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REVIEW

Positioning of antihistamines in the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines

Joaquim Mullol[1,2,3]

[1]*Clinical and Experimental Respiratory Immunoallergy, IDIBAPS,* [2]*ENT Department, Rhinology Unit and Smell Clinic, Hospital Clínic, Barcelona, Catalonia, Spain and* [3]*CIBER de Enfermedades Respiratorias (CIBERES)*

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Correspondence:
Joaquim Mullol, ENT Department, Rhinology Unit and Smell Clinic, Hospital Clínic Villarroel 170, 08036 Barcelona, Catalonia, Spain.
E-mail: jmullol@clinic.ub.es

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Summary

Allergic rhinitis (AR) is a major health problem with high and ever-increasing prevalence worldwide. At least one-fifth of adults in industrialized countries are estimated to have AR, defined as nasal and eye symptoms that are sufficiently severe to have a substantial negative impact on the quality of life (QoL). The former classification of AR comprised seasonal AR (SAR) and perennial AR (PAR), which did not adequately reflect the presentation and clinical course of the disease. The Allergic Rhinitis and its Impact on Asthma (ARIA) classification is based on the duration of symptoms and the disease severity. Both intermittent AR (IAR: symptoms $\leq$ 4 days/week or $\leq$ 4 consecutive weeks) and persistent AR (PER: symptoms > 4 days/week and > 4 consecutive weeks) may be mild, moderate, or severe based on the QOL impairment (sleep, daily activities/leisure, work productivity/school performance) and bothersome symptoms. Despite its disabling effects, AR remains a condition where affected individuals do not seek appropriate treatment, are undertreated and do not adhere well to treatment, which all lead to low disease control and high societal costs. The four pillars of AR treatment are allergen and pollutant avoidance, patient education, pharmacotherapy and allergen-specific immunotherapy. Oral antihistamines, together with intranasal corticosteroids and leucotriene antagonists, constitute important pharmacological options for the treatment of AR at all levels of severity. New second-generation antihistamines are H_1-receptor antagonists with high efficacy (rapid onset of action for AR symptoms, sometimes even on nasal congestion, improvement of QoL and additional anti-allergic effects) and safety (low sedation rates). Although new antihistamines have been studied and approved for SAR and PAR, only some of them have been reported to show efficacy and safety for treatment of AR under the ARIA classification: levocetirizine (high efficacy) and rupatadine (dual antihistamine and anti-PAF effects) for PER, and desloratadine (high safety) for both IAR and PER.

Keywords allergic rhinitis, ARIA, desloratadine, H_1-antihistamines, intermittent allergic rhinitis, levocetirizine, persistent allergic rhinitis, rupatadine

Ten years of the allergic rhinitis and its impact on asthma guidelines

Allergic rhinitis (AR) is an inflammatory disease of the nasal mucosa caused by an immunological mechanism mediated by immunoglobulin E. AR is a global health problem that affects patients of all ages and ethnic groups, causes major illness and disability worldwide, and affects their social life, sleep, school and work [1–3], and its economic impact is substantial. However, rhinitis is still underdiagnosed and undertreated [4, 5]. The former classification of AR comprised seasonal AR (SAR), mainly linked to pollen allergy, and perennial AR (PAR), mainly linked to house-dust mites. Over the years, many shortcomings of this classification have become apparent. For example, many AR patients are polysensitized to pollen and perennial allergens [4] and their symptoms are not restricted to a single season [6], meaning that they cannot be classified as having SAR or PAR. In addition, only certain countries have seasonal pollen, while others have pollen for many months or even perennially. Finally, the SAR/PAR classification does not cover the duration or severity of the disease, which makes it difficult to decide upon the best treatment option.

The Allergic Rhinitis and its Impact on Asthma (ARIA) classification system was introduced in 2001, ten years ago, and is based on the duration and severity of the symptoms and their impact on QoL [7]. The duration of AR is split into intermittent and persistent patterns. Intermittent AR (IAR) is defined by symptoms that occur for up to 4 days per week or up to 4 consecutive weeks, whereas persistent AR (PER) lasts more than 4 days per week and more than 4 consecutive weeks. The severity of AR was originally classified as mild or moderate-to-severe, based on the impact on QoL and symptom severity (sleep; leisure, sport and daily activities; school performance or work productivity; and bothersome symptoms) [8]. Although mild AR has no impact on QoL, moderate-to-severe AR is characterized by impairment of at least one of these items. Compared with patients with IAR, patients with PER have more severe symptoms, have higher rates of self-awareness and a previous diagnosis of AR, differ in their use of medication and have a clearly distinct allergen sensitization pattern [9].

Different modification approaches to the ARIA severity classification have been proposed, by either removing the item of "troublesome symptoms" and recombining the other three items into two items (sleep disturbance and impairment of daily personal and/or professional life) [10, 11] or splitting the severity into mild or severe based on the score of a symptom severity visual analogue scale [12]. More recently, a new set of criteria for discriminating between moderate and severe AR based on the number of affected items (mild, no items; moderate, 1 to 3 items; severe, 4 items) have been proposed, following the ARIA severity classification for treated or untreated AR patients [13, 14]. However, analysis of both control and clearly defined severity phenotypes may help towards the development of new epidemiological, clinical and pharmacoeconomic studies under the umbrella of the new concept of SCUAD (Severe Chronic Upper Airway Disease) [15, 16].

The ARIA classification system is distinct from the classical classification system. Patients classified as having SAR do not necessarily have IAR, while patients classified as having PAR do not always have PER. In previous studies, nearly one-half of SAR patients had PER and nearly one-half of PAR patients only had IAR [9, 17], although the approaches may have been influenced by the strength of the seasonality in different countries [6]. Using the ARIA criteria, studies are now identifying AR in many countries, in both adult [18–21] and child [22] populations.

Another feature of the ARIA classification system is that it acknowledges the relationship of AR with asthma, as well as other comorbidities such as rhinosinusitis and conjunctivitis. Furthermore, 20–40% of patients with rhinitis have asthma and 70–90% of asthmatic patients have rhinitis, regardless of the diagnostic setting [23–25], thus leading to the concept of "one airway, one disease". Consequently, patients with rhinitis should be investigated for asthma and patients with asthma should be investigated for rhinitis, while a combined treatment strategy for the upper and lower airways should be developed for optimal management of the disease [26, 27]. In Spain, the GEMA guidelines, based on the GINA and ARIA consensus, have been developed for both AR and asthma [28].

