

New Therapies for Allergic Rhinitis

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Abstract Because of its burden on patient's lives and its impact on asthma, allergic rhinitis must be treated properly with more effective and safer treatments. According to guidelines by Allergic Rhinitis and Its Impact on Asthma (ARIA), the classification, pathogenesis, and treatment of allergic rhinitis are well defined. Currently, second-generation antihistamines and inhaled steroids are considered the cornerstone of first-line therapy. However, new formulations of available drugs (e.g., loratadine and rupatadine oral solution, ebastine fast-dissolving tablets, and the combination of intranasal fluticasone propionate and azelastine hydrochloride), recently discovered molecules (e.g., ciclesonide, bilastine, and phosphodiesterase-4 inhibitors), immunologic targets (e.g., omalizumab), and unconventional treatments (e.g., homeopathic treatments) are currently under investigation and represent a new frontier in modern medicine and in allergic rhinitis management. The aim of this review is to provide an update on allergic rhinitis treatment, paying particular attention to clinical trials published within the past 20 months that assessed the efficacy and safety of new formulations of available drugs or new molecules.

Keywords Allergic rhinitis · Therapy · Drugs · Symptoms · Quality of life · Immunology · Inflammation

Introduction

Rhinitis is defined as an inflammatory disorder of the nasal epithelium and is characterized clinically by symptoms such as rhinorrhea (anterior or posterior), blockage, sneezing, and itching, which are reversible spontaneously or in response to therapy. There are several different clinical presentations of rhinitis that may overlap. The most common form is allergic rhinitis (AR), which is caused by exposure to an allergen to which a patient is sensitized; for this reason, it is possible to refer to AR in the presence of rhinitis symptoms and allergic sensitization [1]. Typical allergens include house dust mite, grass pollen, tree pollen, weed pollens, cat, dog, and molds [2].

AR diagnosis is clinical and relies on the presence of the aforementioned symptoms [3], which occur generally within minutes after allergen exposure, may last for hours after an isolated exposure, and have a negative impact on quality of life [4]. The etiologic diagnosis is based on the identification of the causative allergen; the assessment may be performed in vivo by skin-prick tests or in vitro by measuring allergen-specific IgE.

With regard to classification, AR has always been divided into “seasonal” or “perennial,” based on the chronologic distribution of symptoms; however, this classification does not consider the possible overlap of multiple allergens, the severity of symptoms, and the physiopathology (chronic inflammation). Therefore, the ARIA (Allergic Rhinitis and Its Impact on Asthma) classification was introduced. ARIA subdivides AR into intermittent or persistent, according to the duration of symptoms [1]. It further divides AR severity into mild and moderate–severe according to its impact on quality of life [1]. This approach is useful both for describing how rhinitis manifests in terms of symptoms and its effects on quality of life and for determining the appropriate treatment (Fig. 1).

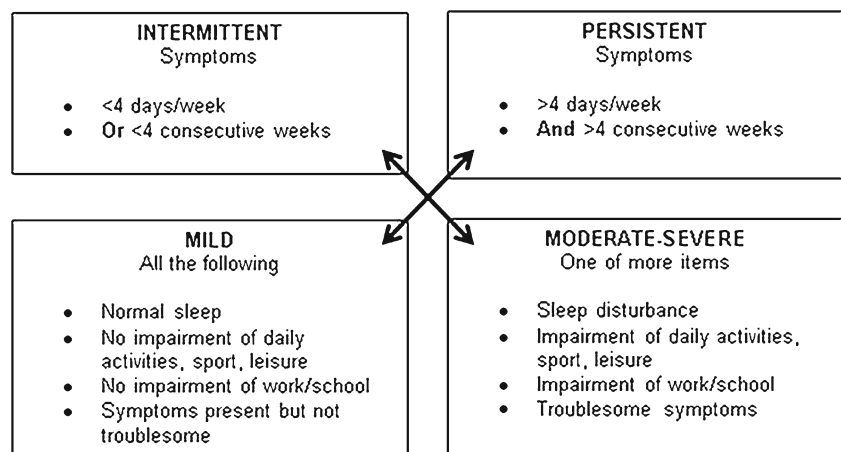
AR often is associated with several comorbidities, including asthma [5, 6•, 7, 8], chronic otitis media [9], rhinosinusitis

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Fig. 1 ARIA classification of allergic rhinitis



[10, 11], and oropharyngeal lymphoid hypertrophy, as well as secondary obstructive sleep apnea and disordered sleep [12–14]. Poorly controlled AR may trigger exacerbations of these comorbidities because they often share pathophysiologic (inflammatory) pathways [15, 16]. Therefore, all these aspects should be investigated and treated in patients with AR. Asthma, in particular, often coexists with AR in the same individual: up to 80 % of asthmatic patients suffer from allergic rhinitis, and up to 40 % of patients with rhinitis also have asthma [17].

The relationship between rhinitis and asthma (i.e., between the upper and lower respiratory airways) was first noted in epidemiologic studies. Moreover, clinical observations provide compelling evidence for the following phenomena: the frequent coexistence of rhinitis and asthma, rhinitis as a risk factor for developing asthma, the occurrence of bronchial hyperresponsiveness in rhinitis, the association between upper respiratory infections and asthma exacerbations, the existence of a common pathogenic mechanism between rhinitis and asthma, and the exacerbating role of sinusitis in asthma [18].

