Reference number to be mentioned by correspondence : **B-ENT/SIGMA**

B-ENT, 2009, **5**, Suppl. 12, 000-000

Treating allergic rhinitis: continuous versus on-demand regime?

Executive summary of the *Supportive Initiative for the Global Management of Allergy (SIGMA): report from the Belgian Working Group*

M. K. Church and J.-B. Watelet**, On behalf of the Belgian SIGMA Group*

SIGMA, acronym for Supportive Initiatives for the Global Management of Allergy, is a project initiated by the UCB Institute of Allergy.

*School of Medicine, University of Southampton School of Medicine, UK, & Allergie-Centrum-Charité/ECARF, Charité-Universitätsmedizin Berlin, Germany; **Department of Otorhinolatyngology, Ghent University Hospital, Belgium

Key-words. Allergic rhinitis; H_1-antihistamines; nasal corticosteroids; continuous treatment; on-demand treatment

Abstract. *Treating allergic rhinitis: continuous versus on-demand regime?* This Supportive Initiative for the Global Management of Allergy (SIGMA) initiative gathered together four multidisciplinary and inter-university groups of Belgian experts in the treatment of allergic rhinitis to review the literature and come to a consensus opinion on the global management of allergy. Their conclusions were as follows. Group 1 concluded that in children suffering from allergic rhinitis, there is sufficient expert opinion in favour of continuous treatment with both H_1-antihistamines and corticosteroids for controlling symptoms during periods of allergen exposure, but not to support continuous treatment during periods when symptoms are negligible in an attempt to prevent the development of new allergic diseases. Group 2 came to similar conclusions in adults. Group 3 considered adults with concomitant asthma and stressed the crucial necessity to screen each asthmatic for allergic rhinitis and institute appropriate therapy for both conditions. Even though efficacious treatment algorithms are available for both rhinitis and asthma, an integrated management of these frequently concomitant diseases is not always prescribed even though there is a proven clinical advantage of adequate treatment of the nose of asthmatics. Group 4 concluded that for both H_1-antihistamines and nasal corticosteroids, safety data indicate that continuous treatment may be given without fears of adverse consequences. With regard to the cost implications of continuous therapy versus on-demand therapy, there are indications that effective treatment of allergic rhinitis by continuous treatment reduces overall drug costs, particularly that of escape medication and indirect costs in the form of days absent from work and school.

Composition of the Belgian SIGMA Group for the initiative "Allergic Rhinitis":

- **Chair:** Van Cauwenberge P. (Otorhinolaryngology, Universiteit Gent (UGent))
- **Primary Care Coordinators:**
  Giet D. (Université de Liège (ULg))
  Heyrman P. (Katholieke Universiteit Leuven (KUL))
  Pestiaux D. (Université Catholique de Louvain (UCL))
  Van Royen P. (Universiteit Antwerp (UA))
- **Secretary:**
  Watelet J. B. (Otorhinolaryngology, UGent)
- **Medical writers:**
  Church M. K. (Immunopharmacology, Southampton, Berlin)
  Eloy P. (Otorhinolaryngology, UCL)

Working group 1: Allergic March

- **Chair:** Casimir G. (Pediatrics, Université Libre de Bruxelles (ULB))
- **Members:**
  – Bauchau V. (Epidemiology, UCB)
  – Bernheim N. (ORL, ULB)
  – Bodart E. (Pediatrics, UCL)
  – De Baets F. (Pediatrics, UGent)
  – De Raeve L. (Dermatology, Vrije Universiteit Brussel VUB)
  – Desager K. (Pediatrics, UA)
  – Duchateau J. (Imunology, ULB)
  – Halloy J. L. (Allergology, Warquignies)
  – Mansbach A. L. (ORL, ULB)
  – Michel O. (Allergology, ULB)
  – Mulier S. (Pediatrics, ULB)
  – Veevaet M. (Primary care, UCL)

Working group 2: Minimal Persistent Inflammation

- **Chair:** Stevens W. (Allergology and Immunology, UA)
- **Members:**
  - Bachert C. (Otorhinolaryngology, UGent)
  - Cataldo D. (Chest diseases, ULg)
  - De Backer W. (Chest diseases, UA)
  - De Vos C. (Institute of Allergy, UCB)
  - Dirven K. (Primary Care, UA)
  - Ebo D. (Allergology, UA)
  - Eloy P. (Otorhinolaryngology, UCL)
  - Hagendorens M. (Allergology, UA)
  - Jorissen M. (Otorhinolaryngology, KUL)
  - Pilette C. (Chest diseases, UCL)
  - Simonis H. (Chest diseases, ULg)

Working group 3: From rhinitis to asthma

- **Chairs:** Louis R. (Chest diseases, ULg)
  Dupont L. (Chest diseases, KUL)
- **Members:**
  - Brusselle G. (Chest diseases, UGent)
  - Daele J. (Otorhinolaryngology, ULg)
  - Hassid S. (Otorhinolaryngology, ULB)
  - Hellings P. (Otorhinolaryngology, KUL)
  - Liistro G. (Chest diseases, UCL)
  - Lilet-Leclercq C. (Otorhinolaryngology, ULg)
  - Malfroot A. (Pediatrics, VUB)
  - Michils A. (Chest diseases, ULB)
  - Montrieux C. (Primary Care, ULg)
  - Stallaert S. (Institute of Allergy, UCB)
  - Vandenplas O. (Chest diseases, UCL)
  - Vincken W. (Chest diseases, VUB)
  - Watelet J. B. (Otorhinolaryngology, UGent)

Working group 4: Pharmacotherapy

- **Chair:** Laekeman G. (Pharmacy, KUL)
- **Members:**
  - Buffels J. (Primary Care, KUL)
  - Gillard M. (Pharmacology, UCB)
  - Robillard T. (Otorhinolaryngology, Namur)
  - Simoens S. (Pharmaco-economics, KUL)
  - Strolin-Benedetti M. (Pharmacology, UCB)

UCB Institute of Allergy:

Ghys L.
Liekendael G.
Sohier B.
Van Houtte M.

Introduction

Allergic rhinitis, an IgE-mediated inflammation of the nasal passages, is usually associated with watery nasal discharge and itching of the nose and eyes. It affects about 20 percent of the European population, reaching 29% of the overall Belgian population.[i]

The symptoms occur when the nose and eyes are exposed to dust, animal dander, or certain seasonal pollens in people that are sensitized to these substances. Two-thirds of all patients have symptoms of allergic rhinitis before the age of 30, but onset can occur at any age. In all cases, because of the reduced quality of life and sleep quality, patients with allergic rhinitis are frequently restricted in their daily activities, resulting in excessive time away from school or work. Even though there is strong genetic predisposition to allergic rhinitis, the precise principles leading to sensitization and the role played by environment remain unclear.

Considering the important impact of allergic rhinitis on quality of life, on the course of comorbidities like asthma, on sleep on school and professional performances and on Health budget, several guidelines have been proposed for optimizing both the diagnosis and therapeutic approaches. Initially published in 2001, the Allergic Rhinitis and its Impact on Asthma (ARIA) working group recently proposed an updated document.[ii]

In a survey conducted among Belgian Otorhinolaryngologists, it appeared that, even if the dissemination of ARIA guidelines was impressive, their effective implementation in daily practice was limited.[iii] The absence of precise recommendations about the moment of initiation, the duration of treatment, the type of monitoring are the criteria for assessing the therapy efficacy in allergic patients were some of the major difficulties identified by the practitioner.

This limited clinical translation can be explained when considering the absence of specific and scientifically validated data on these topics, the extreme variability in

experts' views and the difficult integration of multiple parameters including symptom relieve, improvement of quality of life, safety or pharmaco-economic considerations.

THE *SIGMA* INITIATIVE

SIGMA, acronym for Supportive Initiatives for the Global Management of Allergy, is a project initiated by the UCB Institute of Allergy.

Objectives

It aims to locally support the guideline implementation through a multidisciplinary and inter-university analysis of clinical questions of daily importance, through the dissemination to Health Care Professionals of an updated, scientifically validated and locally applicable answer and through the development of novel multidisciplinary research or communication strategies about the global management of allergy.

Principles

For a better identification of the local needs and expectations, the SIGMA initiative gathers local experts and makes them working in the most effective way for reviewing literature and for finding a consensus on the topics dealing with the global management of allergy.

The recruitment of expertise is based on two fundamentals:

– *multidisciplinarity and interuniversity:* considering the multiple research topics, several medical specialties from different Belgian medical schools are invited to collaborate in the different SIGMA working groups

The collection of evidence is based on two fundamentals:

– *non-commercial action:* no reference to any specific drug or commercial denomination is allowed
– *excellence:* the methodology for collection of evidence is characterized and scientific evidence is scored using international scale of degree of evidence and level of recommendation. Experts' opinion is collected during meeting sessions.

Finally, the final reporting is based on the following fundamentals:

– *consensus:* the consensus is reached on basis of collected evidence and experts' analysis of the evidence and gaps.
– *statements:* the different working groups are summarizing their findings under form of statements amended by their respective level of evidence and degree of recommendation (Table 1).

The targeted populations were primary and secondary care specialists. The deliverables proposed for this first Belgian SIGMA initiative were review publications and educational material for the target populations.

Clinical and research questions of the first Belgian initiative

The research question of this first Belgian initiative was the following: "Does a treatment for allergic rhinitis be "continuous" (during the total period of allergen exposure) or "on-demand" (during symptoms only)?

Even if of evident importance for daily practice, this item was only few investigated in scientific literature, and consequently, remains matter of active debate. Furthermore, in order to completely address the research question, the SIGMA Working Group proposed a stratified argumentation covering different levels of analysis: public health and pharmaco-economics, biology, pharmacology and clinics.

This question was translated into the following four searchable questions:

1. In children suffering from allergic rhinitis, does a continuous treatment regime, in comparison to an on-demand treatment, give better symptomatic or functional control of concomitant allergic disorders and/or a prevention of the development of new allergic disorders?
2. In relation with allergic rhinitis, does continuous treatment, in comparison with on-demand regime, have a biological effect positively influencing the occurrence and/or evolution of nasal allergic symptoms?
3. In adults with concomitant asthma, does a continuous treatment of allergic rhinitis, in comparison with on-demand therapy, have a beneficial effect on lung symptoms and function?
4. When considering allergic rhinitis in Belgian population, what is the proven pharmacological effect and pharmaco-economic consequences of continuous treatment in comparison with on-demand regime?

The distribution of the Belgian experts inside the four working groups took into account the specificities of the research questions and the target groups but respecting the SIGMA principles of interdisciplinarity and interuniversity.

Table 1

Level of evidence

Evidence from	Category
Meta-analysis of randomized controlled trials or systematic review	1
> 1 randomized controlled trial	2
> 1 controlled study without randomization or > 1 other type of quasi-experimental study	3
Non-experimental descriptive studies: Comparative studies, correlation studies, case-control studies	4
Expert committee reports or opinions or clinical experience of respected authorities or both	5

QUESTION 1. In children suffering from allergic rhinitis, does a continuous treatment regime, in comparison to an on-demand treatment, give better symptomatic or functional control of concomitant allergic disorders and/or a prevention of the development of new allergic disorders?

Major findings

The allergic march: definition and concept

The "allergic march" refers to the natural history of atopic diseases and is characterized by a typical sequence of sensitization and manifestation of symptoms which appear during a certain age period, persist over years or decades, and often show a tendency for spontaneous remission with age. This concept was initially proposed by Professor Ulrich Wahn[iv] in attempt to explain the increasing prevalence in atopic diseases, particularly in industrialized societies, in children evidenced in cross-sectional studies, such as the International Study of Asthma and Allergies in Children (ISAAC),[v,vi] and longitudinal follow-up studies including cohorts from birth, such as the Tucson Study on Asthma (USA)[vii] or the Multicenter Allergy Study in Germany[viii] which were designed to clarify the natural history of the disease, to describe associations between phenotypes and genetic, environmental, or lifestyle factors and to generate hypotheses for causal relationships. However, it must be stressed at this stage that the allergic march in individual children does not follow a fixed sequence of clinical symptoms from food allergy and atopic dermatitis to allergic rhinitis and asthma but is a generalized concept that an allergic infant will subsequently develop one or more allergic diseases.

However, strategies of prevention must be clearly defined in an attempt to prevent the progression of natural history of the disease. In this way, according to the medical literature, but considering the lack of evidence based recommendations, experts tried to produce algorithms giving clear lines of diagnosis and therapy to health professionals.