The diagnosis of AR is based on symptoms, physical examination and blood or skin prick tests. The major symptoms are rhinorrhoea, sneezing, nasal itching, nasal congestion and eye symptoms. A recent study showed that a moderate loss of smell is also present and linked to the disease severity in PER patients [29]. Exacerbations of AR should be distinguished from the common cold, while chronic disease should be distinguished from non-allergic rhinitis and chronic rhinosinusitis with or without nasal polyps [30, 31]. AR should also be differentiated from other entities, such as NARES, local AR [32], gustatory rhinitis, rhinitis medicamentosa and hormonal and toxic rhinitis, as well as structural deformities, such as septal deviation and turbinate hypertrophy. In addition, patients usually present with nasal hyperreactivity to non-specific irritants and pollutants.

An update of the ARIA classification system was initiated in 2004 and published in 2008 [33–35]. Several chapters were extensively reviewed using the Shekelle evidence-based model and papers published in peer-reviewed journals [36, 37]. These papers cover the areas of tertiary prevention of allergy, complementary and alternative medicine, pharmacotherapy and anti-IgE treatment, allergen-specific immunotherapy, links between rhinitis and asthma, and the mechanisms of rhinitis. The need arose for a global document to highlight the interactions between the upper and lower airways, including diagnosis, epidemiology, common risk factors, management and prevention. Moreover, attention was also given to allergy in developing countries.

A large number of treatments were considered in the ARIA 2008 update [33, 38]. Intranasal corticosteroids are the first-line therapy in patients with moderate-to-severe disease and are also effective against ocular symptoms. Second-generation H_1-antihistamines are important treatments for all patients, and leucotriene receptor antagonists are particularly important for patients with rhinitis and asthma. Tertiary prevention of allergy is still a matter of debate, as clinical trials do not usually show any efficacy of single allergen avoidance measures. Sublingual immunotherapy has been proven to be safe and effective, but clinical trials need to be standardized [39, 40]. An algorithm for the management of AR is provided (Fig. 1). If an appropriate

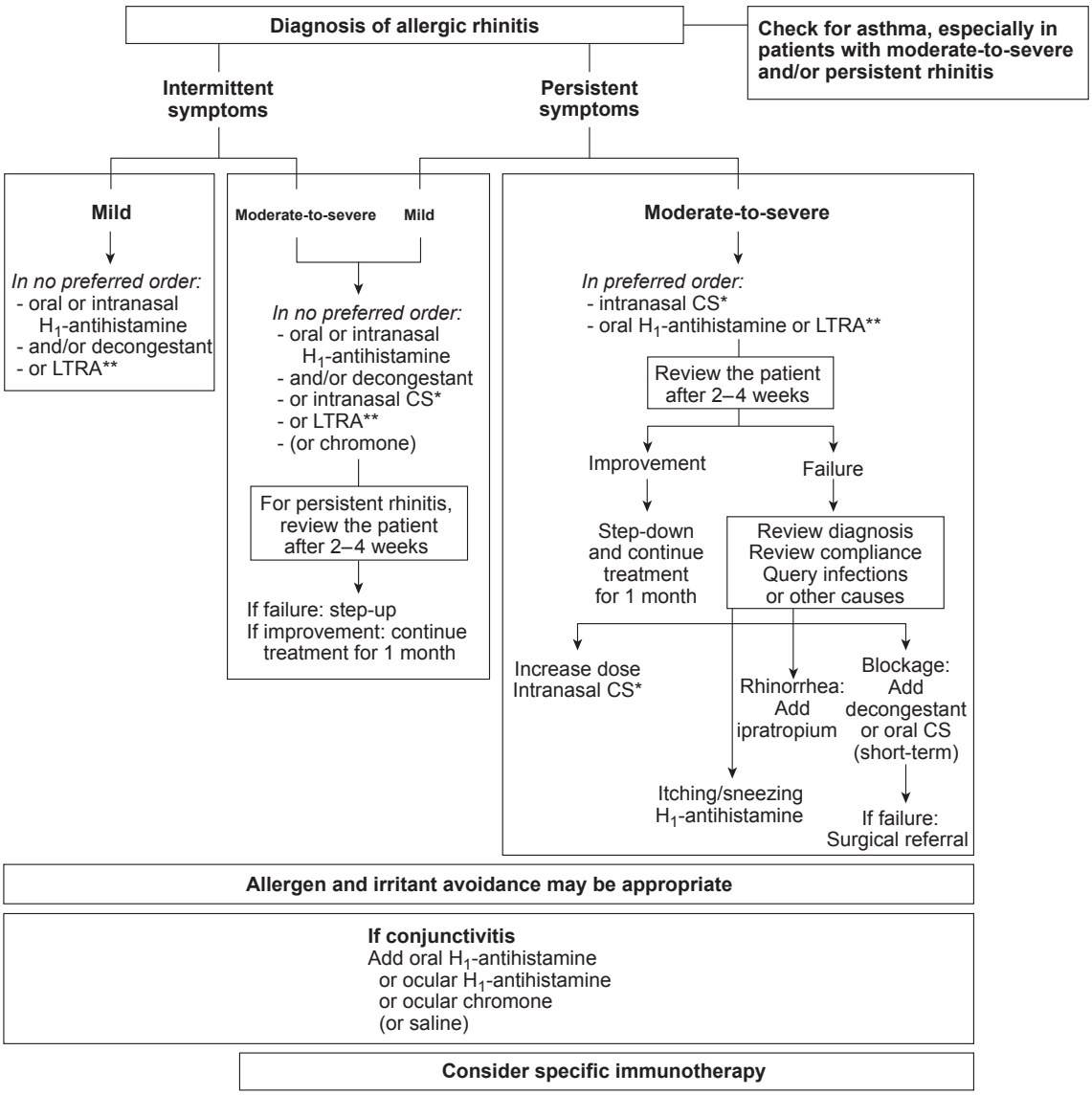

Fig. 1. Stepwise management (diagnosis and treatment) approach for allergic rhinitis depending on its duration and severity following the ARIA classification. Adapted from *Allergy* 2008; **63(Suppl. 86)**:8–160 and *Allergy* 2008; **63**:990–6 with permission. *CS: corticosteroid. Total dose of corticosteroids should be considered if inhaled steroids are used for concomitant asthma. **LTRA: Leucotriene receptor antagonist. For patients with asthma, in particular.

response to treatment is not achieved, other drugs may be considered, such as ipratropium bromide, nasal decongestants, or even a short course of oral steroids. In cases with a poor response, the diagnosis should be re-evaluated owing to the potential associations with concomitant diseases or abnormalities (acute or chronic rhinosinusitis, nasal polyposis, septal deviation, turbinate hypertrophy, or foreign body), with the potential indications for a surgical procedure.