Several studies have suggested that asthma prevalence is higher in patients with moderate–severe rhinitis than in those with milder disease. AR often precedes asthma and represents a relevant and independent risk factor for its development in both adults and children [19, 20]. This is reinforced by the fact that AR treatment influences asthma control [21].

The aim of this review is to provide an update on AR treatment, particularly considering the evidence published in the past 20 months on drugs under investigation for AR management.

Methodology

A PubMed search was performed to identify drugs under investigation and new insights on drugs already available for allergic rhinitis treatment. Particular attention was focused on randomized clinical trials published from January 2012 on,

and the key words *rhinitis* and *treatment/therapy* in the subgroups “clinical trial” and “human” were used for searching. A computer literature search of the MEDLINE database also was performed from January 2012 to September 2013 using the key word *rhinitis treatment* in the subgroups “clinical trial” and “human.”

New Insights into Drugs Already Available for AR Treatment

Newly Formulated Second-Generation Antihistamines

Antihistamines are considered the cornerstone of first-line AR therapy, both in adults and in children. First-generation oral antihistamines, such as cyproheptadine, are safe and effective but have not been recommended since second-generation antihistamines became available, because of their sedative and anticholinergic effects. Wu et al. [22] recently assessed the efficacy of loratadine syrup, a second-generation antihistamine, compared with cyproheptadine HCl solution for treating children 2–12 years old with persistent AR (PAR). Loratadine syrup significantly reduced the total symptom score, with excellent improvement in symptoms without central nervous system (CNS) effects.

Rupatadine is a second-generation antihistamine that has widely been shown to be effective, rapid, and well tolerated for the symptomatic treatment of AR [23, 24]. A new oral formulation of rupatadine was developed recently. Potter et al. [25] performed a multicenter placebo-controlled clinical trial to assess the efficacy and safety of rupatadine oral solution in children 6–11 years old with PAR and found that rupatadine, 1 mg/mL oral solution, is effective in reducing nasal and nonnasal symptoms, ameliorating quality of life [26], and inducing clinical improvement significantly better than placebo [25].

Ebastine is a second-generation antihistamine with a good efficacy and safety profile. The fast-dissolving tablet (FDT), a

new formulation of this drug, is characterized by rapid disintegration in the mouth. This formulation may be particularly pleasing to patients because it is easy to use, portable, and perceived as having a faster onset of action while maintaining the same efficacy and safety profile as the regular tablets. Pharmacokinetic bioequivalence between ebastine FDT and the regular tablet was indeed demonstrated in healthy males [27]. In terms of cost, ebastine FDT is approximately the same price as the regular tablets [28].

Intranasal Corticosteroids

Although intranasal corticosteroids are recommended as first-line therapy in persistent rhinitis, they are currently available only as aqueous formulations and their use may result in undesirable side effects [29]. Beclomethasone dipropionate (BDP) hydrofluoroalkane nasal aerosol has been tested in patients with perennial allergic rhinitis. Once-daily administration of BDP nasal aerosol has been shown to provide statistically significant and clinically meaningful improvement in all four nasal symptoms of PAR (nasal congestion, nasal itching, rhinorrhea, and sneezing) and quality of life compared with placebo [30]. Moreover, BDP nasal aerosol resulted in lower systemic exposure than orally inhaled BDP [31].

Ciclesonide, currently used to treat asthma, is a prodrug converted into its active metabolite, desisobutyryl ciclesonide by the mucosal esterases in the respiratory tract; therefore, its anti-inflammatory effect is seen solely at the bronchial level, with only a fraction of the drug reaching the gastrointestinal tract and becoming inactive [32, 33]. A nasal aerosol solution of ciclesonide with a hydrofluoroalkane propellant (CIC-HFA) is currently in development for AR treatment.

Ratner et al. [34] performed a randomized, double-blind, multicenter study whose objective was to determine the efficacy, safety, and tolerability of CIC-HFA, 74 and 148 µg, administered once daily compared with placebo in patients over 12 years of age with seasonal AR (SAR). All patients treated with CIC-HFA showed statistically significant improvement in signs and symptoms of AR, including ocular symptoms. However, Varshney et al. [35] found that AR patients treated with steroids prefer fluticasone over ciclesonide because of its scent and soothing feel and because it causes less nasal irritation.

Second-Generation Antihistamine/Nasal Corticosteroid Combination in a Single Inhaler

A novel intranasal formulation of fluticasone propionate (FP) and azelastine hydrochloride (MP29-02) was compared with monotherapy with fluticasone, azelastine, and placebo sprays for SAR treatment. MP29-02 showed statistical superiority compared with both an intranasal steroid and an intranasal antihistamine, providing more complete symptom relief and

greater clinical efficacy, and might represent an advance in the therapy of moderate–severe AR. Furthermore, the use of a single delivery device may enhance patient adherence to nasal spray therapy [36].