The facts: rhinitis in children

A birth cohort study from the Isle of Wight' shows that chronic sensitization (positive skin prick test at age 4 as well as at age 10 years) is the most common childhood pattern of atopy and is associated with early, persisting allergic disease. Already at the age 4, aeroallergens predominate over food.[ix,x] Even so, most episodes of rhinitis in childhood are not truly allergic but are related to upper respiratory tract viral infection. In young children, rhinovirus is by far the most frequently found causal virus, followed by respiratory syncytial virus (RSV) and corona virus (REF). Although allergic rhinitis can begin very early in life, it is more frequent in late childhood, adolescence and adulthood.

In children, allergic rhinitis can profoundly affect well-being and quality of life. Children with allergic rhinitis can experience school problems, including absences and poor performance, caused by distraction, fatigue or irritability. There are several reasons responsible for this including disrupted sleep patterns and sleep loss leading to daytime fatigue, poor concentration and reduced attention and uncontrolled rhinitis symptoms during the day which can be bothersome and a source of interruption of school activities causing irritability, poor concentration, attention and memory, all of which reflect negatively on learning ability and work.[xi-16] Also, another aspect which should not be neglected is that older first generation antihistaminic drugs can have CNS side effects which add to the negative effects of the disease augmenting them. Old generation antihistamines cause somnolence which during the day will enhance the tiredness and somnolence caused by the disease itself and will contribute to the disruptive sleep pattern during the night leading to negative effects on the ability of children to learn.[12]

In children, the diagnosis and treatment of the early manifestations of atopy is important, not only to improve health of the child but also to reduce the medical and psychological consequences of allergy. When proposing therapeutic strategies, it is relevant to classify allergic rhinitis as "persistent" or "intermittent" as recommended by the ARIA Guidelines[17] which defines persistent allergic rhinitis as lasting for more than 4 days per week and more than 4 weeks per year and intermittent allergic rhinitis as lasting for less than 4 days per week or less than 4 weeks per year. The guidelines also define moderate to severe allergic rhinitis as that which affects sleep and activities of daily living. The severity of the disease should be always considered in the final decision on initiating, maintaining or finishing the therapy. In general, skin prick tests are a fast, inexpensive and safe way to identify the presence of allergen specific IgE. They can be performed at any age and have a good sensitivity. Aeroallergens should be screened in patients with asthma and allergic rhinitis (house dust mite, pollens, animals and moulds), but in some children other allergens, like food allergens (eggs, cow's milk, fish, peanuts and nuts), should also be considered. The management of severe cases requires a coordinated approach by a multidisciplinary team ideally composed of a paediatrician, a pulmonologist, an ENT specialist, a dermatologist and an ophthalmologist.

Can the development of allergy in children be prevented?

Many approaches to preventing the development of allergy in children have been suggested but, to date, none have been successful.

While dietary intervention, exclusive breast feeding up to 6 months of age (or hydrolyzed formulas when breast feeding is not possible) and late solid food introduction (after 4-6 months) is generally recommended,[18] there is little evidence that it prevents allergic sensitization.[19]

It is thought that interaction between several environmental and genetic factors either potentiate or reduce the risk for developing an atopic disease. Consequently, measures that are regularly proposed for environmental control include avoidance of tobacco smoke, reduction of house dust mite and mould exposure. Certainly, parental smoking should be discouraged as there appears to be a significantly higher prevalence of allergic rhinitis in children with smoking parents.[20] However, preventing sensitization seems to be impossible at the present time. No evidence has been found for prevention of allergic rhinitis by reduced exposure to indoor allergens. No effect of mite allergen impermeable mattress covers on sensitization and atopy at age 4 year was found (PIAMA study).[21] Results of studies on house dust mites avoidance for secondary prevention suggest that house dust mites measures may be of some benefit in reducing rhinitis symptoms, but trials to date are small and of poor methodological quality[22] making it difficult to offer definitive recommendations on house dust mite avoidance. Exposure to endotoxin should have a protective effect on asthma and allergic rhinitis, but this effect depends on individual genetic susceptibility, disease stadium and age.[23] No meta-analysis could be found about early life exposure to antibiotics.

Early control of atopic eczema in its course may be advantageous, both by improving long-term disease management and preventing development of other atopic diseases. Therapeutic strategies used in atopic eczema such as emollients for restoring epidermal barrier dysfunction due to mutations in the filaggrin gene,[24,25] anti-inflammatory treatments, such as topical corticosteroids or topical immunomodulators, and antimicrobial treatment against Staphylococcus aureus are suggested to interfere with the development of the disease.[26]

Finally, education programs for patients and their families remain an important tool in the management of allergic rhinitis[17,27] but to date there are no data available on the real impact of this approach on secondary prevention.

Answer to the research question, consensus view and identified unmet needs

Algorithms for diagnosis and treatment

The expert panel concluded that, although there is no definitive evidence to support the hypothesis that continuous treatment will prevent the progress of the 'allergic march', they felt it necessary to assist primary care physicians and families of allergic children by producing clear statements and "take home" messages that can be used for treatment routines even, as is sometimes the case, evidence-based guidelines don't exist. The algorithm must define functional decision process for diagnosis and treatment of allergic rhinitis in children.

Patients at risk (age, familial history, atopic dermatitis…) must be clearly screened, criteria of diagnosis (target organ, sensitization …) well established; prevention, treatment and possible complications shortly described.

Three situations are considered according to the atopic risk for the child: pregnant women with atopic risk in family, children with atopic risks but without symptoms and children with symptoms.

Pregnant women with atopic risk in family

Physicians should collect familial antecedents, environmental and indoor conditions; they should provide information to the future parents about allergic diseases in general, possible symptoms occurring in allergic diseases and the most frequent allergens. Finally they should encourage smoking avoidance and breast-feeding.

Some uncertainties about precise pathophysiological-mechanisms of allergic disorders could potentially lead to misunderstanding or wrong attitudes. It should be explained clearly to patients that if a child has an allergic predisposition then it is unlikely that allergic sensitization can be avoided. However, it should be stressed that is a wealth of data showing that continuous monitoring and adequate management can reduce the disease severity even if they are not able to avoid the eventual development of allergic diseases.

Children with atopic risks but without symptoms

Physicians should collect complementary data and provide information as above but also provide additional information about symptoms to be detected by parents and definition of severity and persistence of symptoms.

Because of the close link between inflammation and symptoms, parents of an at-risk child should be advised that more severe exacerbations and/or more frequent (more than 3 episodes/year) and/or more persisting than others (more than 7 days), or not reacting to conventional treatment (e.g. antimicrobial) should be examined by the general practitioner.

Physicians should also advise parents to consult their general practitioner again in case of more severe, more frequent (more than 3 episodes), more persisting symptoms and/or no response to conventional treatment.

Child with symptoms

Physicians should collect complementary data and provide information as in the two situations above. They should take a history and perform clinical examination. Clinical signs, like the allergic salute and Dennis-Morgan sign, should be searched for systematically. This can lead to the suspicion of allergic disease, of a suspected allergen and, if confirmed, to the determination of the severity of the disease (categorization into severe and less-severe cases).

Experts consider that the actual reproducibility of skin prick tests is poor because of the extremely difficult interpretation of skin reactions. This is particularly valid for children. Furthermore, the predictive positive or negative values of allergy tests are low. A positive allergy test just detects atopy but is never a final proof of the presence of an allergic disease if a clear correlation with symptoms is not found. Also, a negative test cannot in anyway definitively exclude an atopy. After deliberation, based on the doubtful benefit/misleading information ratio, it was agreed by the panel that allergy tests should not be performed in a primary care setting but only after referral to a specialist allergy clinic.

In less-severe cases, the patient (if older than 1 year) should be treated with a second generation antihistamine. Because of the excellent safety profile, their specific action on histamine-mediated processes, and their high response level, second-generation antihistamines should be tested for two weeks. After clinical re-evaluation by the general practitioner, success or partial improvement should be considered as definitive argument for allergic rhinitis: allergic rhinitis should be considered as diagnosis.

The therapeutic process can be then initiated.

- In the case of a good response to antihistamine treatment, treatment should be prolonged during the whole period of allergen exposure. Additional information on allergen should be given when relevant. Furthermore, nasal lavage should be advocated if necessary.
- In the case of a partial response to the antihistamine treatment, nasal glucocorticosteroids could be added and a re-evaluation planned two weeks later. In the case of successful control of symptoms with these drugs, the treatment scheme should be prolonged during the whole period of exposure with additional nasal lavage if necessary.

- Patients resistant to therapy with antihistamines or insufficiently controlled by the combination antihistamines and nasal glucocorticosteroids should be referred to a specialist for further and specific investigations.

Other therapeutic considerations

In the case of pollen allergy, where pollen avoidance is almost impossible, a second generation antihistamine is the first line of treatment. For other suspected allergens (food, house dust mites, pets…), avoidance should be the first line, followed by an antihistamine.

In all cases, the duration of the treatment, especially in children, must be regularly questioned. However, it should be pointed out that during periods of allergen exposure the development of allergic inflammation exacerbates symptoms and, as a consequence, regular daily therapy should be recommended to reduce the inflammation.[28-31]

When the child with allergic rhinitis presents with other associated symptoms, it must be referred to the appropriate specialist (paediatric pulmonologist when asthma is suspected on the basis of specific symptoms and signs as wheezing, dyspnoea, chest tightness, cough night, cough induced by or after exercise, after exposure); paediatric gastroenterologist for suspicion of gastro-oesophageal reflux, an ENT specialist in the case of all ENT associated diseases and a dermatologist for atopic dermatitis or urticaria.

In all cases, the general practitioner should be at the heart of the monitoring team to enable integration of the management/treatment strategy. A detailed letter summarizing the disease information (type and severity), the therapeutic procedure and the parameters to be monitored should be sent to all physicians in charge of the child with allergic rhinitis.

Conclusions

Considering the final answer to the research question, the panel agreed that there is sufficient expert opinion in favour of continuous treatment for controlling symptoms of allergic rhinitis in children during periods of allergen exposure, especially pollens. In contrast, there is not enough evidence to support continuous treatment during periods of low or no allergen exposure when symptoms are negligible for *preventing* development of new allergic diseases in children with allergic rhinitis.

QUESTION 2. In relation with allergic rhinitis, does continuous treatment, in comparison with on-demand regime, have a biological effect positively influencing the occurrence and/or evolution of nasal allergic symptoms?

After a short description of the biological dimension of the allergic inflammation, the experts tried to identify clinical facts in line with nasal inflammatory background and to estimate if the actual therapeutic options proposed in allergic rhinitis could positively influence its course.

What is what we are calling an allergic inflammation?

Allergic inflammation is an important pathophysiological feature of several medical conditions including allergic rhinitis, allergic asthma, atopic dermatitis and several ocular allergic diseases. In sensitized patients, allergic reactions may generally be divided into two components; the early phase reaction, and the late phase reaction. While the contribution to the development of symptoms from each of the phases varies greatly between diseases, both are usually present.

Tissular and cellular responses during allergic inflammation

The effector phase, that underlies the clinical manifestations of rhinitis (and/or asthma) upon allergen exposure, has been extensively explored during the last decades. It is mediated through the activation of mast cells, basophils and eosinophils that drive the early- and late-phase responses, respectively. Thus, release of pre-formed mast cell mediators including histamine upon antigen-driven IgE cross-linking was seen as the major event accounting for early airway response to allergen exposure, while cysteinyl-leucotrienes and Th2-type cytokines (including the eosinophilic cytokine IL-5) released by T cells and effector cells (basophils, eosinophils) were mostly involved in delayed airway responses, both in the nose and bronchi. The role of mast cells and eosinophils in allergic rhinitis has already been extensively reviewed.[32-34] Notably, the expression of several eosinophilic inflammatory mediators are strongly correlated with symptoms. For example, IL-5, the classical chemokine for eosinophils, was suggested as a key mechanism linked to symptomatic

IN KLEUR !