However, a combined strategy should be the major objective when treating rhinitis and asthma, as an appropriate treatment for rhinitis may improve the symptoms and reduce the need for drugs, as well as improving the evolution of asthma, and conversely, the correct treatment of asthma may improve rhinitis [33, 34].

The grading of evidence and the recommendation for an evidence-based management system in the ARIA 2008 update did not follow the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach. However, a recent update on the ARIA clinical recommendations in collaboration with the Global Allergy and Asthma European Network (GA^2LEN) [41], which followed the transparent and systematic approach suggested by the GRADE working group, has recently been published [42].

H_1-antihistamines in the allergic rhinitis and its impact on asthma guidelines

H_1-antihistamines are medications that block histamine at the H_1-receptor level, and comprise neutral antagonists or inverse agonists [43]. Most H_1-antihistamines also have additional anti-allergic properties [44]. Over the past 25 years, pharmacological research has produced compounds with minimal sedative and cognitive impairment effects, representing second-generation H_1-antihistamines as opposed to first-generation H_1-antihistamines [45]. The term "third-generation" should be reserved for H_1-antihistamines with novel properties [46], and no drugs have exhibited such properties to date.

Although they have potentially dangerous side-effects that are not recognized by the general public, over-the-counter first-generation H_1-antihistamines are the most frequent form of self-medication for allergic diseases, coughs and colds, and insomnia. The GA^{2}LEN task force has recently warned of the side-effects and potential dangers of this kind of drug [45]. The task force recommends that older first-generation H_1-antihistamines should no longer be available as over-the-counter and prescription-free drugs for self-medication of allergic and other diseases, given that newer second-generation non-sedating H_1-antihistamines are widely available at competitive prices and with superior risk/benefit ratios. First-generation H_1-antihistamines, all of which have sedative effects and some of which exhibit cardiotoxicity in overdose, are generally regarded as safe by the general public and healthcare professionals because of their long-standing use. They reduce rapid eye movement in sleep, impair learning and reduce work efficiency; they have been implicated in suicide in teenagers and adults, as well as in civil aviation, motor vehicle and boating accidents, and in deaths resulting from accidental or intentional overdosing in infants and young children.

Second-generation oral H_1-antihistamines are effective against symptoms mediated by histamine (rhinorrhoea, sneezing, nasal itching and eye symptoms), but are less effective on nasal congestion [46–47], and improve the QoL of patients with IAR [48] or PER [49–52]. Oral H_1-antihistamines have been shown to be safe and effective in children. Although some anti-allergic effects have been described, their exact clinical relevance is still unclear. Long-term treatment (years) with oral H_1-antihistamines is safe. Second-generation oral H_1-antihistamines induce no or little sedation or impairment and are not anti-cholinergic. Some, but not all, oral H_1-antihistamines undergo hepatic metabolism via the cytochrome P450 system and are prone to drug interactions. Although cardiotoxicity is not a class effect, major concerns have existed about the arrhythmogenic actions of terfenadine, astemizole and high doses of diphenhydramine, which have rarely been associated with deaths [33, 53]. According to the ARIA guidelines, several properties should be met by oral H_1-antihistamines (Table 1) [33, 44]. H_1-antihistamines are recommended by the ARIA guidelines for all levels of disease severity and for both IAR and PER.

Intranasal H_1-antihistamines are well tolerated and can be effective within 20 minutes at the site of their administration in reducing itching, sneezing, runny nose and nasal congestion, but require twice-daily dosing. When given ocularly, but not intranasally, they are effective in reducing allergic eye symptoms. High doses of azelastine may be more effective than oral H_1-antihistamines, but occasionally have some side-effects, such as mild somnolence or bad taste. To date, no topical H_1-antihistamines, either intranasal or ocular, have been studied for AR following the ARIA classification.

Although oral H_1-antihistamines are not recommended for the treatment of asthma, they may improve concomitant asthma when used for rhinitis [27, 44].

Levocetirizine under the allergic rhinitis and its impact on asthma guidelines – the XPERT Study

Following the ARIA recommendation that the efficacy of H_1-antihistamines should be investigated in patients classified according to the ARIA classification system, levocetirizine was the first H_1-antihistamine to be proven for its efficacy and safety in the treatment of PER patients because of its overall favourable pharmacokinetic and pharmacodynamic profiles [53, 54]. In addition, continuous treatment with levocetirizine appears to be more effective than on-demand treatment, a property that is likely to benefit today's patients with more persistent and severe symptoms [55].

A pilot study in 40 patients with PER showed that levocetirizine 5 mg/day for 4 weeks improved their nasal symptoms, including nasal obstruction, and increased the total nasal airflow [56]. The XPERT (Xyzal in PErsistent Rhinitis Trial) study was a 6-month, double-blind, placebo-controlled, multicentre, multinational (Germany, France, Italy, Belgium and Spain) trial performed in 551 patients with PER. Adults with PER, who were sensitized to both grass pollen and house-dust mites, were randomized to receive levocetirizine 5 mg or placebo once daily for 6 months. A total of 421 patients completed the full study. The study assessed the symptoms (both individual and total scores), QoL (both general and disease-specific), comorbidities, pharmacoeconomics and safety. The results of the study were published in four consecutive articles [49, 50, 57, 58].

In the first article, Bachert et al. [48] analysed, as the two primary objectives, a comparison between levocetirizine 5 mg and placebo on the RQLQ overall score

Table 1. Properties to be met by oral H_1-antihistamines under the ARIA guidelines. Adapted from *Allergy* 2008; **63(Suppl. 86)**:8–160 and *Allergy* 2008; **63**:990–6 with permission.