New Insights into Drugs Under Investigation for Allergic Rhinitis Treatment

β_2 -Adrenoreceptors, although traditionally associated with bronchial smooth muscle, have been identified on several inflammatory cells, including eosinophils, neutrophils, lymphocytes, macrophages, and mast cells [37]. Russo et al. [38] showed that intranasal salbutamol is effective in attenuating adenosine monophosphate (AMP)-induced nasal response in patients with AR, which is probably a result of stimulation of β_2 -adrenoreceptors on nasal mucosal mast cells, thus inhibiting degranulation. Based on these premises, Lipworth et al. [39] performed a study in which they evaluated the effects of intranasal salmeterol and FP alone and in combination on the response to a nasal AMP challenge to assess mast cell activation. Unfortunately, although there was significant protection after single or long-term dosing with fluticasone alone as well as the fluticasone–salmeterol combination, salmeterol alone afforded protection only after the first dose. Indeed, there was no potentiation of fluticasone when given in combination with salmeterol, and this loss of protection with chronic dosages of long-acting β -agonists might be explained by β_2 -adrenoreceptor down-regulation [39]. Thus, salmeterol does not appear to be an effective treatment for AR.

No recent studies are available regarding molecules such as rofleponide palmitate, β -tryptase, adenosine A_{2A} receptor agonist/adenosine A_3 receptor antagonist, and phosphodiesterase-4 (PDE4) inhibitors. The first agent is a prodrug under study for the treatment of AR and asthma. This molecule is designed to provide topical exposure of the mucosa to the inactive lipophilic drug, which is metabolized locally to rofleponide, a more hydrophilic and readily cleared drug [40].

β -Tryptase is a multifunctional mast cell serine protease released during mast cell degranulation. In a study performed in 2006, Erin et al. [41] showed that combined β -tryptase and trypsin inhibition has therapeutic potential in allergic inflammation; however, the effect was dose-dependent so that low doses reduced symptoms, eosinophils, and interleukin (IL)-5 levels after nasal allergen challenge, whereas higher doses caused late eosinophilia and preceded increases in IL-5 [41].

Adenosine plays a role in the pathogenesis of asthma and rhinitis. Rimmer et al. [42] showed that, although intranasal treatment with an adenosine A_{2A} receptor agonist/adenosine A_3 receptor antagonist improved nasal blockage, it did not have a significant effect on rhinorrhea, the number of sneezes, or peak nasal inspiratory flow measurements when compared with placebo [42].

Several preclinical and clinical studies showed the efficacy of PDE4 inhibitors in allergic asthma. Because various epidemiologic and pathogenetic aspects are shared by asthma and AR, this drug likely may also be effective in AR. Thus, PDE4 inhibitors might be a promising treatment option, not only for allergic asthma but also for AR [43].

Prostaglandin D₂ is produced during the early phase of the allergic response and has been proposed to contribute to the accumulation and activation of Th2 lymphocytes, eosinophils, and basophils through high-affinity interaction with CRTH2 [44, 45]. The CRTH2 antagonist OC000459 has previously been shown to reduce airway inflammation and to improve lung function and quality of life in subjects with moderate persistent asthma [46]. A study by Horak et al. [47] compared OC000459 with placebo in subjects with allergic rhinoconjunctivitis. This study showed that the effects of OC000459 on nasal symptoms were at least as good as those of levocetirizine or fexofenadine [48] and approach those observed with fluticasone furoate [49]; however, further study is warranted to confirm these observations.

Bilastine, a new nonsedating H1 receptor inverse agonist, belongs to the piperidine class along with loratadine, desloratadine, and fexofenadine. In vitro studies have shown that bilastine has a high specific affinity for the H1 receptor but no or very low affinity for 30 other tested receptors. This affinity for the H1 receptor is three and six times higher than for cetirizine and fexofenadine, respectively. Bilastine behaves as an H1 mixed antagonist (competitive up to 33 nM; not competitive from 100 nM), as it is 5.5 times more powerful than cetirizine as a competitive antagonist and 10 times more powerful as a noncompetitive antagonist [50]. The effectiveness of bilastine is comparable to that of desloratadine [51]. Besides its H1 antagonism, bilastine has also demonstrated anti-inflammatory properties, including inhibiting the release of proinflammatory cytokines such as IL-4 and tumor necrosis factor- α . Furthermore, in vivo studies in rats demonstrated a significant reduction in histamine-stimulated endothelial permeability, microvascular extravasation, and inhibition of smooth muscular contraction and bronchospasm 11 times that of cetirizine [52].

Laboratory studies also demonstrated that bilastine may reduce passive cutaneous anaphylaxis induced by homologous serum and monoclonal antibodies, along with IgG/IgE-dependent active cutaneous anaphylaxis. Studies in humans have also shown its ability to rapidly inhibit the erythematous area in response to histamine [53]. Moreover, in a comparison performed in the Vienna Challenge Chamber or with natural exposure, bilastine proved to be more effective than fexofenadine and as effective as cetirizine in subjects with grass AR [54, 55].