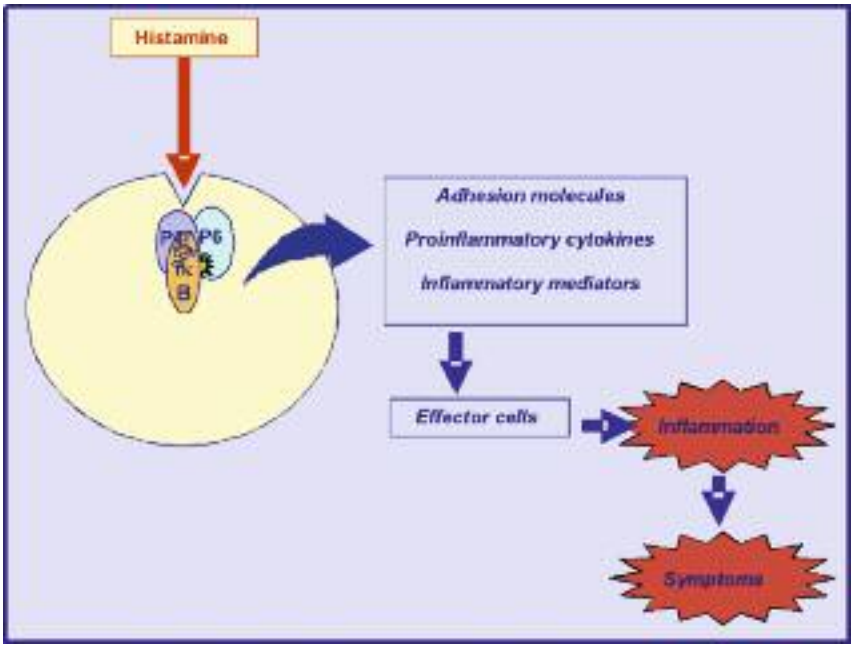

Figure 1
Basic principles of effector phase during allergic inflammation

episodes of seasonal allergic rhinitis in sensitized individuals[35] (Figure 1). The implication of transcription factors like NFkB, involved in cellular reaction to various types of stimuli, is also actively participating to the sustain processes of the inflammatory reaction.

Monitoring of allergic inflammation

A quantification of several of these inflammatory parameters in nasal fluid has been proposed for monitoring the allergic inflammation. For example, eosinophils and their cell products such as eosinophil cationic protein (ECP), eosinophil-derived neurotoxin (EDN) or major basic protein (MBP) as well as intercellular adhesion molecule (ICAM)-1 positive cells or soluble ICAM-1 molecules can be measured and quantified in nasal secretions. Other markers histamine like PGD2, CysLTs, kinins, and tryptase represent possible candidates for monitoring the background inflammation in a group of patients or individuals but, contrarily with eosinophilic mediators, their correlation with the symptom occurrence, severity and relieve remains difficult to establish.

By analogy with lower airway inflammation, other approaches for monitoring persistent inflammation in nasal mucosa could theoretically offer complementary views. The inflammation in the lower airways can be assessed invasively and non-invasively. Invasive methods consist of bronchial and trans-bronchial biopsies, while among less invasive methods, broncho-alveolar lavage (BAL) and induced sputum must be mentioned. BAL implies bronchoscopy and induced sputum can be obtained by inhalation of hypertonic saline which is often not well tolerated, especially by patients with pre-existing airway diseases. Based on the important breakthrough in our knowledge of lower airway inflammation thanks the measurement of NO in the exhaled air (eNO) and the analysis of exhaled breath condensate (EBC), these two other non-invasive could stimulate novel approaches of the nasal inflammation. Even if, in children with allergic rhinitis, nasal exhaled NO correlated with the nasal IL-5 values and with the disease duration,[36] the calibration and standardisation techniques need to be optimized. Finally, normative data and ranges in concentration should be systematically screened in different upper airways conditions. Biopsy data are still seen as a kind of gold standard and some of the other methods have been compared with the biopsy data[37,38] (Figure 2).

In summary, there are no widely accepted criteria for diagnosing persistent inflammation in rhinitis and both evaluation of the number of inflammatory cells (granulocytes, neutrophils and eosinophils) and determination of inflammatory mediators remain only research tools.

Persistent allergic inflammation and minimal persistent inflammation

Benefiting of these knowledge of the biological processes supporting the allergic inflammation, some authors have introduced the concept of "(minimal) persistent inflammation" in allergic rhinitis. This refers to the evidence of mucosal inflammation despite the absence of clinical symptoms of the disease at the time inflammation is assessed. Besides an

IN KLEUR !

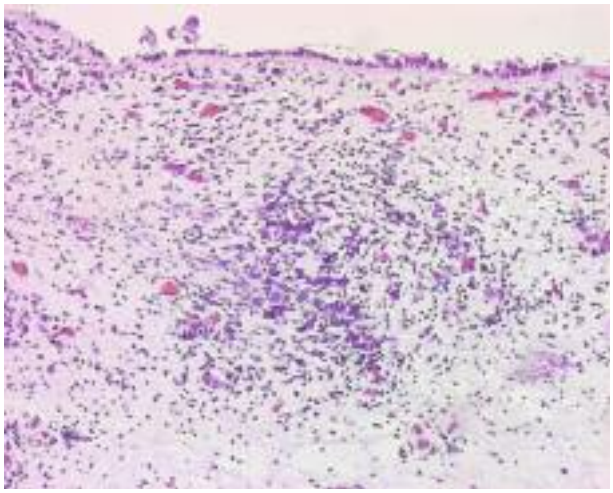

Figure 2
Severe nasal inflammation with: epithelial shedding, congestion of blood vessels, lymphoid follicle, massive oedema, and important recruitment of eosinophils and mast cells (HE staining, ×40).

increased expression of intercellular adhesion molecules in conjunctival and nasal epithelial cells, the original description of the phenomenon was also based on the mild infiltration of eosinophils and neutrophils observed in rhinitis patients allergic to house dust mite during an asymptomatic period.[39] This concept, if confirmed, could potentially relate to the variability of the disease manifestations and to mechanisms of persistence and chronicity of inflammatory responses, which must be accurately considered when addressing the continuous use of anti-allergic drugs.

Do we have scientific data supporting this view?

Based on some recent epidemiologic data, it seems that, when compared to non-infectious and non-allergic rhinitis (NINA), allergic rhinitis (AR) is associated with a more active inflammatory background.[40,41] Interestingly, there were significantly more persistent symptoms in the AR group (40.8%) than in NINA (23.5%) ($p < 0.001$), according to the ARIA classification. More moderate/severe symptom intensity were reported in AR (75.4%) than in NINA (53.1%) ($p < 0.001$). Finally, allergic rhinitis patients suffered from a greater number of symptoms than NINA patients ($p < 0.001$), and asthma, skin and food allergy, as co-morbidities were all found to be significantly more prevalent in the AR vs. the NINA group ($p < 0.05$ for all).[42] These findings could indirectly suggest that the background mechanisms underlying allergic rhinitis seem to be more severe than those found in other chronic nasal inflammatory reactions.

Furthermore, studies on cell infiltration in nasal mucosa during pollen season have shown a dramatic increase of various inflammatory cells like eosinophils and mast cells. Interestingly, this increase is correlated to the severity of symptoms[43-45] and nasal non-specific hyperreactivity.[46-51] In patients allergic to pollens, an increase in Cys-LTs,[52] ECP,[53] histamine, Th2 cytokines,[54-59] eotaxin[60] and edema[61] was found during pollen season when compared to pre-season levels (Figure 2). Tissue histamine levels were also found correlated with the increased symptoms during the pollen season.[62]

However, there are conflicting findings and no clear consensus opinion regarding the mechanisms of persistency of inflammatory and remodelling (neurogenic reaction and vascular change in the structure of the nose) responses in the upper airway in allergic rhinitis. Several mechanisms of inflammation and remodelling processes are engaged in allergic rhinitis, regardless of the presence of clinical symptoms.

Can pharmacotherapy influence the background allergic inflammation?

When quantifying parameters susceptible to reflect the background inflammation, it has been established that both local and oral antihistamines could reduce eosinophilic inflammation and expression of adhesion molecules (eg ICAM-1)[63-65] even in allergic patients with minimal persistent inflammation.[66] Furthermore, Ciprandi *et al.*[67,68] reported that continuous treatment with antihistamines during the pollen season was able to non-significantly reduce the inflammatory parameters (eosinophils, neutrophils and ICAM-1), whereas short treatment not.

Topical glucocorticosteroids produce their antiinflammatory effects on inflammatory cells by transactivating antiinflammatory cytokines and by transrepressing

proinflammatory ones. However, the extent to which cells and cytokines are reduced differs.[69,70] For example, antigen-presenting cells are highly sensitive to treatment with intranasal glucocorticosteroids[71] such as eosniophils and eosinophil products.[72-75] Finally, they were shown to reduce the levels of mRNA and protein for IL-3, IL-4, IL-5, IL-13 and their receptors[76] and they may reduce the release of preformed or newly generated mediators such as histamine.[77]

In children, leucotriene antagonists were shown to reduce eosinophil count,[78] decrease IL-4 and IL-13 and increase IFN-g.[79] A combination of antihistamines and antagonists of cysteinyl leukotriene receptor has additional anti-inflammatory effects through a reduction in nasal inflammatory infiltrate, IL-5 and IL-8 levels.[80]

Is there any clinical evidence confirming the positive influence of pharmacotherapy on this allergic inflammation?

Finally, the effects of long-term use of medication on biological parameters could offer another important source of information. For example, children with pollen rhino-conjunctivitis continuously treated with antihistamines presented significantly lower symptom scores, drug consumption[81] and lower incidence of polysensitization[82] in comparison to the placebo group. Short treatment with antihistamines was equally active in reducing symptoms only, when compared with continuous treatment. But only a continuous therapy was able to reduce non-significantly the biological parameters of inflammation.[67-68]

In a meta-analysis of randomized controlled studies reporting the symptomatic relieve of intranasal corticosteroids in comparison with antihistamines, intranasal corticosteroids proved to be clinically superior.[83] The treatment appears to be more effective when given continuously, when compared to a "as required" regimen.[84] Their maximal efficacy develops over days and weeks.[85-87] Furthermore, considering that symptoms of allergic rhinitis are consequent to the minimal persistent inflammation, priming effects and hyperreactivity, it may be preferable to start with a local steroid treatment before the onset of symptoms.[88-90] for reducing the recruitment of inflammatory cells.[69] Other authors have demonstrated that continuous treatment of rhinitis with intranasal corticosteroids could slightly but non significantly improve asthma control.[91]

When Specific Immunotherapy (SIT) was compared with continuous oral antihistamine treatment versus on-demand oral antihistamine treatment, both SIT and continuous oral antihistamine proved superior to on demand treatment in reducing inflammatory markers, associated with a marked reduction in symptoms.[92] Finally, in patients with pollen or house dust mite allergy, it was shown that 3 years of Specific Immunotherapy was economically advantageous when compared to continuous symptomatic treatment.[93]

Conclusion

Based on an exclusive biological approach, there is not enough evidence supporting a continuous treatment of allergic rhinitis. The available results highlight the limited knowledge of the fine processes underlying the allergic inflammation. But, even if the evidence for supporting a continuous treatment in allergic rhinitis is limited, there are encouraging data suggesting that existing medication could, at least partially, influence the background inflammation, reduce significantly the allergic symptoms and, when taken before the onset of symptoms, could in some way prevent their appearance.

QUESTION 3. In adults with concomitant asthma, does a continuous treatment of allergic rhinitis, in comparison with on-demand therapy, have a beneficial effect on lung symptoms and function?

Since several decades, the relationship between rhinitis and asthma has been the scope of numerous epidemiological surveys, basic research studies, and clinical trials. Before trying to answer the research question, some important preliminary issues should be addressed. The panel reviewed the major epidemiological, pathophysiological and clinical data supporting the concept of integrated upper and lower airways (Figure 3).

The following observations summarized the extensive literature review.

Observation 1: In adults there is epidemiological evidence underlying a close relationship between rhinitis and asthma. This is not true for children.

According to the European Respiratory Health Survey based on a validated questionnaire, the

prevalence of asthma is estimated to reach 3-5% in Belgium.[94] There is a strong association between allergic rhinitis and asthma in adults at the epidemiological level.[95] Among people with asthma in Europe or United States, the point prevalence of allergic rhinitis ranged from 24 to 94% and from 50 to 100% respectively.[96] In the European Community Respiratory Health Survey, it was found that 74-80% of patients with asthma reported also rhinitis symptoms.[97] For instance it has been shown that 99.9% of patients with pollen-induced asthma have also allergic rhinitis meaning that there is virtually no patient with pollen-induced asthma who don't have rhinitis at the same time. Conversely asthma is reported in roughly 25% of patients with pollen allergic rhinitis and in 50% of rhinitis patients sensitized to house dust mites.[98] In the European Community Respiratory Health Survey, Leynaert *et al.*[99] observed that adult patients with perennial allergic rhinitis are 8 times more likely to develop asthma. Although the association between AR and asthma is strongly documented in adults, the body of evidence to support this relationship is much less in children (expert view-paediatrician).