1. Pharmacologic properties
   - Potent and selective H_1-receptor blockage
   - Additive anti-allergic / anti-inflammatory activities
   - No clinically relevant pharmacokinetic interference by food, medications or intestinal transport proteins
   - No known interaction with cytochrome P4503A (CYP3A)
   - No known interactions with the disease to avoid toxic reactions
2. Efficacy
   - Effective in the treatment of intermittent and persistent allergic rhinitis as defined by the ARIA guidelines
   - Effective for all nasal symptoms including nasal obstruction
   - Improvement of eye symptoms
   - If a claim for asthma is made:
     - Improvement of asthma symptoms (short-term studies)
     - Reduction of asthma exacerbation (long-term studies)
     - Improvement of pulmonary function tests, even though FEV_1 and peak-flow rates are not usually altered in pollen-induced bronchial symptoms
   - If a claim of a preventive effect is proposed, appropriate trials should be conducted
   - Studies should be carried out on young children and elderly patients to assess efficacy
3. Side effects
   - No sedation and no cognitive or psychomotor impairment
   - No anticholinergic effects
   - No weight gain effects
   - No cardiac side effects
   - Possible use in pregnancy and breast feeding
   - Studies should be carried out on young children and elderly patients to assess safety
   - Prospective post-marketing safety analyses should be conducted
4. Pharmacodynamics
   - Rapid onset of action
   - Long duration of action, comprising persistence of the clinical effects until at least the end of a 24-hour dosing period, so that the drug can be administered once daily
   - No likelihood of development of tolerance (tachyphylaxis).

and T5SS (rhinorrhoea, sneezing, nasal congestion, and nasal and ocular pruritus) over a period of 4 weeks. The secondary endpoints included similar evaluations at 1 week and 3, 4.5 and 6 months, summary scores for a general health status questionnaire (SF-36), a pharmacoeconomic assessment, comorbidities and a safety evaluation. Levocetirizine significantly improved both the RQLQ overall score and the T5SS from 1 week to 6 months ($P < 0.001$), and the SF-36 summary scores were also improved in the levocetirizine group ($P < 0.01$) compared with the placebo group. Treatment cessation because of lack of effect, comorbidities, and overall costs of disease and comorbidities per working patient and month were lower in the levocetirizine group (108.2, $P < 0.01$) than in the placebo group (160.3). Although adverse events were similar in the two groups, levocetirizine caused more somnolence (6.8%) than the placebo (1.8%) over the 6-month treatment period.

In the second paper, Bousquet et al. [58] assessed the total costs of PER, as well as the effects of long-term treatment with levocetirizine on these costs from several perspectives (societal, social security system and employers). Direct medical cost parameters (medications, physician visits and hospitalizations) and time loss parameters [loss of workdays and Usual Daily Activities (UDA)] related to PER and its comorbidities (asthma, rhinosinusitis, otitis and upper respiratory infection) were evaluated. The cost analysis was performed using French costing data (2002). From a societal perspective, the total cost of PER without long-term treatment was estimated to be 355 Euro per patient and month. Although active treatment caused an additional cost of 2.80 Euro per patient and month compared with no treatment, levocetirizine reduced the total cost of PER and its comorbidities by 152.90 Euro per patient and month from a societal perspective and by 64.70 Euro per patient and month from an employer perspective. Most of these gains resulted from decreases in lost workdays (0.88 vs. 1.49 days/patient/month) and UDA (1.51 vs. 2.90 days/patient/month) in the levocetirizine group compared with the placebo group.

In the third paper, Canonica et al. [49] determined whether long-term treatment with levocetirizine 5 mg was able to improve the HRQoL (RQLQ) and health status (SF-36) in PER patients over a 6-month period. The sensitivities of the RQLQ and SF-36 for disease severity were tested to ensure their suitability for use in PER patients. Treatment effects were assessed by means of repeated-measures analyses. After 6 months of treatment, levocetirizine showed significant improvements over the placebo in the HRQoL for all the RQLQ domains and overall scores ($P < 0.001$) and the health status for the SF-36 physical and mental summary scores ($P < 0.01$). The relative improvement in the levocetirizine group over the placebo group exceeded the pre-defined clinically meaningful threshold of 30% for all the RQLQ scores and the improvement from baseline was three times higher than the established minimal important difference for the RQLQ.

In the fourth and last paper, Klimek et al. [50] determined the effects of long-term treatment with levocetirizine on the five most affected daily activities and all sleep parameters of the QOL (RQLQ) in PER patients. Levocetirizine 5 mg provided significant ($P < 0.5$ to $P < 0.001$) and clinically relevant improvements in the baseline RQLQ scores for the five activities most important to patients (doing housework, playing sport, driving, outdoor activities and activities at work) and three sleep items (difficulty getting to sleep, waking during the night and lack of a good night's sleep) compared

with the placebo after 6 months of treatment. All of the improvements were pronounced and significantly greater for levocetirizine at each time point (1 and 4 weeks, and 3, 4.5 and 6 months) throughout the treatment period.

In an independent phase IV, randomized, open-label, parallel-group, single-centre, pilot study, Canonica et al. [55] determined whether levocetirizine 5 mg administered continuously once daily in the morning was better than levocetirizine 5 mg on-demand in symptomatic subjects with PER ($N = 62$) over a period of 6 months (24 weeks). Symptoms (individual and T4SS) were recorded in a diary card throughout the study. The QoL (Rhinasthma), quality of sleep, nasal cytology, rate of drug intake and safety were also assessed at pre-defined time points. Only adult patients ($\geq$18 years, 31 in each group) were enrolled, of whom 13 (41.9%) for the on-demand regimen and 9 (29%) for the continuous regimen dropped out. Both treatment regimens decreased the total and individual symptom scores from the baseline and achieved similar levels up to week 14. For the T4SS, continuous treatment was generally better than on-demand treatment from week 15 onward, reaching statistical significance from weeks 17 to 23 ($P < 0.05$). Both regimens substantially ($P < 0.05$) improved the QoL and sleep quality. No significant changes in the nasal inflammatory cells (eosinophils, neutrophils, macrophages, lymphocytes and epithelial cells) and ICAM-1 were observed for both treatment regimens. Both treatments were well tolerated, although the on-demand group reported more adverse events (somnolence: 9.7% vs. 3.2%).