With regard to pharmacokinetics, in the fasting state, bilastine is absorbed quickly and does not undergo significant metabolism. Bilastine has no impact on the cytochrome

P450 enzyme system of the liver, and there is no evidence of interaction with other drugs except for an increased uptake of bilastine when taken concomitantly with ketoconazole, erythromycin, or diltiazem. Approximately 95 % is excreted intact in feces (67 %) and urine (33 %) [56].

Bilastine presents a favorable safety profile with regard to CNS and cardiovascular effects. Its safety profile in terms of adverse effects was very similar to that of placebo in all phase I, II, and III clinical trials. Its distribution in the brain is undetectable. Bilastine (20 mg), unlike cetirizine, does not increase the effects of alcohol on the CNS, does not increase the CNS depressant effect of lorazepam, and is similar to placebo in the driving test [57]. No prolongation of the QTc interval (even at doses higher than the therapeutic dose) has been seen [58].

Bilastine is well tolerated at all doses in the healthy population. The incidence of side effects was similar to that of placebo and lower than that of cetirizine with regard to fatigue and somnolence. These studies indicate that this new antihistamine has a rapid onset of action (within an hour after administration), is long acting (more than 26 h), is effective in relieving AR nasal/nonnasal symptoms, and can improve the discomfort associated with the illness.

Recently, new antihistamine drugs, such as histamine H₃/H₄R antagonists/inverse agonists, were studied for the treatment of AR and allergic respiratory diseases in general. However, the data available in the literature do not demonstrate an additional benefit compared with H1 antagonism in reducing nasal blockage [59–61].

Suplatast tosilate (IPD-1151 T) is an immunomodulator compound that appears to restore the Th1/Th2 balance in allergic subjects and is currently available in Japan. It acts as a selective Th2 cytokine inhibitor, suppressing the production of IL-4 and IL-5 in vitro or in animal models, and has been proven to be clinically effective in treating AR. Furukido et al. [62] demonstrated that IPD-1151 T could reduce the Th2 pathway in human nasal mucosa. It has been hypothesized that it might have a role in the GATA binding protein 3 (GATA-3)/IL-5 signaling pathway, but its mechanism(s) of action in the inhibition of allergic disorders remain to be elucidated [63].

Omalizumab is a humanized monoclonal antibody directed against IgE. This molecule binds free IgE in serum, thus reducing the amount available to form complexes with the cells involved in allergic reaction (called, in fact, IgE-mediated) and reducing allergic symptoms. Many studies examining the use of omalizumab in AR are available. Casale and colleagues [64, 65] showed that omalizumab reduced the level of free IgE, and that this was associated with suppressed allergic symptoms, reduction of concomitant rescue medication use, and improvement in rhinitis-specific quality of life.

Specific immunotherapy is recommended as a treatment option for AR, with the aim of reducing symptoms and the need for rescue medications. Sublingual immunotherapy is a viable alternative to subcutaneous immunotherapy, with a

very favorable safety profile, and new approaches are in progress [66]. In particular, intralymphatic immunotherapy and the epicutaneous route are being studied. Intralymphatic immunotherapy consists of the injection of allergens directly into lymph nodes. Through this mode of administration, specific immunotherapy has been demonstrated to be as effective as traditional subcutaneous delivery, but with lower doses and fewer injections [67]. Favorable data are also available with regard to the epicutaneous route (via patches) [68].

Bacterial (unmethylated CpG DNA sequences; lipopolysaccharide [LPS] in Gram-negative, muramic acid in Gram-positive), viral (double-stranded RNA), and fungal (chitin contained in spores and hyphae) substances can stimulate specific Toll-like receptors (TLRs) on antigen-presenting cells. Activation of these receptors may result in a protective immune response by up-regulating the expression of Th1, Th3, and Treg T lymphocytes, thereby inhibiting Th2-mediated allergic sensitization [69]. In light of this, controlled infection-like stimulation of the immune system in this context may be beneficial and may be achieved by the use of TLR agonists.

Bacterial LPS, viral RNA, and bacterial/viral CpG DNA act as TLR4, TLR7, and TLR9 ligands. It has been shown that sequences of bacterial DNA possibly may act as potent inducers of Th1 via TLR4 [70, 71]. Moreover, repeated intranasal stimulation of TLR7 causes a sustained reduction in the responsiveness to an allergen by means of a selective TLR7 agonist optimized for topical airway treatment [72]. Beyond allergen extract standardization, the clinical use of recombinant allergens is promising but still under investigation [73].

Transient receptor potential vanilloid type 1 (TRPV1), a ligand-gated ion channel, is a polymodal nociceptor widely expressed within pain-transmitting/modulating areas of the peripheral nervous system and CNS. This receptor is implicated as a mediator of itch in AR and is activated by heat, protons, capsaicin, and various membrane-derived lipids. SB-705498 is a TRPV1 antagonist developed to reduce the symptoms of rhinitis associated with neuronal hyperresponsiveness due to the stimulation of these receptors. Bareille et al. [74] performed a randomized, double-blind, three-way incomplete block crossover study to evaluate the effects on nasal symptoms of 8 days of treatment with SB-705498, 12 mg, alone; SB-705498 plus FP, 200 µg; FP alone; or placebo. They showed that SB-705498 plus FP does not provide an improvement in nasal symptoms compared with FP alone, and there was no difference between SB-705498 and placebo [74].

