on the nose and/or the lungs. Clin Exp Allergy 1998; 2: 37-40.
93. Taramarcaz P, Gibson PG. The effectiveness of intranasal corticosteroids in combined allergic rhinitis and asthma syndrome. Clin Exp Allergy 2004; 34: 1883-1889.
94. Taramarcaz P, Gibson PG. Intranasal corticosteroids for asthma control in people with coexisting asthma and rhinitis. Cochrane Database Syst Rev 2003; 4: CD003570.
95. Corren J, Adinoff AD, Buchmeier AD, Irvin CG. Nasal beclomethasone prevents the seasonal increase in bronchial responsiveness in patients with allergic rhinitis and asthma. J Allergy Clin Immunol 1992; 90: 250-256.
96. Camargos PA, Rodriguez ME, Lasmar LM. Simultaneous treatment of asthma and allergic rhinitis. Pediatr Pulmonol 2004; 38: 186-192.
97. Ozturk F, Turktas I, Asal K, Ileri F, Munevver Pinar N. Effect of intranasal triamcinolone acetonide on bronchial hyper-responsiveness in children with seasonal allergic rhinitis and comparison of perceptional nasal obstruction with acoustic rhinometric assessment. Int J Pediatr Otorhinolaryngol 2004; 68: 1007-1015.
98. Sandrini A, Ferreira IM, Jardim JR, Zamel N, Chapman KR. Effects of nasal triamcinolone acetonide on lower airway inflammatory markers in patients with allergic rhinitis. J Allergy Clin Immunol 2003; 111: 313-320.
99. Failla M, Biondi G, Provvidenza Pistorio M, Gili E, Mastruzzo C, Vancheri C et al. Intranasal steroid reduces exhaled bronchial cysteinyl leucotrienes in allergic patients. Clin Exp Allergy 2006; 36: 325-330.
100. Stelmach R, do Patrocinio T Nunes M, Ribeiro M, Cukier A. Effect of treating allergic rhinitis with corticosteroids in patients with mild-to-moderate persistent asthma. Chest 2005; 128: 3140-3147.
101. Suissa S, Ernst P. Bias in observational study of the effectiveness of nasal corticosteroids in asthma. J Allergy Clin Immunol 2005; 115: 714-719.
102. Perry TT, Corren J, Philip G, Kim EH, Conover-Walker MK, Malice MP et al. Protective effect of montelukast on lower and upper respiratory tract responses to short-term cat allergen exposure. Ann Allergy Asthma Immunol 2004; 93: 431-438.
103. Virchow JC. Efficacy and safety of montelukast in adults with asthma and allergic rhinitis. Respir Med 2006; 12: epub ahead of print
104. Yeoh KH, Wang DY, Gordon BR. Safety and efficacy of radioallergosorbent test-based allergen immunotherapy in treatment of perennial allergic rhinitis and asthma. Otolaryngol Head Neck Surg 2004; 131: 673-678.
105. Marogna M, Spadolini I, Massolo A, Canonica GW, Passalacqua G. Randomized controlled open study of sublingual immunotherapy for respiratory allergen in real-life: clinical efficacy and more. Allergy 2004; 59: 1205-1210.
106. Crimi N, Li Gotti F, Mangano G, Paolino G, Mastruzzo C,