In the CIRANO study, a recent, randomized, double-blind, placebo-controlled, single-centre, pilot study by Guilemany et al. [Guilemany JM, A Garcia-Piñero, I Alobid, S Centellas, C Picado, A Valero, J Mullol. Levocetirizine improves the loss of the sense of smell in persistent allergic rhinitis. Int Arch Allergol Immunol (In press)] investigated the effects of levocetirizine 5 mg once daily in patients with PER and subjective loss of smell ($N = 27$). The sense of smell by the VAS and other nasal symptoms (individual and T4SS), acoustic rhinometry, nasal peak-flow by the PNIF, nasal nitric oxide and subjective olfactometry by the BAST-24 were evaluated in all PER patients at baseline and after 1 and 4 weeks of treatment. In addition to the significant effects on nasal symptoms at 1 and 4 weeks (no nasal congestion), levocetirizine 5 mg significantly improved the loss of smell by the VAS at 1 week compared with the placebo ($P < 0.05$), which was strongly correlated ($r = 0.72$; $P < 0.05$) with smell identification measured by the BAST-24. After 1 week, levocetirizine also reduced the level of nasal nitric oxide ($P < 0.05$) compared with the placebo. The CIRANO study concluded that, in addition to its effects on nasal symptoms and QoL, levocetirizine improves the loss of smell in PER patients, with this olfactory improvement being more closely related to the decrease in nasal inflammation than to nasal patency.

Rupatadine under the allergic rhinitis and its impact on asthma guidelines – the ESPRINT program

Although histamine is the primary mediator involved in the pathophysiology of AR, it is clearly not the only mediator involved in the inflammatory cascade. Rupatadine is a once-daily, non-sedative, selective, long-acting H_1-antihistamine with antagonistic PAF effects through its interactions with specific receptors. Rupatadine significantly improves nasal symptoms in patients with AR, has a good safety profile and is devoid of arrhythmogenic effects. All these factors make rupatadine a suitable first-line H_1-antihistamine for the treatment of AR [59]. In clinical trials, rupatadine has been proven to be an effective and well-tolerated treatment for AR in both SAR and PAR patients [60], and two recent consecutive studies have shown its clinical efficacy [51] and safety [61] in the treatment of PER patients. In addition, the ESPRINT (*cuestionario ESPañol de calidad de vida en RINiTis alérgica*) program has developed both long [62] and short [63, 64] versions of the ESPRINT QoL questionnaire validated for the Spanish population.

In a randomized, double-blind, multicentre, parallel-group, placebo-controlled study, Fantin et al. [51] investigated the efficacy of rupatadine in controlling symptoms over a 12-week period in adolescent ($\geq$12 years) and adult patients with PER. Patients with an instantaneous total symptom score (i6TSS) of $\geq$ 45, a nasal obstruction score of $\leq$ 12 and an overall assessment of PER of $\geq$ 2 (moderate) during the first visit were included in the study. The primary efficacy endpoint was the 12-week i6TSS change from the baseline. Among all the selected patients ($N = 736$), 73.8% ($N = 543$) were randomized into three treatment groups: placebo, cetirizine 10 mg/day and rupatadine 10 mg/day. The onset of action was significant ($P < 0.05$) after the first 24 hours for both treatments compared with the placebo. After 12 weeks of treatment, rupatadine (47.8%, $P < 0.01$), but not cetirizine (44.7%, $P = 0.07$), significantly reduced the i6TSS from baseline compared with the placebo (38.8%) and improved the patients' QoL (RQLQ). Although the incidence of adverse effects was similar in all three groups, somnolence was more frequent for rupatadine (10%) and cetirizine (8%) than for the placebo (4.3%).

As a continuation of the previous study, Valero et al. [61] assessed the safety and tolerability of rupatadine 10 mg/day for 12 months in adolescent and adult patients with PER in a multicentre, open-label, phase IV

study. Of the 324 eligible patients starting treatment, 37% needed to be treated for more than 6 months and were followed up for 12 months. All the patients received rupatadine 10 mg/day and were allowed to continue their normal concomitant medications for all conditions, other than rhinitis, for up to 6 or 12 months. Safety was assessed by adverse events reported by the patients or investigators, ECG with special attention to the Bazzet-corrected QT interval and standard laboratory investigations. The treatment compliance rates were 90% of the patients (1–6 months) and 83% of the patients (1–12 months). Overall, 74.1% (1–6 months) and 65.8% (1–12 months) of the patients reported at least one adverse event during treatment. In particular, somnolence was the most common adverse event reported at 1–6 months (7.7%) and 1–12 months (5.8%) by the patients. No clinically relevant abnormal ECG findings or any QT interval increases of > 60 milliseconds or values of > 470 milliseconds were found in any of the patients during the treatment period. Serious adverse events were reported in seven patients, of which only one involving increased blood enzyme levels was considered to be possibly related to the rupatadine treatment.

Desloratadine under the allergic rhinitis and its impact on asthma guidelines – the ACCEPT/GA^{2}LEN program

Desloratadine was one the first H_1-antihistamines to follow the rules for efficacy, safety and pharmacology in the new ARIA guidelines [65], and was approved by the European Medicines Evaluation Agency (EMEA) for the treatment of IAR and PER [66]. More recently, the ACCEPT (Aerius Control Clinical and Evaluative Profile of Treatment) programme has provided an opportunity to collaborate with the GA^{2}LEN, a consortium of leading European research centres specializing in allergic diseases. Two studies were developed, one for IAR (ACCEPT-1) [48] and the other for PER (ACCEPT-2) [52], to assess the efficacy and safety of desloratadine for AR using the ARIA classification. According to the ARIA guidelines, second-generation H_1-antihistamines are a cornerstone of pharmacological therapy for AR, and desloratadine has been proven to be effective for the treatment of AR across all classifications of the disease, either SAR/PAR or IAR/PER.