Observation 2: Allergic rhinitis is a risk factor for asthma but different types of rhinitis, and not exclusively allergic rhinitis, are associated with asthma

This assumption is supported by the temporal relationship between AR and asthma. Prospective longitudinal studies have clearly shown that allergic rhinitis actually precedes the emergence of asthma and both the duration and the severity of rhinitis are critical in favouring the emergence of asthma.[100] Interestingly however, the association between rhinitis and asthma holds true even in the absence of atopy.[99]

Based on this epidemiological evidence in adults, asthmatics should be asked about the presence of persistent or recurrent upper airway symptoms. Although the epidemiological evidence is less apparent, patients with allergic rhinitis should be systematically asked for the presence of the lower airway symptoms.

Observation 3: The clinical sequence of allergic respiratory disease is variable in relation to age

If the sequence of allergic respiratory diseases is well documented in adults, the literature is much poorer in children. Based on their clinical experience, paediatricians believe that it is uncommon that rhinitis precedes asthma in children, although rhinitis is a common finding in young children.

Observation 4: A clinical and pathophysiological link between rhinitis and asthma is supported by scientific evidence

Considering the clinical and pathophysiological link between rhinitis and asthma, the multiple similarities between rhinitis and asthma reinforce the need to ask for upper and lower respiratory symptoms.

Due to its strategic position at the entry of the airway, the nose plays a crucial role in airway homeostasis. By warming up, humidifying and filtering the incoming air, the nose is essential in the protection and homeostasis of lower airways. Nose and bronchi seem also to communicate via more indirect mechanisms such as neural and systemic pathways. The occurrence of a slight bronchoconstriction following cold air challenge to the nose suggests that neural reflexes connect nose and lung.[101] The precise origin of the nasobronchial reflex has not been studied in detail so far. Recently, the systemic nature of the interaction between nose and bronchi and its potential relevance in several inflammatory airway diseases has been proposed.[102] In addition, genetic factors may also play a role in the manifestation of nasal and/or bronchial disease.[103]

It is likely that nasal inflammation may worsen bronchial asthma. The number of eosinophils in nasal smears correlates well with abnormalities of pulmonary function tests and the level of non-specific bronchial hyperresponsiveness as measured by metacholine bronchial challenge test.[104] Rhinitis can act as a trigger for asthma exacerbations. On the other hand, it was shown that infiltration by eosinophils of the nasal mucosa is observed in atopic asthmatics, regardless of the presence of clinical rhinitis.[105] In a mouse model, there is simultaneous development of upper and lower airway inflammation after inhalation of the allergen.[106] Local challenge in lower airways induces upper airways inflammation and vice versa. Mechanisms of this bi-directional nasobronchial crosstalk remain unexplained. Besides systemic pathways, other mechanisms may play a role in the induction of inflammatory changes at a distance, such as neural reflexes, post-nasal drip with aspiration of allergens, inflammatory cells or mediators, or nasal obstruction resulting in decreased

air conditioning and other physiologic functions of the nose.[107]

Finally, in sensitized patients, allergen exposure can trigger the same inflammation in upper and lower airways. Eosinophilic inflammation has been found in the lower airways of allergic rhinitis patients without asthma[108,109] and in the upper airways of asthmatic patients without nasal complaints.[110]

Observation 5: Besides the standard criteria necessary for the diagnosis of rhinitis and asthma, their impact on quality of life should always be considered

Asthma diagnosis is based on the conjunction of symptoms and assessment of transient variations of airways calibre, while diagnosis of allergic rhinitis is mainly based on nasal symptoms associated with positive allergy tests. In the latest GINA guidelines 2006 (*Global Initiative for Asthma. National Heart and Lung Institute, National Institutes of Health USA, and the world health Organization. Updated november 2006. Available at: http://www.ginasthma.org*), asthma is classified according to the level of control. In the ARIA guidelines 2001 and update 2008,[111,112] allergic rhinitis is classified according to the duration of symptoms and their impact on patient's daily life. Intermittent and persistent allergic rhinitis as well as asthma are associated with a significant impairment on health related quality of life.[113,114]

Coexistence of both diseases makes Quality of Life even worse and makes asthma control more difficult.

In summary, considering these numerous and validated findings, the panelists stressed the close link between rhinitis and asthma and insisted on the absolute necessity to check systematically the concomitance of a chronic inflammation at both upper and lower airways.

For answering the research question, the experts proposed an overview on the actual therapeutic opportunities available in rhinitis and asthma in order to, finally, extract several pivotal statements (Table 2).

Statement 1: Many therapeutic solutions are possible for both rhinitis and asthma. Therapeutic algorithms are available but allergic rhinitis and asthma are too frequently treated as separate disorders.

Statement 2: Currently, as demonstrated by the first SIGMA working group, it is unknown whether long-term treatment of rhinitis with anti-inflammatory medications reduces the risk of developing asthma. In favour of this hypothesis is the fact that certain drugs, including intranasal corticosteroids, leukotriene receptor antagonists and omalizumab are able to reduce the systemic inflammatory response to allergen challenge.

Statement 3: In patients suffering from both allergic rhinitis and asthma, an adequate treatment of allergic rhinitis in asthmatics may improve asthma outcome measures.

Data suggest that an adequate management of allergic rhinitis in asthmatics improves asthma symptoms,[115,116] pulmonary function tests and may reduce costs.[117] The treatment of allergic rhinitis in asthmatics patients reduces the number of severe exacerbations[118,119] and the degree of bronchial hyperresponsiveness.[120,121]

Nasal steroids have been shown to reduce bronchial hyperresponsiveness in allergic rhinitis patients with or without clinical asthma.[122,123] Nasal steroids reduce asthma symptoms in patients with concomitant rhinitis and decrease asthma-related emergency department visits.[124] In contrast, a recent large randomized placebo-controlled study, performed by the SPIRA study group,[125] showed no beneficial effect of the use of nasal glucocorticosteroids on asthmatic symptoms, bronchial responsiveness or inflammation in patients with allergic rhinitis and asthma. A recent Cochrane airways review concluded that since AR and asthma patients treated with intranasal steroids did not show an overall appreciable difference compared to patients that were not treated.[126]

Clinical trials performed over the past 40 years have demonstrated that treatment of rhinitis with oral antihistamines has variable effects upon asthma. More recent large-scale studies using antihistamines[127,128] have demonstrated small but statistically significant improvements in lower airway symptoms in patients with mild asthma, while one small study[129] suggested that antihistamines have an additive effect when combined with inhaled corticosteroids. Overall, beneficial effects observed with this class of drugs are small, and may be most important in patients with mild intermittent asthma and concomitant nasal allergy who are not using other controller therapies for asthma.

Leucotriene receptor antagonists were initially approved for

use in chronic asthma, and current national asthma guidelines recommend its use as an alternative to low-dose inhaled corticosteroids in mild persistent asthma and as adjunctive therapy in patients with moderate-severe asthma. Overall, given its beneficial effects on both rhinitis and asthma, leucotriene receptor antagonists provide an alternative therapeutic option for patients with upper and lower airway disease.

Statement 4: There are virtually no evidence supporting that treating asthma in rhinitics and that a continuous treatment of allergic rhinitis should be more efficacious than on demand in asthmatics with allergic rhinitis. There are no controlled data concerning a possible effect of the treatment of asthma on allergic rhinitis. On the other hand, there are virtually no data comparing continuous versus on-demand treatment of allergic rhinitis in patients with asthma. Dizdar *et al*. [130] compared the clinical efficacy and the anti-inflammatory activity of a regularly administered anti-histamine to its on-demand use in 37 children with allergic rhinitis due to pollen allergy in an open label randomized parallel group study. Though nasal symptoms were lower in the evening than in the morning, there was no difference between the two groups. Nasal flow rate and inflammatory markers failed to show any difference between the groups. There was no difference between the groups with respect to medication score except that the use of beta2-agonists was lower in the regular treatment group during the fourth week in the pollen season. This study suggests that regular treatment might provide better control of lower airway symptoms and airway reactivity. However, poor study methodology warrants careful interpretation of these data and additional studies are needed. Although treatment of allergic rhinitis may improve asthma outcome measures, the expert panel concludes that there is currently insufficient evidence in favour of a continuous treatment of concomitant allergic rhinitis in asthmatics when compared to an on-demand regime.

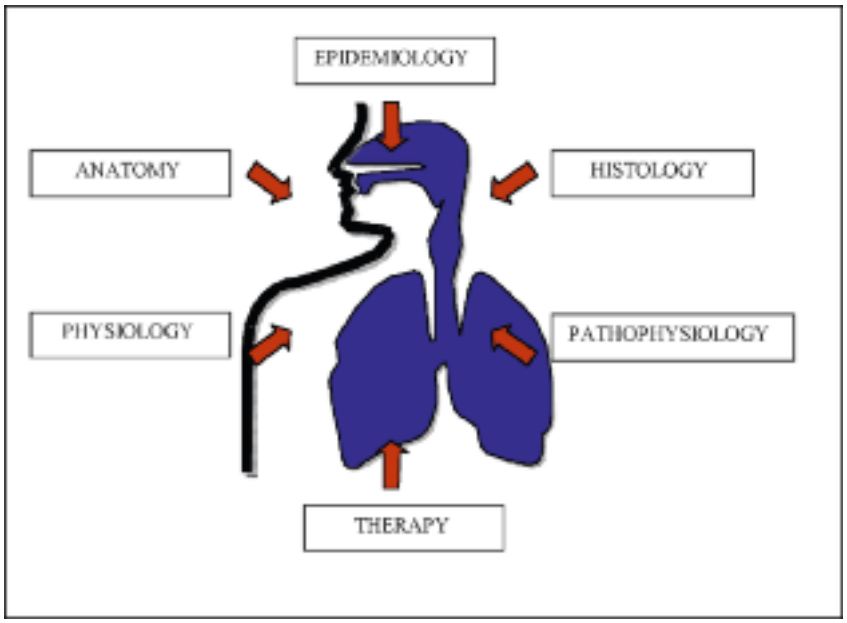

Figure 3
Relationship between upper and lower airways

IN KLEUR !

Table 2
Statements from Working Group "From rhinitis to asthma"

Topic	Statement	Level of evidence
Treatment	1. Allergic rhinitis and asthma are often treated as separate disorders	CE5
	2. There is not enough evidence to confirm a positive influence of the treatment of AR on the development of asthma	CE5
	3. An adequate treatment of AR in asthmatics may improve asthma outcome measures	CE2, CE4
	4. There is no controlled data concerning a possible effect of the treatment of asthma on allergic rhinitis	CE5
	5. There are virtually no data comparing continuous versus on demand anti-histamine treatment of allergic rhinitis in patients with asthma	CE5

Conclusion

This multidisciplinary literature analysis revealed the major epidemiological, pathophysiologic and clinical facts underlying the close relationship between, on one hand, upper and lower airways, and, on the other hand, rhinitis and

asthma. Furthermore, they stressed the crucial necessity to screen each asthmatic for upper airway symptoms. Even if efficacious treatments and updated algorithms are available for both rhinitis and asthma, an integrated management of these frequently concomitant diseases is not always prescribed. This therapeutic necessity is further supported by the proven clinical advantage to treat adequately the nose of asthmatics. At this regard, there is virtually no evidence supporting the clinical superiority of a continuous treatment of allergic rhinitis in asthmatics when compared to an on-demand regimen. Well-conducted trials profiting of the most recent advances in diagnosis and monitoring tools of this particular population of patients with rhinitis and asthma should be conducted.

QUESTION 4. When considering allergic rhinitis in Belgian population, what are the proven pharmacological effect and pharmacoeconomical consequences of continuous treatment in comparison with on-demand regime?

Continuous Versus on-demand Pharmacotherapy of Allergic Rhinitis: Evidence and Practice

Introduction

Allergic rhinitis is a common medical disorder with an estimated 20 to 30% of the adult population and up to 40% of children in the western world affected.[131] Although not life-threatening and considered by many to be a trivial disease with mild symptoms, both general health questionnaires and disease specific questionnaires shows a dramatic impairment of the quality of life and usual daily activities with the patients with more severe disease experiencing the highest level of impairment.[132] Although the presence of the symptoms is perceived as a disturbing element in itself, in a recent patient survey, 85% of the patients felt that their daily activities, particularly those relating to their professional, personal and social life, their outdoor activities and their ability to function properly at work or at school and their sleep were impaired either moderately or severely.[133] Furthermore, a large proportion of patients report that their disease causes sleep disturbances, such as trouble in going to sleep or awakening during the night and more than 50% report that they felt tired upon waking.[133-135]

As allergic rhinitis is one of the most frequent diseases encountered in clinical practice, the cost implications to society are enormous.[136] In Germany, the average annual cost of seasonal allergic rhinitis has been estimated to be € 1,089 per child/adolescent and € 1,543 per adult[137] while a study using 2002 French costing data calculated an annual cost of € 4,260 per patient for allergic rhinitis of which only 2% could be attributed to direct medical costs, the remainder constituted by workdays lost due absence from work or poor productivity and the inability to perform usual daily activities.[138]

This factual evidence justifies the search for optimizing the treatment of allergic rhinitis. The main objective of this review is to find an answer to the research question: pharmacotherapy of allergic rhinitis: continuous or on-demand? The purpose is to make recommendations applicable to daily practice. The recommendations should be easy and functional to primary care. They must be based upon a multidisciplinary approach.