Probiotics may modulate immune responses beneficial for the prevention and treatment [75, 76] of early allergic disease by modulating inflammatory response and immunity [77]. Indeed, consumption of probiotics has been shown to reduce the level of eosinophils in allergic patients [78], the production of allergic and proinflammatory cytokines, and the activation of basophil cells and to induce the development of a population of CD4⁺ T cells that produce transforming growth

factor-β and IL-10 [79], which suppress the allergen-induced inflammatory response [80–82].

Lue et al. [76] provided crossover treatment to 63 children aged 7–12 years to assess the clinical efficacy of *Lactobacillus johnsonii* EM1 (*Lj* EM1) as a supplement to the antihistamine levocetirizine for treating SAR in children. Indeed, they found an improvement in symptoms that persisted at least 3 months after discontinuation of *Lj* EM1 treatment. Similarly, Singh et al. [83] conducted a randomized placebo-controlled trial demonstrating the effectiveness of orally administered *Bifidobacterium lactis* NCC2818 on immune parameters and nasal symptoms in patients with SAR.

Evidence that mucosal barrier disorders play an important role in the pathologic mechanisms of AR has led to a new approach to its treatment. Böhm et al. [84] studied liposomes, which consist of phospholipids that form up to 75 % of the protective nasal surfactant layer [85, 86]. Their observational study demonstrated that nasal application of liposomal-based sprays, given as monotherapy or combination therapy, reduces AR symptoms by integrating into damaged cell membranes and stabilizing respiratory barriers, leading to an improvement in quality of life comparable to the effect of standard treatment with an antihistamine/glucocorticosteroid spray.

In addition to new molecules, mechanical approaches (e.g., nasal filters) and nasal lavages recently were tested. Nasal filters might represent a novel approach to preventing exacerbations of SAR symptoms by reducing pollen's access to nasal cavities; however, further studies are needed to confirm this hypothesis [87]. Marchisio et al. [88] used nasal irrigation in children with SAR and found that normal saline did not improve their symptoms substantially, but hypertonic saline (a 2.7 % sodium chloride solution) administered twice daily was safe and well tolerated, and led to a significant improvement in symptoms and less need for antihistamines to achieve disease control. Although the reason for hypertonic saline's effectiveness is unknown, it is reasonable to assume the hypertonicity of the fluid may play an important role in modifying the secretion of inflammatory mediators, improving mucociliary function and decreasing mucosal edema [89, 90].

Update on Unconventional Treatments

The prevalence of allergic disorders such as AR, allergic conjunctivitis, and bronchial asthma steadily increased in nearly all Western, industrialized countries during the past three decades [91, 92]. Affected people are turning to complementary treatment methods because of their fear that long-term or prolonged use of conventional medications, such as corticosteroids, antihistamines, chromones, and leukotriene antagonists, may be related to potential adverse effects [92]. According to Gründling et al. [93], the symptoms of patients undergoing homeopathic treatment improved substantially;

however, a reduction in rescue pharmacologic therapies was not seen. A recent study from Asia examined the role of acupuncture in the treatment of PAR. This multicenter, randomized, controlled trial found greater improvement in patient symptoms and quality of life compared with sublingual immunotherapy [94]. Interestingly, the clinical effect persisted for more than 4 weeks after the final acupuncture treatment. Obviously, further studies with a longer follow-up period are needed because even if effective, acupuncture for AR may not be a cost-effective intervention [95].

Conclusions

AR is a burdensome disorder that affects many patients around the world. An accurate diagnosis of AR is crucial to increase the likelihood of treatment success. Guidelines for AR management have been established, and the use of all appropriate therapeutic options (both conventional and unconventional) will improve outcomes in AR patients.

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Compliance with Ethics Guidelines

Conflict of Interest Fulvio Braido, F. Scilifò, M. Ferrando, and G.W. Canonica declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. 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.
2. Burbach GJ, Heinzerling LM, Edenharter G, et al. GA(2)LEN skin test study II: clinical relevance of inhalant allergen sensitizations in Europe. *Allergy*. 2009;64:1507–15.
3. Scadding GK, Durham SR, Mirakian R, et al. BSACI guidelines for the management of allergic and non-allergic rhinitis. *Clin Exp Allergy*. 2008;38:19–42.
4. Juniper E, Stahl E, Doty R, et al. Clinical outcomes and adverse effect monitoring in allergic rhinitis. *J Allergy Clin Immunol*. 2005;115:S390–413.