Bousquet et al. [48] reported the first large trial (ACCEPT-1) to show that desloratadine was effective and safe for IAR. In this placebo-controlled, multicentre, multinational (14 European countries and Canada), randomized clinical trial, the objectives were to assess the efficacy and safety of desloratadine 5 mg ($N = 276$) or placebo ($N = 271$) in adolescent ($\geq$12 years) and adult patients with IAR treated once daily over 15 days. The primary endpoint was the AM/PM reflective Total 5 Symptom Score (rT5SS), while the secondary endpoints included the AM/PM instantaneous Total 5 Symptom Score (iT5SS) and individual symptoms, therapeutic response, symptom severity by a visual analogue scale and QoL. After 15 days, desloratadine caused greater improvements in the AM/PM rT5SS and AM iT5SS than the placebo ($P < 0.001$). These effects started on day 2 and were significant on each individual day. The improvement in the QoL was also significantly greater for desloratadine than for the placebo ($P < 0.001$). The incidences of treatment-related adverse events were low and similar between the desloratadine (7.2%) and placebo (7.0%) groups.

In a placebo-controlled, multicentre, multinational, randomized clinical trial, Bousquet et al. [52] assessed the efficacy and safety of desloratadine in patients with PER. Adolescent ($\geq$12 years) and adult patients with PER were assessed over 85 days for once-daily treatment with desloratadine 5 mg ($N = 360$) or placebo ($N = 356$). The primary endpoint was the AM/PM rT5SS averaged over days 1–29. Secondary endpoints included the AM/PM iT5SS and individual symptoms, therapeutic response, symptom severity assessed by a visual analogue scale and QoL. Desloratadine caused a reduction in the AM/PM rT5SS over days 1–29 ($P < 0.001$) and on each individual day ($P < 0.05$) compared with the placebo. The AM iT5SS was also reduced with desloratadine compared with the placebo as early as day 2 ($P < 0.001$). Desloratadine also improved the therapeutic response and QoL compared with the placebo ($P < 0.001$ for each). The incidences of treatment-related adverse events were low and similar between the desloratadine (10.0%) and placebo (8.4%) groups.

In a recent pharmacoeconomic study, Sullivan et al. [67] simulated the cost-effectiveness of desloratadine compared with a placebo in the treatment of PER. From the French societal perspective (prices, tariffs and national wages were estimated from French national sources), a decision analysis was used to model the costs, effectiveness and cost-effectiveness over 12 months. Costs included medical expenditures (physician visits and prescription drugs) attributable to PER and related comorbidities, as well as loss of productivity owing to absenteeism and presenteeism. Effectiveness included symptoms measured by the VAS and T5SS, QoL (RQLQ), categorical improvement in the therapeutic response, interference with activities of daily living (ADL) and sleep outcomes. Mild or symptom-free days and "responders" were also used as outcomes. Treatment with desloratadine dominated over the placebo, with lower costs and greater effectiveness, for all measures. An increased number of responders were found among the patients treated with desloratadine (46.8%, $P < 0.01$) compared with the placebo (34.8%). Individuals taking desloratadine experienced an

Table 2. Levels of evidence and recommendations of oral H_1-antihistamines for the treatment of allergic rhinitis (AR) under the ARIA guidelines

	Intermittent AR		Persistent AR	
Oral H_1-antihistamines	Level of evidence[1]	Recommendation[2]	Level of evidence[1]	Recommendation[2]
Desloratadine	Ib	A	Ib	A
Levocetirizine	No data	D	Ib	A
Rupatadine	No data	D	Ib	A

1 CATEGORY OF EVIDENCE [36]:
Ia, evidence from meta-analysis of randomized controlled trials
Ib, evidence from at least one randomized controlled trial
IIa, evidence from at least one controlled study without randomisation
IIb, evidence from at least one other type of quasi-experimental study
III, evidence from non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies
IV, evidence from expert committee reports or opinion or clinical experience of respected authorities, or both
2 STRENTGH OF RECOMMENDATION [36]:
A, directly based on category I evidence
B, directly based on category II evidence or extrapolated recommendation from category I evidence
C, directly based on category III evidence or extrapolated recommendation from category I or II evidence
D, directly based on category IV evidence or extrapolated recommendation from category I, II or III evidence

increased number of study days with no or mild symptoms (57.6%, $P < 0.01$) compared with the placebo (36.5%). The expected annual cost of treatment was lower for desloratadine (1,819 Euro) than for the placebo (2,618 Euro), with lost productivity being the most significant contributor to the total cost. Finally, the results of 10,000 Monte Carlo simulations showed that the treatment was cost-saving in 99.6% of simulations.

Conclusions & key messages

1 Allergic rhinitis is a major health problem with high and ever-increasing prevalence worldwide, with major impacts on symptoms, quality of life and costs.
2 A novel ARIA classification has been proposed and validated, based on the duration of symptoms (intermittent or persistent) and the disease severity (mild, moderate, or severe).
3 Allergic rhinitis is a major risk factor for developing asthma.
4 When possible, the treatment of allergic rhinitis should combine patient education, allergen and irritant avoidance, pharmacotherapy and specific immunotherapy.
5 H_1-antihistamines are recommended by the ARIA guidelines for all levels of disease severity and for both intermittent and persistent allergic rhinitis.
6 For intermittent allergic rhinitis, only desloratadine has high levels of evidence (Ib) and recommendation (A) (Table 2).
7 For persistent allergic rhinitis, levocetirizine, rupatadine and desloratadine have high levels of evidence (Ib) and recommendation (A) (Table 2).
8 Finally, patients with rhinitis should be investigated for asthma, and conversely patients with asthma should be investigated for rhinitis. A combined treatment strategy to treat both rhinitis and asthma should be developed for optimal united airway management.