A working party with experts in the field of pharmacology, pharmacokinetics, pharmacotherapy, pharmacoepidemiology and pharmacoeconomy focused on a global approach of optimization of therapy for allergic rhinitis. The working party limited itself to antihistamines, nasal corticosteroids and leukotriene antagonists as the therapeutic agents and considered the following questions:

- What is the clinical approach used at present with regard to continuous or 'on-demand' therapy?
- Do pharmacokinetic and pharmacodynamic considerations indicate a preference for continuous or 'on-demand' therapy?
- To what extent do safety considerations influence the choice between continuous versus 'on-demand' therapy?
- What are the cost implications of continuous therapy versus 'on-demand' therapy?

What is the clinical approach used at present with regard to continuous or 'on-demand' therapy?

The ARIA (Allergic Rhinitis and its Impact on Asthma) guidelines in 2003[139] and updated most recently in 2008[140] were the first to recommend an international approach to the treatment of allergic rhinitis. According to these guidelines first line treatment of allergic rhinitis consists of three steps:

1. oral or intranasal H_1-antihistamines with limited use of decongestants for mild intermittent rhinitis
2. oral or intranasal H_1-antihistamines or intranasal corticosteroids with limited use of decongestants and chromones for moderate-to-severe intermittent and mild rhinitis
3. intranasal corticosteroids with step-down and step-up options, in conjunction with H_1-antihistamines, nasal decongestants, ipratropium and oral corticosteroids for moderate to severe persistent rhinitis

For mild intermittent rhinitis, the treatment should be when necessary and of short duration. For moderate-to-severe intermittent, the treatment should be continued to prevent the development of persistent rhinitis. For persistent rhinitis, continuous treatment is considered as more efficient than 'on-demand' therapy. Antihistamines and intranasal corticosteroids are perceived as being more efficient if the therapy is continuous.[141]

To obtain further evidence if clinical practice, Summaries of Product Characteristics (SmPC's) of 24 registered medicines were reviewed. The selection was taken from the groups of medicines defined in the concept paper. As generic medicines refer to the original ones, the analysis was limited to the medicines originally put on the market. For one active product one medicine was taken.

Apart from the leukotriene antagonists and some oral corticosteroids, all other medicines contained the labelling 'allergic rhinitis' or 'allergic conditions of the respiratory tract'. Symptomatic as well as prophylactic and chronic treatment is mentioned in the indications.

Divergent information is given on the duration of treatment for different drugs:

- *Oral decongestants*: the duration of treatment should be as short as possible
- *H_1-antihistamines*: mostly no instructions with regard to duration of therapy are given. Cetirizine and levocetirizine are most explicit with specific durations according to the complaints. For both products time limits are specified (e.g. 3 to 6 weeks for levocetirizine in case of hay fever). Most probably limited experience in clinical trials causes this warning (SmPC dated January 2004), as for cetirizine clinical experience covers at least one year
- *Local corticosteroids*: it is recommended to use the spray 'regularly', preventively or continuously
- *Oral corticosteroids*: use of betamethasone is restricted to 10-14 days
- *Sodium cromoglycate*: preventive treatment does not allow an interruption of treatment

Do pharmacokinetic and pharmacodynamic considerations indicate a preference for continuous or 'on-demand' therapy?

H_1-antihistamines

Only two studies specifically designed to compare continuous versus on-demand therapy, both from the same research group, were retrieved. Some comparative data were also obtained from a third study used to assess the use of rescue medication in children.

In the first study,[142] cetirizine was administered either continuously or on-demand to twenty adults with seasonal allergic rhinitis over a 4-week period of natural allergen exposure during the pollen season. The results showed that although on-demand therapy can achieve acceptable clinical control, patients treated with continuous therapy achieved significant better symptomatic relief and inflammatory control. In the second study,[143] one group of 31 adults with persistent allergic rhinitis took levocetirizine daily for six months while a parallel group only took it on-demand. Both treatment regimens achieved similar levels up to week 14 but continuous treatment was generally better than on-demand from week 15 onwards, reaching statistical significance from weeks 17 to 21 (from week 19 to 21 for nasal pruritus). Both regimens substantially improved quality of life and sleep quality. In the third study,[144] the use of rescue medications, including antibiotics, paracetamol, b_2-agonists, inhaled and systemic corticosteroids, in children with persistent allergic rhinitis and asthma due to house dust mite allergy was significantly lower ($p<0.05$) in those taking cetirizine regularly for 24 weeks compared with those taking it on-demand. Furthermore, the cost of treatment was lower with continuous therapy because more co-medication was taken in the placebo group due to poorer symptom control.[144]

These results of these pilot studies support the continuous use of antihistamines as being more effective than on-demand therapy. The observation that inflammatory variables, such as nasal congestion, are suppressed better

by continuous therapy supports the hypothesis that reduction of allergic inflammation requires long term therapy with antihistamines.[138,145] However, there is a need for more clinical evidence, particularly with other antihistamines. In addition, pharmacological and pharmacokinetic parameters could help to look for a certain level of evidence.

Nasal corticosteroids

Because the effect of corticosteroids is primarily to reduce allergic inflammation, their onset of action is slow. While a statistically significant improvement may occur quite rapidly, it takes much longer for nasal corticosteroids to become truly effective. For example, by twelve hours after the first administration of mometasone during the pollen season, only 28% of patients experienced clinically significant relief 28% while by 72 hours 64% of the patients experienced at least moderate relief.[146] However, in many studies with nasal corticosteroids one to two weeks is required for significant clinical activity.[147,148] Also, whether the scoring is performed by the physician of by the patient can make a difference. In one study,[149] subjective assessments made by the physician showed a clinical difference after one week whereas assessments by the patients themselves required two weeks to achieve significant differences.

As continuous therapy with corticosteroids may reduce mast cell numbers,[150] some authors strongly recommend starting the treatment with nasal corticosteroids before the pollen season to achieve a prophylactic reduction of mast cells in the nasal epithelium. To this end, the SmPC for mometasone states: … *The start of the pollen season may vary, depending mainly on the geographic area and the prevailing weather conditions, so 'safe' advice is to start pre-treatment 2 to 4 weeks before start of the pollen season and to continue treatment throughout the pollen season.*… The study that stimulated this recommendation[151] was one which started administration of nasal mometasone as prophylactic treatment starting 2 to 4 weeks before the pollen season and continued for four months. An overwhelming majority of patients (84%) were satisfied with this type of treatment.

Thus, with corticosteroids, which act primarily to reduce allergic inflammation, continuous therapy is essential for them to be clinically effective.

To what extent do safety considerations influence the choice between continuous versus 'on-demand' therapy?

For drugs used for symptomatic relief of non-lethal conditions, such as allergic diseases, safety is of paramount importance. As no comparative data are available for continuous versus on-demand therapy with respect to safety, this review will consider the long term safety aspects of antihistamines and intra-nasal corticosteroids in relation to their use in both situations .

H_1-antihistamines

The first generation antihistamines are associated with a number of adverse events, including central nervous system depression and anticholinergic and cardiovascular effects. Despite these potentially toxic effects, first-generation H_1-antihistamines, including chlorpheniramine, brompheniramine, diphenhydramine and promethazine, are still widely prescribed. The introduction of terfenadine in 1978[152] saw the first of the minimally sedating H_1-antihistamines, a list which now contains many drugs including azelastine, cetirizine, clemastine, desloratadine, ebastine, fexofenadine, levocetirizine, loratadine and mequitazine. Second generation H_1-antihistamines are recognized as being highly effective treatments for allergic disease and are among the most frequently prescribed and safest drugs in the world.[153]

Perhaps the most serious toxic event reported was the association between the consumption of astemizole or terfenadine and the occurrence of prolongation of the QT interval, leading to the appearance of polymorphic ventricular arrhythmias, syncope, and even cardiac arrest.[145] Following the recognition of over 200 cases of potentially-fatal cardiac arrhythmias, both terfenadine and astemizole have been withdrawn from the market in most countries. All H_1-antihistamines on the market today are free from clinically demonstrable cardiotoxicity.

Another adverse effect of H_1-antihistamines that has given cause for concern is their potential to cause a degree of somnolence in some individuals. Most of the clinical trials report drowsiness, sedation, or somnolence as a common adverse effect. However, most sedation studies with H_1-antihistamines have been performed in either healthy individuals or individuals with mild disease rather than in conditions,

such as severe allergic rhinitis or chronic urticaria, both of which cause sleep deprivation.[154-156] So is drug-induced daytime somnolence a problem with such patients? Two studies, one with fexofenadine and the other with levocetirizine, found that chronic urticaria patients taking regular H_1-antihistamine therapy experienced significantly less interference with sleep and improved daily activities.[157] Two possible reasons may be suggested to explain the decreased somnolence. The first possibility is the relief from physical discomfort ensuing from the psychological status of the patients and the associated sleep deprivation. The second possibility is the development of tolerance to the central nervous sedative effects of the H_1-antihistamines which has been reported repeatedly to occur after 4 to 5 days of administration of both first and second generation.[158-160] Thus, although direct comparisons between continuous and on-demand therapy with H_1-antihistamines have not been performed, it is tempting to speculate that continuous therapy may be preferable to reduce somnolence.

In conclusion, H_1-antihistamines are very safe medicines when taken long term. Of the major H_1-antihistamines, cetirizine and loratadine have been on the market for 20 years and desloratadine, fexofenadine and levocetirizine for more than 8 years without safety issues arising. In adults, formal studies of two to three years duration have shown cetirizine to be safe when given continuously[161,162] while in children of 1 to 2 years of age, both cetirizine and levocetirizine have been shown to be safe when given for periods of 18 months.[163-165]

Nasal corticosteroids

Intranasal corticosteroids are considered relatively safe.[150,166] Local adverse effects are usually mild and include mucosal irritation and epistaxis. Nasal septal perforation is rare. The most commonly reported adverse effects for individual intranasal corticosteroids are as follows:

- **Beclometasone:** epistaxis, upper respiratory tract infection and headache
- **Betamethasone:** sore throat, flushing and headache
- **Budesonide:** unpleasant taste, headache, coughing, nose dryness and epistaxis
- **Flunisolide:** nasal burning, drowsiness, and nasal irritation
- **Fluticasone:** headache, epistaxis, sore throat, nasal dryness/blowing and diarrhoea. There have been case reports of anaphylaxis and flushing as well as central nervous system, cardiac, and dermatological reactions
- **Mometasone:** headache, epistaxis, and pharyngitis. In clinical trials, the rate of treatment discontinuation with mometasone furoate nasal spray because of adverse events was ≤3%, a rate similar to those reported with placebo and active controls; the most frequently reported adverse effects were headache, viral infection, pharyngitis, and epistaxis
- **Triamcinolone:** headache, sneezing, and nasal irritation

Clinical and histopathological examination of nasal mucosa after long term intranasal budesonide or mometasone use has failed to show significant changes. Although intranasal steroids can result in systemic bioavailability, no significant adverse effects have been reported on bone metabolism. Influence of adrenal function should be considered. Based on morning salivary cortisol concentrations, for 58% of patients on nasal betamethasone sodium phosphate and for 4% of patients on mometasone furoate biochemical evidence of adrenal suppression was apparent.[167] Mometasone 100 µg/day does neither influence growth in children between 3 and 9 years old, nor interfere with the hypothalamic-pituiary-adrenocortical-axis function.[168]

What are the cost implications of continuous therapy versus 'on-demand' therapy?

To date, no study has compared costs of continuous and on-demand treatment of allergic rhinitis. As it is difficult to determine the economic impact of allergic rhinitis, Table 3 identifies the major cost items that need to be considered when contrasting costs of continuous and on-demand treatment of allergic rhinitis from a societal perspective. In addition to direct healthcare costs, studies need to focus on eliciting direct non-healthcare costs and indirect costs. With respect to the latter, attention needs to be paid to calculating the indirect costs of days lost to education and work, costs of reduced productivity at work, and the costs of reduced ability to carry out usual daily activities. Indirect costs need to be calculated for patients suffering from allergic rhinitis.