5. Montoro J, Del Cuvillo A, et al. Validation of the modified allergic rhinitis and its impact on asthma (ARIA) severity classification in allergic rhinitis children: the PEDRIAL study. *Allergy*. 2012;67:1437–42.
6. Brozek JL, Bousquet J, Baena-Cagnani CE, Global Allergy and Asthma European Network; Grading of Recommendations Assessment, Development and Evaluation Working Group, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol*. 2010;126:466–76. *This article provides a clear and detailed example of the application of the GRADE approach to compiling evidence and evaluating the quality of evidence, and also provides a grading of recommendation in updating ARIA guidelines.*
7. Price D. Asthma and allergic rhinitis: linked in treatment and outcomes. *Ann Thorac Med*. 2010;5:63–4.
8. Compalati E, Ridolo E, Passalacqua G, et al. The link between allergic rhinitis and asthma: the united airways disease. *Expert Rev Clin Immunol*. 2010;6:413–23.
9. Knight LC, Eccles R, Morris S. Seasonal allergic rhinitis and its effects on eustachian tube function and middle ear pressure. *Clin Otolaryngol Allied Sci*. 1992;17:308–12.
10. Pinto JM, Baroody FM. Chronic sinusitis and allergic rhinitis: at the nexus of sinonasal inflammatory disease. *J Otolaryngol*. 2002;31:S10–7.
11. Slavin RG. Complications of allergic rhinitis: implications for sinusitis and asthma. *J Allergy Clin Immunol*. 1998;101:S357–60.
12. Craig TJ, Sherkat A, Safaee S. Congestion and sleep impairment in allergic rhinitis. *Curr Allergy Asthma Rep*. 2010;10:113–21.
13. Muliol J, Maurer M, Bousquet J. Sleep and allergic rhinitis. *J Investig Allergol Clin Immunol*. 2008;18:415–9.
14. Storms W, Yawn B, Fromer L. Therapeutic options for reducing sleep impairment in allergic rhinitis, rhinosinusitis, and nasal polypsis. *Curr Med Res Opin*. 2007;23:2135–46.
15. Bachert C, Vignola AM, Gevaert P, et al. Allergic rhinitis, rhinosinusitis, and asthma: one airway disease. *Immunol Allergy Clin North Am*. 2004;24:19–43.
16. Jeffery PK, Haahtela T. Allergic rhinitis and asthma: inflammation in a one airway condition. *BMC Pulm Med*. 2006;6 Suppl 1:S5.
17. Cruz AA, Popov T, Pawankar R, ARIA Initiative Scientific Committee, et al. Common characteristics of upper and lower airways in rhinitis and asthma: ARIA update, in collaboration with GA(2)LEN. *Allergy*. 2007;62:1–41.
18. Passalacqua G, Ciprandi G, Canonica GW. The nose–lung interaction in allergic rhinitis and asthma: united airways disease. *Curr Opin Allergy Clin Immunol*. 2001;1:7–13.
19. Leynaert B, Bousquet J, Neukirch C, et al. Perennial rhinitis: an independent risk factor for asthma in nonatopic subjects: results from the European Community Respiratory Health Survey. *J Allergy Clin Immunol*. 1999;104:301–4.
20. Rochat MK, Illi S, Ege MJ, Multicentre Allergy Study (MAS) group. Allergic rhinitis as a predictor for wheezing onset in school-aged children. *J Allergy Clin Immunol*. 2010;126:1170–5.
21. Smart BA. Is rhinosinusitis a cause of asthma? *Clin Rev Allergy Immunol*. 2006;30:153–64.
22. Wu KG, Li TH, Wang TY, et al. A comparative study of loratadine syrup and cyproheptadine HCL solution for treating perennial allergic rhinitis in Taiwanese children aged 2–12 years. *Int J Immunopathol Pharmacol*. 2012;25:231–7.
23. Fantin S, Maspero J, Bisbal C, International Rupatadine Study Group, 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.
24. Guadano EM, Serra-Batlles J, Meseguer J, Rupatadine Study Group, et al. Rupatadine 10 mg and ebastine 10 mg in seasonal allergic rhinitis: a comparison study. *Allergy*. 2004;59:766–71.