References

1 Canonica GW, Bousquet J, Mullol J et al. A survey of the burden of allergic rhinitis in Europe. *Allergy* 2007; **62**(Suppl 85):17–25.
2 Schatz M. A survey of the burden of allergic rhinitis in the USA. *Allergy* 2007; **62**(Suppl 85):9–16.
3 Mullol J. A survey of the burden of allergic rhinitis in Spain. *J Invest Allergol Clin Immunol* 2009; **19**:27–34.
4 Bauchau V, Durham SR. Prevalence and rate of diagnosis of allergic rhinitis in Europe. *Eur Respir J* 2004; **24**:758–64.
5 Maurer M, Zuberbier T. Undertreatment of rhinitis symptoms in Europe: findings from a cross-sectional questionnaire survey. *Allergy* 2007; **62**:1057–63.
6 Canonica GW, Mullol J, Pradalier A, Didier A. Patient perceptions of allergic rhinitis and quality of life: findings from a survey conducted in Europe and the United States. *WAO J* 2008; **1**:138–44.
7 Bousquet J, Van Cauwenberge P, Khaltaev N, and the ARIA Workshop Group. Allergic rhinitis and its impact on asthma. ARIA Workshop Report. *J Allergy Clin Immunol* 2001; **108**: S147–334.
8 Mullol J, Maurer M, Bousquet J. Sleep and allergic rhinitis. *J Investig Allergol Clin Immunol* 2008; **18**:415–9.
9 Bauchau V, Durham SR. Epidemiological characterization of the intermittent and persistent types of allergic rhinitis. *Allergy* 2005; **60**:350–3.
10 Van Hoecke H, Vastesaeger N, Dewulf L et al. Is the allergic rhinitis and its impact on asthma classification useful in daily primary care practice? *J Allergy Clin Immunol* 2006; **118**: 758–9.
11 Van Hoecke H, Vastesaeger N, Dewulf L et al. Classification and management of allergic rhinitis patients in general practice during pollen season. *Allergy* 2006; **61**:705–11.

12 Bousquet PJ, Combescure C, Neukirch F et al. Visual analog scales can assess the severity of rhinitis graded according to ARIA guidelines. *Allergy* 2007; **62**:367–72.
13 Valero A, Ferrer M, Sastre J et al. A new criterion by which to discriminate between patients with moderate allergic rhinitis and patients with severe allergic rhinitis based on the Allergic Rhinitis and its Impact on Asthma severity items. *J Allergy Clin Immunol* 2007; **120**:359–65.
14 Valero A, Ferrer M, Baró E et al. Discrimination between moderate and severe disease may be used in patients with either treated or untreated allergic rhinitis. *Allergy* 2010; **65**:1609–13.
15 Bousquet J, Bachert C, Canonica GW et al. Unmet needs in severe chronic upper airway disease (SCUAD). *J Allergy Clin Immunol* 2009; **124**:428–33.
16 Bousquet PJ, Bachert C, Canonica GW et al. Uncontrolled allergic rhinitis during treatment and its impact on quality of life: a cluster randomized trial. *J Allergy Clin Immunol* 2010; **126**:666–8. e1–5.
17 Demoly P, Allaert FA, Lecasble M, Bousquet J. Validation of the classification of ARIA (allergic rhinitis and its impact on asthma). *Allergy* 2003; **58**:672–5.
18 Park HS, Choi GS, Cho JS, Kim YY. Epidemiology and current status of allergic rhinitis, asthma, and associated allergic diseases in Korea: ARIA Asia-Pacific workshop report. *Asian Pac J Allergy Immunol* 2009; **27**:167–71.
19 Van Hoecke H, Van Cauwenberge P, Thas O, Watelet JB. The ARIA guidelines in specialist practice: a nationwide survey. *Rhinology* 2010; **48**:28–34.
20 del Cuvillo A, Montoro J, Bartra J et al. Validation of ARIA duration and severity classifications in Spanish allergic rhinitis patients – The ADRIAL cohort study. *Rhinology* 2010; **48**:201–5.
21 Bousquet J, Bodez T, Gehano P et al. Implementation of guidelines for allergic rhinitis in specialist practices. A randomized pragmatic controlled trial. *Int Arch Allergy Immunol* 2009; **150**:75–82.
22 Jáuregui I, Dávila I, Sastre J et al. Validation of ARIA (Allergic Rhinitis and its Impact on Asthma) classification in a pediatric population: The PEDRIAL study. *Pediatr Allergy Immunol* 2011; **22**:388–92.
23 Navarro A, Valero A, Juliá B, Quirce S. Coexistence of asthma and allergic rhinitis in adult patients attending allergy clinics: ONEAIR Study. *J Investig Allergol Clin Immunol* 2008; **18**: 233–8.
24 Castillo JA, Mullol J. Comorbidity of rhinitis and asthma in Spain. The RINAIR study. *Arch Bronconeumol* 2008; **44**:593–9.
25 Castillo JA, Molina J, Valero A, Mullol J. Prevalence and characteristics of rhinitis in asthmatic patients attending primary care in Spain (RINOASMAIR Study). *Rhinology* 2010; **48**:35–40.
26 Van Cauwenberge P, Watelet J-B, Van Zele T et al. Does rhinitis lead to asthma? *Rhinology* 2007; **45**:112–21.
27 Cruz AA, Popov T, Pawankar R et al. Common characteristics of upper and lower airways in rhinitis and asthma: ARIA update, in collaboration with GA^{2}LEN. *Allergy* 2007; **62**(Suppl. 84):1–41.
28 Aguarón J, Alonso E, Cabrera P et al. GEMA (Spanish asthma management guide). *Arch Bronconeumol* 2009; **45**(Suppl. 7): 2–35.
29 Guilemany JM, García-Piñero A, Alobid I et al. Persistent allergic rhinitis has a moderate impact on the sense of smell depending on both nasal congestion and inflammation. *Laryngoscope* 2009; **119**:233–8.
30 Bousquet J, Fokkens W, Burney P et al. Important research questions in allergy and related diseases: nonallergic rhinitis: a GA^{2}LEN paper. *Allergy* 2008; **63**:842–53.
31 Bachert C, Van Braune N, Toskala E et al. Important research questions in allergy and related diseases: 3 – chronic rhinosinusitis and nasal polyposis – a GA^{2}LEN study. *Allergy* 2009; **64**:520–33.
32 Rondón C, Canto G, Blanca M. Local allergic rhinitis: a new entity, characterization and further studies. *Curr Opin Allergy Clin Immunol* 2010; **10**:1–7.
33 Bousquet J, Khaltaev N, Cruz A 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.
34 Bousquet J, Reid J, Van Weel C et al. Allergic rhinitis management pocket reference 2008. *Allergy* 2008; **63**:990–6.
35 Mullol J, Valero A, Alobid I et al. Allergic Rhinitis and its Impact on Asthma Update (ARIA 2008). The perspective from Spain. *J Invest Allergol Clin Immunol* 2008; **18**:327–34.
36 Shekelle PG, Woolf SH, Eccles M, Grimshaw J. Clinical guidelines: developing guidelines. *BMJ* 1999; **318**:593–6.
37 Mullol J, Valero A, Alobid I. The nose – from symptoms to evidence-based medicine. *Allergy* 2007; **62**:339–43.
38 Bousquet J, Van Cauwenberge P, and Members of the ARIA Science Committee. Pharmacologic and anti-IgE treatment of allergic rhinitis. ARIA Update (in collaboration with GA^{2}LEN). *Allergy* 2006; **61**:1086–96.
39 Passalacqua G, Durham SR, on behalf of ARIA. Allergic Rhinitis and its Impact on Asthma Update: Allergen Immunotherapy. *J Allergy Clin Immunol* 2007; **119**:881–91.
40 Zuberbier T, Bachert C, Bousquet PJ et al. GA^{2}LEN/EAACI pocket guide for allergen-specific immunotherapy for allergic rhinitis and asthma. *Allergy* 2010; **65**:1525–30.
41 Bousquet J, Burney PG, Zuberbier T et al. GA^{2}LEN (Global Allergy and Asthma European Network) addresses the allergy and asthma "epidemic". *Allergy* 2009; **64**:969–77.
42 Brozek J, Bousquet J, Baena-Cagnani CE et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines - 2010 Revision. *J Allergy Clin Immunol* 2010; **126**:466–76.
43 Leurs R, Church MK, Taglialatela M. H_1-antihistamines: inverse agonism, anti-inflammatory actions and cardiac effects. *Clin Exp Allergy* 2002; **32**:489–98.
44 Bousquet J, Van Cauwenberge P, Bachert C et al. Requirements for medications commonly used in the treatment of allergic rhinitis. *Allergy* 2003; **58**:192–7.
45 Church MK, Maurer M, Simons FE et al. Risk of first-generation H_1-antihistamines: a GA^{2}LEN position paper. *Allergy* 2010; **65**:459–66.
46 Holgate S, Canonica G, Simons F et al. Consensus group on new-generation antihistamines (CONGA): present status and recommendations. *Clin Exp Allergy* 2003; **33**:1305–24.
47 Simons FE. Advances in H_1-antihistamines. *N Engl J Med* 2004; **351**:2203–17.
48 Bousquet J, Bachert C, Canonica GW et al. Efficacy of desloratadine in intermittent allergic rhinitis: a GA^{2}LEN study. *Allergy* 2009; **64**:1516–23.