Conclusions

This review has examined the pharmacological and pharmaco-

Table 3

Cost items of continuous/on-demand treatment of allergic rhinitis

Direct healthcare costs			Direct non-health care costs	Indirect costs
Medication	Healthcare providers	Other		
Oral and intranasal antihistaminics Intranasal corticosteroids Oral and intranasal decongestants Intranasal anticholinergic agents	General practitioner Pneumologist Ear, nose and throat specialist	Diagnostic tests Immunotherapy Accident and emergency visit Alternative medicine (e.g. homeopathy)	Transportation to healthcare provider Child care costs while in treatment Home adaptations	Absence from work Reduced productivity at work Time lost from education Reduced ability to carry out usual daily activities

economical evidence for the use of continuous treatment in comparison with an on-demand regime? Clearly, for corticosteroids, their mechanism of action in allergic rhinitis of reducing allergic inflammation requires continuous therapy at least for the duration of symptoms. For H_1-antihistamines the conclusion is equivocal. Some trials suggest that continuous treatment is preferable but more studies are needed to confirm this. For both H_1-antihistamines and nasal corticosteroids safety data indicate that continuous treatment may be given without fears of adverse consequences. With regard to the cost implications of continuous therapy versus on-demand therapy, more studies are necessary before definitive conclusions may be made.

Conclusions

When considering children, the panel agreed that there is sufficient expert opinion in favour of continuous treatment with both H_1-antihistamines and corticosteroids for controlling symptoms of allergic rhinitis in children during periods of allergen exposure, especially pollens. However, there is not enough evidence to support continuous treatment during periods of low or no allergen exposure when symptoms are negligible in an attempt to prevent the development of new allergic diseases in children with allergic rhinitis.

In adults, the effect of corticosteroids in reducing allergic inflammation in allergic rhinitis requires continuous therapy at least for the duration of symptoms. However, for H_1-antihistamines the argument for continuous use is equivocal. Some trials suggest that continuous treatment is preferable as it reduces, at least partially, allergic inflammation resulting in a reduction of symptoms and, when taken before the onset of symptoms, may prevent their appearance. However, more studies are needed to confirm this.

With close relationship between allergic rhinitis and asthma, the expert groups stressed the crucial necessity to screen each asthmatic for allergic rhinitis and institute appropriate therapy for both conditions. Even though efficacious treatment algorithms are available for both rhinitis and asthma, an integrated management is not always prescribed even though there is a proven clinical advantage of adequate treatment of the nose of asthmatics.

For both H_1-antihistamines and nasal corticosteroids safety data indicate that continuous treatment may be given without fears of adverse consequences. With regard to the cost implications of continuous therapy versus on-demand therapy, there are indications that effective treatment of allergic rhinitis by continuous treatment reduces overall drug costs, particularly that of escape medication and indirect costs in the form of days absent from work and school.

References

1. Bauchau V, Durham SR. Prevalence and rate of diagnosis of allergic rhinitis in Europe. *Eur Respir J.* 2004;24:758-764.
2. Bousquet J, Kalthaiev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et ARIA Working Group. Allergic rhinitis and its impact on asthma. Update 2008 (in collaboration with World health organization, GA2LEN, AllerGen). *Allergy*. 2008;63 Suppl 86:8-160.
3. Van Hoecke H, Van Cauwenberge P, Watelet JB. Dissemination and implementation of ARIA guidelines among Belgian Otorhinolaryngologists. *Rhinology*. In press.

4. Wahn U. What drives the allergic march? *Allergy.* 2000;55:591-599.
5. ISAAC Study. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. *Lancet*. 2008;351:1225-1232.
6. Asher MI, Montefort S, Bjorksten B, *et al*. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC phases one and three repeat multicountry cross-sectional surveys. *Lancet.* 2006;368:733-743.
7. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med.* 1995;332:133-138.
8. Bergmann RL, Bergmann KE, Lau-Schadensdorf S, *et al*. Atopic diseases in infancy. The german multicenter atopy study (MAS-90). *Pediatr Allergy Immunol*. 1994;5:19-25.
9. Arshad SH, Tariq SM, Matthews S, Hakim E. Sensitization to common allergens and its association with allergic disorders at Age 4 years: a whole population birth cohort study. *Pediatrics.* 2001;108:E33.
10. Arshad SH, Kurukulaaratchy RJ, Fenn M, Waterhouse L, Matthews S. Rhinitis in 10-year-old children and early life risk factors for its development. *Acta Paediatr.* 2002;91:1334-1338.
11. Valovirta E, Myrseth SE, Palkonen S. The voice of the patients: allergic rhinitis is not a trivial disease. *Curr Opin Allergy Clin Immunol.* 2008;8:1-9.
12. Vuurman EF, van Veggel LM, Uiterwijk MM, Leutner D, O'Hanlon JF. Seasonal allergic rhinitis and antihistamine effects on children's learning. *Ann Allergy.* 1993;71:121-126.
13. Juniper EF, Guyatt GH, Dolovich J. Assessment of quality of life in adolescents with allergic rhinoconjunctivitis: Development and testing of a questionnaire for clinical trials. *J Allergy Clin Immunol.* 1994;93: 413-423.
14. Meltzer EO. Quality of life in adults and children with allergic rhinitis. *J Allergy Clin Immunol.* 2001;108: S45-S53.
15. Blaiss MS. Allergic rhinitis and impairment issues in schoolchildren: a consensus report. *Curr Med Res Opin.* 2004;20:1937-1952.
16. Blaiss MS. Pediatric allergic rhinitis: physical and mental complications. *Allergy Asthma Proc.* 2008;29:1-6.
17. Bousquet J, Khaltaev N, Cruz AA, *et al*. Allergic rhinitis and its impact on asthma (ARIA) 2008 Update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy.* 2008;63 Suppl 86:8-160.
18. Kull I, Bohme M, Wahlgren CF, Nordvall L, Pershagen G, Wickman M. Breast-feeding reduces the risk for childhood eczema. *J Allergy Clin Immunol.* 2005;116:657-661.
19. Kramer MS, Kakuma R. Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child. *Cochrane Database Syst Rev.* 2006;3:CD000133.
20. Biagini JM, LeMasters GK, Ryan PH, *et al*. Environmental risk factors of rhinitis in early infancy. *Pediatr Allergy Immunol.* 2006;17:278-284.
21. Corver K, Kerkhof M, Brussee JE, *et al*. House dust mite allergen reduction and allergy at 4 yr: Follow Up of the PIAMA-Study. *Pediatr Allergy Immunol*. 2006;17:329-336.
22. Sheikh A, Hurwitz B. House dust mite avoidance measures for perennial allergic rhinitis: a systematic review of efficacy. *Br J Gen Pract*. 2003;53:318-322.
23. Simpson A, John SL, Jury F, *et al*. Endotoxin exposure, CD14, and allergic disease: an interaction between genes and the environment. *Am J Respir Crit Care Med.* 2006;174:386-392.
24. Palmer CN, Irvine AD, Terron-Kwiatkowski A, *et al*. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet.* 2006;38:441-446.
25. Cork MJ, Robinson DA, Vasilopoulos Y, *et al*. New perspectives on epidermal barrier dysfunction in atopic dermatitis: Gene-Environment Interactions. *J Allergy Clin Immunol.* 2006;118:3-21.
26. Darsow U, Lubbe J, Taieb A, *et al*. Position paper on diagnosis and treatment of atopic dermatitis. *J Eur Acad Dermatol Venereol.* 2005;19:286-295.
27. Gregory C, Cifaldi M, Tanner LA. Targeted intervention programs: creating a customized practice model to improve the treatment of allergic rhinitis in a managed care population. *Am J Manag Care.* 1999;5:485-496.
28. Ciprandi G, Cirillo I, Vizzaccaro A, Tosca MA. Levocetirizine improves nasal obstruction and modulates cytokine pattern in patients with seasonal allergic rhinitis: a pilot study. *Clin Exp Allergy*. 2004;34:958-964.
29. Ciprandi G, Ricca V, Passalacqua G, Fasolo A, Canonica GW. Intranasal fluticasone propionate reduces ICAM-1 on nasal epithelial cells both during early and late phase after allergen challenge. *Clin Exp Allergy.* 1998;28:293-299.
30. Fokkens WJ, Godthelp T, Holm AF, Blom H, Klein-Jan A. Allergic rhinitis and inflammation: the effect of nasal corticosteroid therapy. *Allergy.* 1997;52:29-32.
31. Dizdar EA, Sekerel BE, Keskin O, *et al*. The effect of regular versus on-demand desloratadine treatment in children with allergic rhinitis. *Int J Pediatr Otorhinolaryngol.* 2007;71: 843-849.
32. Pawankar R. Mast cells in allergic airway disease and chronic rhinosinusitis. *Chem Immunol Allergy.* 2005;87:111-129.
33. Pawankar R. Mast cells as orchestrators of the allergic reaction: the IgE-IgE receptor mast cell network. *Curr Opin Allergy Clin Immunol*. 2001;1:3-6.
34. Pawankar R, Ra C. Heterogeneity of mast cells and T cells in the nasal mucosa. *J Allergy Clin Immunol.* 1996;98:S248-262.
35. Ohashi H, Takei M, Ide Y, *et al*. Effect of interleukin-3, interleukin 5 and hyaluronic acid on cultured eosinophils derived from human umbilical cord blood mononuclear cells. *Int Arch Allergy Immunol*. 1999;118:44-50.
36. Profita M, La Grutta S, Carpagnano E, *et al*. Noninvasive