25. Potter P, Maspero JF, Vermeulen J, et al. Rupatadine oral solution in children with persistent allergic rhinitis: a randomized, double-blind, placebo-controlled study. *Pediatr Allergy Immunol.* 2013;24:144–50.
26. Juniper EF, Howland WC, Roberts NB, et al. Measuring quality of life in children with rhinoconjunctivitis. *J Allergy Clin Immunol.* 1998;101:163–70.
27. Salvà M, Carreno B, Pintos M, et al. Phase I, single dose, open-label, randomized, cross-over bio-equivalence studies of ebastine 10 mg and 20 mg fast-dissolving tablets in healthy male volunteers. *J Investig Allergol Clin Immunol.* 2004;14:S5.
28. Ciprandi G. Clinical utility and patient adherence in the use of ebastine for allergic rhinitis. *Patient Prefer Adherence.* 2010;4:389–95.
29. Luskin AT, Blaiss MS, Farrar JR, et al. Is there a role for aerosol nasal sprays in the treatment of allergic rhinitis. *Allergy Asthma Proc.* 2011;32:168–77.
30. Meltzer EO, Jacobs RL, LaForce CF, et al. Safety and efficacy of once-daily treatment with beclomethasone dipropionate nasal aerosol in subjects with perennial allergic rhinitis. *Allergy Asthma Proc.* 2012;33:249–57.
31. Ratner PH, Melchior A, Dunbar SA, et al. Pharmacokinetic profile of beclomethasone dipropionate hydrofluoroalkane after intranasal administration versus oral inhalation in healthy subjects: results of a single-dose, randomized, open-label, 3-period crossover study. *Clin Ther.* 2012;34:1422–31.
32. Passalacqua G, Ciprandi G. Novel therapeutic interventions for allergic rhinitis. *Expert Opin Investig Drugs.* 2006;15:1615–25.
33. Chervinsky P, Kunjibettu S, Miller DL, et al. Long-term safety and efficacy of intranasal ciclesonide in adult and adolescent patients with perennial allergic rhinitis. *Ann Allergy Asthma Immunol.* 2007;99:69–76.
34. Ratner PH, Andrews C, Martin B, et al. A study of the efficacy and safety of ciclesonide hydrofluoroalkane nasal aerosol in patients with seasonal allergic rhinitis from mountain cedar pollen. *Allergy Asthma Proc.* 2012;33:27–35.
35. Varshney J, Varshney H, Dutta SK, et al. Comparison of sensory attributes and immediate efficacy of intranasal ciclesonide and fluticasone propionate in allergic rhinitis: a randomized controlled trial. *Indian J Pharmacol.* 2012;44:550–4.
36. Meltzer EO, LaForce C, Ratner P, et al. MP29-02 A novel intranasal formulation of azelastine hydrochloride and fluticasone propionate in the treatment of seasonal allergic rhinitis: a randomized, double-blind, placebo-controlled trial of efficacy and safety. *Allergy Asthma Proc.* 2012;33:324–32.
37. Barnes PJ. Effect of beta-agonists on inflammatory cells. *J Allergy Clin Immunol.* 1999;104:S10–7.
38. Russo C, Zeng D, Prosperini G, et al. Effect of salbutamol on nasal symptoms and mast cell degranulation induced by adenosine 5' monophosphate nasal challenge. *Clin Exp Allergy.* 2005;35:1192–6.
39. Lipworth BJ, Short P, Burns P, Nair A. Effects of intranasal salmeterol and fluticasone given alone and in combination in persistent allergic rhinitis. *Ann Allergy Asthma Immunol.* 2012;108:54–9.
40. Ahlström-Emanuelsson C, Andersson M, Persson C, et al. Topical treatment with aqueous solutions of rofleponide palmitate and budesonide in a pollen-season model of allergic rhinitis. *Clin Exp Allergy.* 2004;34:731–5.
41. Erin EM, Leaker BR, Zachariasiewicz A, et al. Effects of a reversible beta-tryptase and trypsin inhibitor (RWJ-58643) on nasal allergic responses. *Clin Exp Allergy.* 2006;36:458–64.
42. Rimmer J, Peake HL, Santos CM. Targeting adenosine receptors in the treatment of allergic rhinitis: a randomized, double-blind, placebo-controlled study. *Clin Exp Allergy.* 2007;37:8–14.
43. Schmidt BM, Kusma M, Feuring M, et al. The phosphodiesterase 4 inhibitor roflumilast is effective in the treatment of allergic rhinitis. *J Allergy Clin Immunol.* 2001;108:530–6.
44. Hirai H, Tanaka K, Yoshie O, et al. Prostaglandin D2 selectively induces chemotaxis in T helper type 2 cells, eosinophils, and basophils via seven-transmembrane receptor CRTH2. *J Exp Med.* 2001;193:255–61.
45. Pettipher R. The roles of the prostaglandin D2 receptors DP1 and CRTH2 in promoting allergic responses. *Br J Pharmacol.* 2008;153:S191–9.
46. Barnes N, Pavord I, Chuchalin A, et al. A randomized, double-blind, placebo-controlled study of the CRTH2 antagonist OC000459 in moderate persistent asthma. *Clin Exp Allergy.* 2012;42:38–48.
47. Horak F, Zieglmayer P, Zieglmayer R, et al. The CRTH2 antagonist OC000459 reduces nasal and ocular symptoms in allergic subjects exposed to grass pollen, a randomised, placebo-controlled, double-blind trial. *Allergy.* 2012;67:1572–9.
48. Horak F, Stubner P, Zieglmayer R, et al. Controlled comparison of the efficacy and safety of cetirizine 10 mg o.d. and fexofenadine 120 mg o.d. in reducing symptoms of seasonal allergic rhinitis. *Int Arch Allergy Immunol.* 2001;125:73–9.
49. Zieglmayer P, Zieglmayer R, Bareille P, et al. Fluticasone furoate versus placebo in symptoms of grass-pollen allergic rhinitis induced by exposure in the Vienna Challenge Chamber. *Curr Med Res Opin.* 2008;24:1833–40.
50. Corcóstegui R, Labeaga L, Innerarity A, et al. Preclinical pharmacology of bilastine, a new selective histamine H1 receptor antagonist: receptor selectivity and in vitro antihistaminic activity. *Drugs R D.* 2005;6:371–84.
51. Bachert C, Kuna P, Sanquer F, Bilastine International Working Group, et al. Comparison of the efficacy and safety of bilastine 20 mg vs desloratadine 5 mg in seasonal allergic rhinitis patients. *Allergy.* 2009;64:158–65.
52. Corcóstegui R, Labeaga L, Innerarity A, et al. In vivo pharmacological characterisation of bilastine, a potent and selective histamine H1 receptor antagonist. *Drugs R D.* 2006;7:219–31.
53. Church MK. Comparative inhibition by bilastine and cetirizine of histamine-induced wheal and flare responses in humans. *Inflamm Res.* 2011;60(12):1107–12.
54. Horak F, Zieglmayer P, Zieglmayer R, et al. The effects of bilastine compared with cetirizine, fexofenadine, and placebo on allergen-induced nasal and ocular symptoms in patients exposed to aeroallergen in the Vienna Challenge Chamber. *Inflamm Res.* 2010;59:391–8.
55. Kuna P, Bachert C, Nowacki Z, Bilastine International Working Group, et al. Efficacy and safety of bilastine 20 mg compared with cetirizine 10 mg and placebo for the symptomatic treatment of seasonal allergic rhinitis: a randomized, double-blind, parallel-group study. *Clin Exp Allergy.* 2009;39:1338–47.
56. Jauregizar N, Fuente LDL, Lucero ML, et al. Pharmacokinetic-pharmacodynamic modelling of the antihistaminic (H1) effect of bilastine. *Clin Pharmacokinet.* 2009;48:543–54.
57. Scaglione F. Safety profile of bilastine: 2nd generation H1-antihistamines. *Eur Rev Med Pharmacol Sci.* 2012;16:1999–2005.
58. Tyl B, Kabbaj M, Azzam S, et al. Lack of significant effect of bilastine administered at therapeutic and supratherapeutic doses and concomitantly with ketoconazole on ventricular repolarization: results of a thorough QT study (TQTS) with QT-concentration analysis. *J Clin Pharmacol.* 2012;52:893–903.
59. Lazewska D, Kiec-Kononowicz K. Azines as histamine H4 receptor antagonists. *Front Biosci (Schol Ed).* 2012;4:967–87.
60. Kiss R, Keserü GM. Histamine H4 receptor ligands and their potential therapeutic applications: an update. *Expert Opin Ther Pat.* 2012;22:205–21.
61. Daley-Yates P, Ambery C, Sweeney L, et al. The efficacy and tolerability of two novel H(1)/H(3) receptor antagonists in seasonal allergic rhinitis. *Int Arch Allergy Immunol.* 2012;158:84–98.
62. Furukido K, Takeno S, Ueda T, et al. Suppression of the Th2 pathway by suplatast tosilate in patients with perennial nasal allergies. *Am J Rhinol.* 2002;16:329–36.