49 Canonica GW, Bousquet J, Van Hammée G et al. Levocetirizine improves health-related quality of life and health status in persistent allergic rhinitis. *Respir Med* 2006; **100**: 1706–15.
50 Klimek L, Bachert C, Canonica GW et al. Long-term treatment of persistent allergic rhinitis with levocetirizine. Improvements in activity and sleep items of the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). *Allergy Clin Immunol Int: J World Allergy Org* 2007; **19**:4–10.
51 Fantin S, Maspero J, Bisbal C et al. A 12-week placebo-controlled study of rupatadine 10 mg once daily compared with cetirizine 10 mg once daily, in the treatment of persistent allergic rhinitis. *Allergy* 2008; **63**:924–31.
52 Bousquet J, Bachert C, Canonica GW et al. Efficacy of desloratadine in persistent allergic rhinitis – A GA^{2}LEN study. *Int Arch Allergol Immunol* 2010; **153**:395–402.
53 Mullol J, Bachert C, Bousquet J. Management of persistent allergic rhinitis: evidence-based treatment with levocetirizine. *Ther Clin Risk Manag* 2005; **1**:265–71.
54 Klimek L. Levocetirizine: from scientific evidence to a potent modern-day treatment of today's allergic patients. *Drugs Today (Barc)* 2009; **45**:213–25.
55 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**:2829–39.
56 Ciprandi G, Cirillo I, Vizzaccaro A et al. Levocetirizine improves nasal symptoms and airflow in patients with persistent allergic rhinitis: a pilot study. *Allerg Immunol (Paris)* 2005; **37**:25–9.
57 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**:838–44.
58 Bousquet J, Demarteau N, Mullol J et al. Costs associated with persistent allergic rhinitis are reduced by levocetirizine. *Allergy* 2005; **60**:788–94.
59 Katiyar S, Prakash S. Pharmacological profile, efficacy and safety of rupatadine in allergic rhinitis. *Prim Care Respir J* 2009; **18**:57–68.
60 Mullol J, Bousquet J, Bachert C et al. Rupatadine in allergic rhinitis and chronic urticaria. *Allergy* 2008; **63**(Suppl. 87): 1–28.
61 Valero A, De La Torre F, Castillo JA et al. Safety of rupatadine administered over a period of 1 year in the treatment of persistent allergic rhinitis: a multicentre, open-label study in Spain. *Drug Saf* 2009; **32**:33–42.
62 Valero A, Alonso J, Antépara I et al. Development and validation of a new Spanish instrument to measure health-related quality of life in patients with allergic rhinitis: the ESPRINT questionnaire. *Value Health* 2007; **10**:466–77.
63 Valero A, Alonso J, Antepara I et al. Health-related quality of life in allergic rhinitis: comparing the short form ESPRINT-15 and mini-RQLQ questionnaires. *Allergy* 2007; **62**:1372–8.
64 Valero A, Baró E, Sastre J et al. Reference values for facilitating the interpretation of the ESPRINT-15 questionnaire (Spanish version). *J Invest Allergol Clin Immunol* 2009; **19**:396–403.
65 Bousquet J, Bindslev-Jensen C, Canonica GW et al. The ARIA/EAACI criteria for antihistamines: an assessment of the efficacy, safety and pharmacology of desloratadine. *Allergy* 2004; **59**(Suppl. 77):4–16.
66 Bachert C, Van Cauwenberge P. Desloratadine treatment for intermittent and persistent allergic rhinitis: a review. *Clin Ther* 2007; **29**:1795–802.
67 Sullivan PW, Navaratnam P, Lorber R, Shekar T. The cost-effectiveness of treatment with desloratadine in patients with persistent allergic rhinitis. *Curr Med Res Opin* 2010; **26**:1389–97.