methods for the detection of upper and lower airway inflammation in atopic children. *J Allergy Clin Immunol*. 2006;118:1068-1074.
37. Lemiere C, Ernst P, Olivenstein R, *et al*. Airway inflammation assessed by invasive and noninvasive means in severe asthma: eosinophilic and noneosinophilic phenotypes. *J Allergy Clin Immunol.* 2006;118: 1033-1039.
38. Turktas H, Oguzulgen K, Kokturk N, Memis L, Erbas D. Correlation of exhaled nitric oxide levels and airway inflammation markers in stable asthmatic patients. *J Asthma*. 2003;40:425-430.
39. Ciprandi G, Buscaglia S, Pesce G, *et al*. Minimal persistent inflammation is present at mucosal level in patients with asymptomatic rhinitis and mite allergy. *J Allergy Clin Immunol.* 1995;96:971-979.
40. Bauchau V, Durham SR. Prevalence and rate of diagnosis of allergic rhinitis in Europe. *Eur Respir J*. 2004;24:758-764.
41. Bauchau V, Durham SR. Epidemiological characterization of the intermittent and persistent types of allergic rhinitis. *Allergy*. 2005;60:350-353.
42. Bachert C, van Cauwenberge P, Olbrecht J, van Schoor J. Prevalence, classification and perception of allergic and nonallergic rhinitis in Belgium. *Allergy*. 2006;61:693-698.
43. Pipkorn U. Hay fever: in the laboratory and at natural allergen exposure. *Allergy*. 1988;43 Suppl 8:41-44.
44. Juliusson S, Pipkorn U, Karlsson G, Enerback L. Mast cells and eosinophils in the allergic mucosal response to allergen challenge: changes in distribution and signs of activation in relation to symptoms. *J Allergy Clin Immunol*. 1992;90: 898-909.
45. Hakansson L, Rak S, Dahl R, Venge P. The formation of eosinophil and neutrophil chemotactic activity during a pollen season and after allergen challenge. *J Allergy Clin Immunol*. 1989;83:933-939.
46. Corrado OJ, Gould CA, Kassab JY, Davies RJ. Nasal response of rhinitic and non-rhinitic subjects to histamine and methacholine: a comparative study. *Thorax.* 1986;41:863-868.
47. Gerth van Wijk RG, de Graaf-in 't Veld C, Garrelds IM. Nasal hyperreactivity. *Rhinology*. 1999;37:50-55.
48. Gerth van Wijk R. Perennial allergic rhinitis and nasal hyperreactivity. *Am J Rhinol*. 1998;12:33-35.
49. de Graaf-in 't Veld T, Koenders S, Garrelds IM, Gerth van Wijk R. The relationships between nasal hyperreactivity, quality of life, and nasal symptoms in patients with perennial allergic rhinitis. *J Allergy Clin Immunol.* 1996;98:508-513.
50. de Graaf-in t Veld C, Garrelds IM, Koenders S, Gerth van Wijk R. Relationship between nasal hyperreactivity, mediators and eosinophils in patients with perennial allergic rhinitis and controls. *Clin Exp Allergy*. 1996;26:903-908.
51. Gerth van Wijk R. Nasal hyperreactivity: its pathogenesis and clinical significance. *Clin Exp Allergy.* 1991;21:661-667.
52. Skoner DP, Lee L, Doyle WJ, Boehm S, Fireman P. Nasal physiology and inflammatory mediators during natural pollen exposure. Ann Allergy. 1990 Sep;65(3):206-10.
53. Rasp G, Thomas PA, Bujia J. Eosinophil inflammation of the nasal mucosa in allergic and non-allergic rhinitis measured by eosinophil cationic protein levels in native nasal fluid and serum. *Clin Exp Allergy*. 1994;24:1151-1156.
54. Linden M, Svensson C, Andersson M, *et al*. Circulating eosinophil/basophil progenitors and nasal mucosal cytokines in seasonal allergic rhinitis. *Allergy*. 1999;54:212-219.
55. Linden M, Greiff L, Andersson M, *et al*. Nasal cytokines in common cold and allergic rhinitis. *Clin Exp Allergy*. 1995;25:166-172.
56. Bachert C, van Kempen M, Van Cauwenberge P. Regulation of proinflammatory cytokines in seasonal allergic rhinitis. *Int Arch Allergy Immunol*. 1999;118:375-379.
57. Bachert C, Hauser U, Prem B, Rudack C, Ganzer U. Proinflammatory cytokines in allergic rhinitis. *Eur Arch Otorhinolaryngol*. 1995;252 Suppl 1:S44-S49.
58. Ohashi Y, Nakai Y, Tanaka A, *et al*. Seasonal rise in interleukin-4 during pollen season is related to seasonal rise in specific IgE for pollens but not for mites. *Acta Otolaryngol*. 1998;118:243-247.
59. Ying S, Durham SR, Jacobson MR, *et al*. T lymphocytes and mast cells express messenger RNA for interleukin-4 in the nasal mucosa in allergen-induced rhinitis. *Immunology*. 1994;82:200-206.
60. Minshall EM, Cameron L, Lavigne F, *et al*. Eotaxin mRNA and protein expression in chronic sinusitis and allergen-induced nasal responses in seasonal allergic rhinitis. *Am J Respir Cell Mol Biol*. 1997;17:683-690.
61. Eccles R. Plasma exudation in rhinitis. *Clin Exp Allergy*. 1992;22:319-320.
62. Pipkorn U, Karlsson G, Enerback L. Nasal mucosal response to repeated challenges with pollen allergen. *Am Rev Respir Dis*. 1989;140:729-736.
63. Ciprandi G, Pronzato C, Passalacqua G, *et al.* Topical azelastine reduces eosinophil activation and intercellular adhesion molecule-1 expression on nasal epithelial cells: an antiallergic activity. *J Allergy Clin Immunol*. 1996;98:1088-1096.
64. Buscaglia S, Paolieri F, Catrullo A, *et al.* Topical ocular levocabastine reduces ICAM-1 expression on epithelial cells both in vivo and in vitro. *Clin Exp Allergy*. 1996;26: 1188-1196.
65. Ciprandi G, Pronzato C, Ricca V, Varese P, Del Giacco GS, Canonica GW. Terfenadine exerts antiallergic activity reducing ICAM-1 expression on nasal epithelial cells in patients with pollen allergy. *Clin Exp Allergy*. 1995;25:871-878.
66. Fasce L, Ciprandi G, Pronzato C, *et al*. Cetirizine reduces ICAM-I on epithelial cells during nasal minimal persistent inflammation in asymptomatic children with mite-allergic asthma. *Int Arch Allergy Immunol*. 1996;109:272-276.
67. Ciprandi G, Buscaglia S, Catrullo A, *et al*. Azelastine eye drops reduce and prevent allergic conjunctival reaction and exert anti-allergic activity. *Clin Exp Allergy*. 1997;27:182-191.
68. Ciprandi G, Passalacqua G, Mincarini M, Ricca V, Canonica GW. Continuous versus on demand treatment with cetirizine for

allergic rhinitis. *Ann Allergy Asthma Immunol.* 1997;79:507-511.
69. Holm A, Dijkstra M, Kleinjan A, *et al*. Fluticasone propionate aqueous nasal spray reduces inflammatory cells in unchallenged allergic nasal mucosa: effects of single allergen challenge. *J Allergy Clin Immunol*. 2001;107:627-633.
70. Fokkens WJ, Godthelp T, Holm AF, Klein-Jan A. Local corticosteroid treatment: the effect on cells and cytokines in nasal allergic inflammation. *Am J Rhinol*. 1998;12:21-26.
71. Holm AF, Fokkens WJ, Godthelp T, Mulder PG, Vroom TM, Rijntjes E. Effect of 3 months' nasal steroid therapy on nasal T cells and Langerhans cells in patients suffering from allergic rhinitis. *Allergy*. 1995;50:204-209.
72. Bradding P, Feather IH, Wilson S, Holgate ST, Howarth PH. Cytokine immunoreactivity in seasonal rhinitis: regulation by a topical corticosteroid. *Am J Respir Crit Care Med.* 1995;151:1900-1906.
73. Garrelds IM, De Graaf-in 't Veld T, Nahori MA, Vargaftig BB, Gerth van Wijk R, Zijlstra FJ. Interleukin-5 and eosinophil cationic protein in nasal lavages of rhinitis patients. *Eur J Pharmacol*. 1995;275:295-300.
74. Jacobson MR, Juliusson S, Lowhagen O, Balder B, Kay AB, Durham SR. Effect of topical corticosteroids on seasonal increases in epithelial eosinophils and mast cells in allergic rhinitis: a comparison of nasal brush and biopsy methods. *Clin Exp Allergy*. 1999;29:1347-1355.
75. Mullol J, Xaubet A, Lopez E, Roca-Ferrer J, Picado C. Comparative study of the effects of different glucocorticosteroids on eosinophil survival primed by cultured epithelial cell supernatants obtained from nasal mucosa and nasal polyps. *Thorax*. 1995;50:270-274.
76. Masuyama K, Jacobson MR, Rak S, *et al*. Topical glucocorticosteroid (fluticasone propionate) inhibits cells expressing cytokine mRNA for interleukin-4 in the nasal mucosa in allergen-induced rhinitis. *Immunology*. 1994;82:192-199.
77. Pipkorn U, Proud D, Lichtenstein LM, Kagey-Sobotka A, Norman PS, Naclerio RM. Inhibition of mediator release in allergic rhinitis by pretreatment with topical glucocorticosteroids. *N Engl J Med*. 1987;316:1506-1510.
78. Razi C, Bakirtas A, Harmanci K, Turktas I, Erbas D. Effect of montelukast on symptoms and exhaled nitric oxide levels in 7- to 14-year-old children with seasonal allergic rhinitis. *Ann Allergy Asthma Immunol*. 2006;97:767-774.
79. Ciprandi G, Frati F, Marcucci F, *et al.* Nasal cytokine modulation by montelukast in allergic children: a pilot study. *Eur Ann Allergy Clin Immunol*. 2003;35:295-299.
80. Ciprandi G, Tosca MA, Milanese M, Schenone G, Ricca V. Antihistamines added to an antileukotriene in treating seasonal allergic rhinitis: histamine and leukotriene antagonism. *Eur Ann Allergy Clin Immunol*. 2004;36:67-70, 72.
81. Ciprandi G, Tosca M, Passalacqua G, Canonica GW. Long-term cetirizine treatment reduces allergic symptoms and drug prescriptions in children with mite allergy. *Ann Allergy Asthma Immunol.* 2001;87:222-226.
82. Ciprandi G, Frati F, Marcucci F, Sensi L, Milanese M, Tosca MA. Long-term cetirizine treatment may reduce new sensitisations in allergic children: a pilot study. *Eur Ann Allergy Clin Immunol.* 2003;35:208-211.
83. Weiner JM, Abramson MJ, Puy RM. Intranasal corticosteroids versus oral H1 receptor antagonists in allergic rhinitis: systematic review of randomised controlled trials. *BMJ*. 1998;317:1624-1629.
84. Juniper EF, Guyatt GH, O'Byrne PM, Viveiros M. Aqueous beclomethasone diproprionate nasal spray: regular versus "as required" use in the treatment of seasonal allergic rhinitis. *J Allergy Clin Immunol*. 1990;86:380-386.
85. Berkowitz RB, Bernstein DI, LaForce C, *et al.* Onset of action of mometasone furoate nasal spray (NASONEX) in seasonal allergic rhinitis. *Allergy.* 1999;54:64-69.
86. Selner JC, Weber RW, Richmond GW, Stricker WE, Norton JD. Onset of action of aqueous beclomethasone dipropionate nasal spray in seasonal allergic rhinitis. *Clin Ther.* 1995;17:1099-1109.
87. Holm AF, Fokkens WJ, Godthelp T, Mulder PG, Vroom TM, Rijntjes E. A 1-year placebo-controlled study of intranasal fluticasone propionate aqueous nasal spray in patients with perennial allergic rhinitis: a safety and biopsy study. *Clin Otolaryngol Allied Sci.* 1998;23:69-73.
88. Mygind N, Andersson M. Topical glucocorticosteroids in rhinitis: clinical aspects. *Acta Otolaryngol.* 2006;126:1022-1029.
89. Andersson M, Andersson P, Pipkorn U. Allergen-induced specific and non-specific nasal reactions. Reciprocal relationship and inhibition by topical glucocorticosteroids. *Acta Otolaryngol*. 1989;107:270-277.
90. Andersson M, Andersson P, Pipkorn U. Topical glucocorticosteroids and allergen-induced increase in nasal reactivity: relationship between treatment time and inhibitory effect. *J Allergy Clin Immunol.* 1988;82:1019-1026.
91. Stelmach R, do Patrocinio TNM, Ribeiro M, Cukier A. Effect of treating allergic rhinitis with corticosteroids in patients with mild-to-moderate persistent asthma. *Chest.* 2005;128:3140-3147.
92. Lauriello M, Muzi P, Di Rienzo L, Di Stanislao C, Tirelli GC, Bologna M. A two-year course of specific immunotherapy or of continuous antihistamine treatment reverse eosinophilic inflammation in severe persistent allergic rhinitis. *Acta Otorhinolaryngol Ital.* 2005;25:284-291.
93. Schadlich PK, Brecht JG. Economic evaluation of specific immunotherapy versus symptomatic treatment of allergic rhinitis in Germany. *Pharmacoeconomics*. 2000;17:37-52.
94. Variations in the prevalence of respiratory symptoms, self-reported asthma attacks, and use of asthma medication in the European Community Respiratory Health Survey (ECRHS). *Eur Respir J*. 1996;9:687-695.
95. Bousquet J, Vignola AM, Demoly P. Links between rhinitis and asthma. *Allergy*. 2003;58:691-706.
96. Gaugris S, Sazonov-Kocevar V, Thomas M. Burden of concomitant