Vancheri C et al. A randomized, controlled study of specific immunotherapy in monosensitized subjects with seasonal rhinitis: effect of bronchial hyperesponsiveness, sputum inflammatory markers and development of asthma symptoms. Ann Ital Med Int 2004; 19: 98-108.
107. Bahceciler NN, Isik U, Barlan IB, Basaran MM. Efficacy of sublingual immunotherapy in children with asthma and rhinitis: a double-blind, placebo-controlled study. Pediatr Pulmonol 2001; 32: 49-55.
108. Niggeman B, Jacobsen L, Dreborg S, Ferdousi HA, Halken S, Host A et al. Fiveyear follow-up on the PAT study: specific immunotherapy and long-term prevention of asthma in children. Allergy 2006; 61: 855-859.
109. Calamita Z, Saconato H, Pela AB, Atallah AN. Efficacy of sublingual immunotherapy in ashma: systematic rebiew of randomized-clinical trials using the Cochrane Collaboration method. Allergy 2006; 61: 1162-1172.
110. Vignola AM, Humbert M, Bousquet J, Boulet LP, Hedgecock S, Blogg M et al. Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with concomitant allergic asthma and persistent allergic rhinitis: SOLAR. Allergy 2004; 59: 709-717.
111. Greiff L, Andersson M, Svensson C, Linden M, Wollmer P, Brattsand R et al. Effects of orally inhaled budesonide in seasonal allergic rhinitis. Eur Respir J 1998; 11: 1268-1273.
112. Naclerio RM, Bartenfelder D, Proud D, Togias AG, Meyers DA, Kagey-Sobotka A et al. Theophylline reduces histamine release during pollen-induced rhinitis. J Allergy Clin Immunol 1986; 78: 874-876.
113. Aubier M, Levy J, Clerici C, Neukirch F, Cabrieres F, Herman D. Protective effect of theophylline on bronchial hyperresponsiveness in patients with allergic rhinitis. Am Rev Respir Dis 1991; 143: 346-350.
114. Ferguson B, Powell-Davis A. The link between upper and lower respiratory disease. Curr Opin Otolaryngol Head Neck Surg 2003; 11: 192-195.
115. ETAC®-study group. Allergic factors associated with the development of asthma and influence of cetirizine in a double-blind, randomized, placebo-controlled trial: first results of ETAC®. Ped Allergy Immunol 1998; 9: 116-124.
116. Barnes P. Is there a role for immunotherapy in the treatment for asthma? No. Am J Respi Crit Care Med 1996; 154: 1227-1228.
117. Norman P. Is there a role for immunotherapy in the treatment of asthma? Yes. Am J Respi Crit Care Med 1996; 154: 1225-1226.
118. Polosa R, Al-Delaimy WK, Russo C, Picillo G, Sarva M. Greater risk of incident asthma cases in adults with allergic rhinitis and effect of allergen immunotherapy: a retrospective cohort study. Resp Res 2005; 6: 153-164.
119. Marogna M, Falagiani P, Bruno M, Massolo A, Riva G. The allergic march: natural history and therapeutic implications. Int Arch Allergy Immunol 2004; 135: 336-342.
120. Polosa R, Li Gotti F, Mangano G, Paolino G, Mastruzzo C, Vancheri C et al. Effect of immunotherapy on asthma progression, BHR and sputum eosinophils in allergic rhinitis. Allergy 2004; 59: 1224-1228.
121. Jacobsen L. Preventive aspects of immunotherapy: prevention for children at risk of developing asthma. AnnAllergy Immunol 2001; 87: 43-46.
122. Moller C, Dreborg S, Ferdousi HA et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT study). J Allergy Clin Immunol 2002; 109: 251-256.
123. Novembre E, Galli E, Landi F, Caffarelli C, Pifferi M, De Marco E et al. Coseasonal sublingual immunotherapy reduces the development of asthma in children with allergic rhinoconjunctivitis. J Allegry Clin Immunol 2004; 114: 851-857.
124. Olivieri M, Mohaddes Zadeh MR, Talamini G, Lampronti G, Lo Cascio V. Local nasal immunotherapy and bronchial hyperreactivity in seasonal allergic rhinitis: an observational pilot study. J Investig Allergol Clin Immunol 2000; 10: 300-304.
125. Corren J, Harris AG, Aaronson D, Beaucher W, Berkowitz R, Bronsky E et al. Efficacy and safety of loratadine plus pseudoephedrine in patients with seasonal allergic rhinitis and mild asthma. J Allergy Clin Immunol 1997; 100: 781-788.
126. Nathan RA, Yancey SW, Waitkus-Edwards K, Prillaman BA, Stauffer JL, Philpot E et al. Fluticasone proprionate nasal spray is superior to Montelukast for allergic rhinitis while neither affects overall asthma control. Chest 2005; 128: 1910-1920.
127. Benitez HH, Arvizu VM, Gutierrez DJ, Fogelbach GA, Castellanos Olivares A, Vazquez Nava F et al. Nasal budesonide plus zafirlukast vs nasal budesonide plus loratadine-pseudoephedrine for controlling the symptoms of rhinitis and asthma. Rev Alergol Mex 2005; 52: 90-95.
128. Dahl R, Nielsen LP, Kips J, Foresi A, Van Cauwenberge P, Tudoric N et al. Intranasal and inhaled fluticasone proprionate for pollen-induced rhinitis and asthma. Allergy 2005; 60: 875-881.
129. Walsh GM. Second-generation antihistamines in asthma therapy: is there a protective affect ? Am J Respir Med 2002; 1: 27-34.
130. Wilson AM. Are antihistamines useful in managing asthma? Curr Opin Allergy Clin Immunol 2002; 2: 53-59.
131. Roquet A, Dahlen B, Kumlin M, Ihre E, Anstren G, Binks et al. Combined antagonism of leukotrienes and histamine produces predominant inhibition of allergen-induced early and late phase airway obstruction in asthmatics. Am J Respir Crit Care Med 1997; 155: 1856-1863.
132. Price DB, Swern A, Tozzi CA, Philip G, Polos P. Effect of montelukast on lung function in asthma patients with allergic rhinitis: analysis from COMPACT trial. Allergy 2006; 61: 737-742.
133. Currie GP, Srivastava P, Dempsey OJ, Lee DK. Therapeutic modulation of allergic airways disease with leukotriene receptor antagonists. Q J Med 2005; 98: 171-183.

Jean-Baptiste Watelet, MD, PhD
Department of Otorhinolaryngology
University of Ghent
De Pintelaan, 185
B-9000 Gent
Belgium

Tel: +32-9-240 2332
Fax: +32-9-240 4993
E-mail: jeanbaptiste.watelet@ugent.be