allergic rhinitis in adults with asthma. *J Asthma*. 2006;43:1-7.
97. Leynaert B, Neukirch C, Kony S, *et al*. Association between asthma and rhinitis according to atopic sensitization in a population-based study. *J Allergy Clin Immunol*. 2004;113:86-93.
98. Linneberg A, Nielsen NH, Madsen F, Frolund L, Dirksen A, Jorgensen T. Factors related to allergic sensitization to aeroallergens in a cross-sectional study in adults: The Copenhagen Allergy Study. *Clin Exp Allergy*. 2001;31:1409-1417.
99. Leynaert B, Bousquet J, Neukirch C, 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.
100. 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.
101. Johansson A, Bende M, Millqvist E, Bake B. Nasobronchial relationship after cold air provocation. *Respir Med*. 2000;94:1119-1122.
102. Togias A. Systemic effects of local allergic disease. *J Allergy Clin Immunol*. 2004;113 Suppl 1:S8-S14.
103. Barnes KC. Genetic epidemiology of health disparities in allergy and clinical immunology. *J Allergy Clin Immunol*. 2006;117:243-254; quiz 255-256.
104. 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.
105. Chanez P, Vignola AM, Vic P, *et al*. Comparison between nasal and bronchial inflammation in asthmatic and control subjects. *Am J Respir Crit Care Med*. 1999;159:588-595.
106. Hellings PW, Hessel EM, Van Den Oord JJ, Kasran A, Van Hecke P, Ceuppens JL. Eosinophilic rhinitis accompanies the development of lower airway inflammation and hyper-reactivity in sensitized mice exposed to aerosolized allergen. *Clin Exp Allergy*. 2001;31:782-790.
107. Braunstahl GJ, Hellings PW. Allergic rhinitis and asthma: the link further unraveled. *Curr Opin Pulm Med*. 2003;9:46-51.
108. Alvarez MJ, Olaguibel JM, Garcia BE, Rodriquez A, Tabar AI, Urbiola E. Airway inflammation in asthma and perennial allergic rhinitis. Relationship with nonspecific bronchial responsiveness and maximal airway narrowing. *Allergy*. 2000;55:355-362.
109. Foresi A, Leone C, Pelucchi A, *et al*. Eosinophils, mast cells, and basophils in induced sputum from patients with seasonal allergic rhinitis and perennial asthma: relationship to methacholine responsiveness. *J Allergy Clin Immunol*. 1997;100:58-64.
110. Gaga M, Lambrou P, Papageorgiou N, *et al*. Eosinophils are a feature of upper and lower airway pathology in non-atopic asthma, irrespective of the presence of rhinitis. *Clin Exp Allergy*. 2000;30:663-669.
111. Bousquet J, Khaltaev N, Cruz AA, *et al*. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy.* 2008;63 Suppl 86:8-160.
112. Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol*. 2001;108 Suppl 5:S147-S334.
113. Leynaert B, Neukirch C, Liard R, Bousquet J, Neukirch F. Quality of life in allergic rhinitis and asthma. A population-based study of young adults. *Am J Respir Crit Care Med.* 2000;162:1391-1396.
114. Baiardini I, Braido F, Brandi S, Canonica GW. Allergic diseases and their impact on quality of life. *Ann Allergy Asthma Immunol*. 2006;97:419-428; quiz 429-430, 476.
115. 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.
116. Meltzer EO. The relationships of rhinitis and asthma. *Allergy Asthma Proc*. 2005;26:336-340.
117. Price D, Zhang Q, Kocevar VS, Yin DD, Thomas M. Effect of a concomitant diagnosis of allergic rhinitis on asthma-related health care use by adults. *Clin Exp Allergy*. 2005;35:282-287.
118. 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.
119. Crystal-Peters J, Neslusan C, Crown WH, Torres A. Treating allergic rhinitis in patients with comorbid asthma: the risk of asthma-related hospitalizations and emergency department visits. *J Allergy Clin Immunol*. 2002;109:57-62.
120. 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.
121. Henriksen JM, Wenzel A. Effect of an intranasally administered corticosteroid (budesonide) on nasal obstruction, mouth breathing, and asthma. *Am Rev Respir Dis*. 1984;130:1014-1018.
122. Watson WT, Becker AB, Simons FE. Treatment of allergic rhinitis with intranasal corticosteroids in patients with mild asthma: effect on lower airway responsiveness. *J Allergy Clin Immunol*. 1993;91:97-101.
123. Foresi A, Pelucchi A, Gherson G, Mastropasqua B, Chiapparino A, Testi R. Once daily intranasal fluticasone propionate (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.
124. 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.
125. Dahl R, Nielsen LP, Kips J, *et al*. Intranasal and inhaled fluticasone propionate for pollen-induced rhinitis and asthma. *Allergy.* 2005;60:875-881.

126. Taramarcaz P, Gibson PG. Intranasal corticosteroids for asthma control in people with coexisting asthma and rhinitis. *Cochrane Database Syst Rev*. 2003(4):CD003570.
127. Grant JA, Nicodemus CF, Findlay SR, *et al*. Cetirizine in patients with seasonal rhinitis and concomitant asthma: prospective, randomized, placebo-controlled trial. *J Allergy Clin Immunol*. 1995;95:923-932.
128. Baena-Cagnani CE, Berger WE, DuBuske LM, *et al*. Comparative effects of desloratadine versus montelukast on asthma symptoms and use of beta 2-agonists in patients with seasonal allergic rhinitis and asthma. *Int Arch Allergy Immunol*. 2003;130:307-313.
129. Lee DK, Jackson CM, Haggart K, Lipworth BJ. Repeated dosing effects of mediator antagonists in inhaled corticosteroid-treated atopic asthmatic patients. *Chest*. 2004;125:1372-1377.
130. Dizdar EA, Sekerel BE, Keskin O, *et al*. The effect of regular versus on-demand desloratadine treatment in children with allergic rhinitis. *Int J Pediatr Otorhinolaryngol.* 2007;71: 843-849.
131. Arshad SH, Tariq SM, Matthews S, Hakim E. Sensitization to common allergens and its association with allergic disorders at age 4 years: a whole population birth cohort study. *Pediatrics*. 2001;108:E33.
132. Bousquet J, Neukirch F, Bousquet PJ, *et al*. Severity and impairment of allergic rhinitis in patients consulting in primary care. *J Allergy Clin Immunol*. 2006;117: 158-162.
133. Valovirta E, Myrseth SE, Palkonen S. The voice of the patients: allergic rhinitis is not a trivial disease. *Curr Opin Allergy Clin Immunol*. 2008;8:1-9.
134. Canonica GW, Bousquet J, Mullol J, Scadding GK, Virchow JC. A survey of the burden of allergic rhinitis in Europe. *Allergy*. 2007;62 Suppl 85:17-25.
135. Schatz M. A survey of the burden of allergic rhinitis in the USA. *Allergy*. 2007;62 Suppl 85:9-16.
136. Simoens S, Laekeman G. Pharmacotherapy of allergic rhinitis: a pharmaco-economic approach. *Allergy*. 2009;64:85-95.
137. Schramm B, Ehlken B, Smala A, Quednau K, Berger K, Nowak D. Cost of illness of atopic asthma and seasonal allergic rhinitis in Germany: 1-yr retrospective study. *Eur Respir J*. 2003;21:116-122.
138. Bachert C, Bousquet J, Canonica GW, *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.
139. Bousquet J, Van CP, Bachert C, *et al*. Requirements for medications commonly used in the treatment of allergic rhinitis. European Academy of Allergy and Clinical Immunology (EAACI), Allergic Rhinitis and its Impact on Asthma (ARIA). *Allergy*. 2003;58:192-197.
140. Bousquet J, Khaltaev N, Cruz AA, *et al*. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy*. 2008;63 Suppl 86:8-160.
141. Bousquet J, Demoly P. Le traitement de la rhinite allergique persistante doit-il être poursuivi au long cours? *Revue Officielle de la Société Française d'ORL*. 2002;74:1-5.
142. Ciprandi G, Passalacqua G, Mincarini M, Ricca V, Canonica GW. Continuous versus on demand treatment with cetirizine for allergic rhinitis. *Ann Allergy Asthma Immunol.* 1997;79:507-511.
143. Canonica GW, Fumagalli F, Guerra L, *et al*. Levocetirizine in persistent allergic rhinitis: continuous or on-demand use? A pilot study. *Curr Med Res Opin*. 2008;24:2829-2839.
144. Ciprandi G, Tosca M, Passalacqua G, Canonica GW. Long-term cetirizine treatment reduces allergic symptoms and drug prescriptions in children with mite allergy. *Ann Allergy Asthma Immunol*. 2001;87:222-226.
145. Leurs R, Church MK, Taglialatela M. H1-antihistamines: inverse agonism, anti-inflammatory actions and cardiac effects. *Clin Exp Allergy*. 2002;32:489-498.
146. Berkowitz RB, Bernstein DI, Laforce C, *et al*. Onset of action of mometasone furoate nasal spray (NASONEX) in seasonal allergic rhinitis. *Allergy*. 1999;54:64-69.
147. Gawchik S, Goldstein S, Prenner B, John A. Relief of cough and nasal symptoms associated with allergic rhinitis by mometasone furoate nasal spray. *Ann Allergy Asthma Immunol*. 2003;90:416-421.
148. Frieri M, Therattil J, Chavarria V, *et al.* Effect of mometasone furoate on early and late phase inflammation in patients with seasonal allergic rhinitis. *Ann Allergy Asthma Immunol.* 1998;81:431-437.
149. Meltzer EO, Jalowayski AA, Orgel HA, Harris AG. Subjective and objective assessments in patients with seasonal allergic rhinitis: effects of therapy with mometasone furoate nasal spray. *J Allergy Clin Immunol*. 1998;102:39-49.
150. Minshall E, Ghaffar O, Cameron L, *et al*. Assessment by nasal biopsy of long-term use of mometasone furoate aqueous nasal spray (Nasonex) in the treatment of perennial rhinitis. *Otolaryngol Head Neck Surg*. 1998;118:648-654.
151. Pitsios C, Papadopoulos D, Kompoti E, *et al*. Efficacy and safety of mometasone furoate vs nedocromil sodium as prophylactic treatment for moderate/severe seasonal allergic rhinitis. *Ann Allergy Asthma Immunol*. 2006;96:673-678.
152. Kulshrestha VK, Gupta PP, Turner P, Wadsworth J. Some clinical pharmacological studies with terfenadine, a new antihistamine drug. *Br J Clin Pharmacol.* 1978;6:25-29.
153. Walsh GM, Annunziato L, Frossard N, *et al*. New insights into the second generation antihistamines. *Drugs*. 2001;61:207-236.
154. Kakumanu S, Glass C, Craig T. Poor sleep and daytime somnolence in allergic rhinitis: significance of nasal congestion. *Am J Respir Med*. 2002;1:195-200.
155. Baiardini I, Giardini A, Pasquali M, *et al*. Quality of life and patients' satisfaction in chronic urticaria and respiratory allergy. *Allergy*. 2003;58:621-623.
156. Baiardini I, Pasquali M, Giardini A, *et al*. Rhinasthma: a new specific QoL questionnaire for patients with rhinitis and asthma. *Allergy*. 2003;58:289-294.

157. Nelson HS, Reynolds R, Mason J. Fexofenadine HCl is safe and effective for treatment of chronic idiopathic urticaria. *Ann Allergy Asthma Immunol*. 2000;84:517-522.
158. Richardson GS, Roehrs TA, Rosenthal L, Koshorek G, Roth T. Tolerance to daytime sedative effects of H1 antihistamines. *J Clin Psychopharmacol*. 2002;22:511-515.
159. Verster JC, Volkerts ER. Antihistamines and driving ability: evidence from on-the-road driving studies during normal traffic. *Ann Allergy Asthma Immunol*. 2004;92:294-303.
160. Garcia-Gea C, Martinez-Colomer J, Antonijoan RM, Valiente R, Barbanoj MJ. Comparison of peripheral and central effects of single and repeated oral dose administrations of bilastine, a new H1 antihistamine: a dose-range study in healthy volunteers with hydroxyzine and placebo as control treatments. *J Clin Psychopharmacol.* 2008;28:675-685.
161. Lauriello M, Muzi P, Di Rienzo L, Di Stanislao C, Tirelli GC, Bologna M. A two-year course of specific immunotherapy or of continuous antihistamine treatment reverse eosinophilic inflammation in severe persistent allergic rhinitis. *Acta Otorhinolaryngol Ital.* 2005;25:284-291.
162. Giovannini M, Braccioni F, Sella G, *et al*. Comparison of allergen immunotherapy and drug treatment in seasonal rhinoconjunctivitis: a 3-years study. *Eur Ann Allergy Clin Immunol*. 2005;37:69-71.
163. Simons FE. Prospective, long-term safety evaluation of the H1-receptor antagonist cetirizine in very young children with atopic dermatitis. ETAC Study Group. Early Treatment of the Atopic Child. *J Allergy Clin Immunol*. 1999;104:433-440.
164. Simons FE. Safety of levocetirizine treatment in young atopic children: An 18-month study. *Pediatr Allergy Immunol*. 2007;18:535-542.
165. Stevenson J, Cornah D, Evrard P, *et al*. Long-term evaluation of the impact of the h1-receptor antagonist cetirizine on the behavioral, cognitive, and psychomotor development of very young children with atopic dermatitis. *Pediatr Res.* 2002;52: 251-257.
166. Weiner JM, Abramson MJ, Puy RM. Intranasal corticosteroids versus oral H1 receptor antagonists in allergic rhinitis: systematic review of randomised controlled trials. *BMJ*. 1998;317:1624-1629.
167. Patel RS, Shaw SR, Wallace AM, McGarry GW. Efficacy and systemic tolerability of mometasone furoate and betamethasone sodium phosphate. *J Laryngol Otol.* 2004;118:866-871.
168. Schenkel EJ, Skoner DP, Bronsky EA, *et al*. Absence of growth retardation in children with perennial allergic rhinitis after one year of treatment with mometasone furoate aqueous nasal spray. *Pediatrics.* 2000;105:E22.

J. B. Watelet, M.D., Ph.D.
Department of Otorhinolaryngology
Ghent University Hospital
De Pintelaan, 185
B-9000 Gent, Belgium
E-mail: jeanbaptiste.watelet@ugent.be