63. Tan Y, Li Y, Liu D, et al. Suplatast tosilate ameliorates airway hyperreactivity and inflammation through inhibition of the GATA 3/IL 5 signaling pathway in asthmatic rats. *Mol Med Rep.* 2013;8:161–7.
64. Casale TB. Experience with monoclonal antibodies in allergic mediated disease: seasonal allergic rhinitis. *J Allergy Clin Immunol.* 2001;108:S84–8.
65. Grundmann SA, Hemfort PB, Luger TA, et al. Anti-IgE (omalizumab): a new therapeutic approach for chronic rhinosinusitis. *J Allergy Clin Immunol.* 2008;121:257–8.
66. Casale TB, Stokes JR. Future forms of immunotherapy. *J Allergy Clin Immunol.* 2011;127:8–15.
67. Senti G, Prinz Vavricka BM. Intralymphatic allergen administration renders specific immunotherapy faster and safer: a randomized controlled trial. *Proc Natl Acad Sci U S A.* 2008;105:17908–12.
68. Senti G, von Moos S, Kündig TM. Epicutaneous allergen administration: is this the future of allergen-specific immunotherapy? *Allergy.* 2011;66:798–809.
69. Holgate ST. The epidemic of asthma and allergy. *J R Soc Med.* 2004;97:103–10.
70. Creticos PS, Eiden JJ, Broide DH, et al. Immunotherapy with immunostimulatory oligonucleotides linked to purified ragweed Amb a1 allergen: effects on antibody production, nasal allergen provocation, and ragweed seasonal rhinitis. *J Allergy Clin Immunol.* 2002;109:743–4.
71. Drachenber KJ, Wheeler A, Stubner P, et al. A well tolerated grass pollen specific allergy vaccine containing a novel adjuvant MPL reduces allergy symptoms after only four preseasonal injections. *Allergy.* 2001;56:498–505.
72. Greiff L, Cervin A, Ahlström-Emanuelsson C, et al. Repeated intranasal TLR7 stimulation reduces allergen responsiveness in allergic rhinitis. *Respir Res.* 2012;13:53.
73. Pauli G, Larsen TH, Rak S, et al. Efficacy of recombinant birch pollen vaccine for the treatment of birch-allergic rhinoconjunctivitis. *J Allergy Clin Immunol.* 2008;122:951–60.
74. Bareille P, Murdoch RD, Denyer J, et al. The effects of a TRPV1 antagonist, SB-705498, in the treatment of seasonal allergic rhinitis. *Int J Clin Pharmacol Ther.* 2013;51:576–84.
75. Saito H, Morikawa H, Howie K. Effects of a cysteinyl leukotriene receptor antagonist on eosinophil recruitment in experimental allergic rhinitis. *Immunology.* 2004;113:246–52.
76. Lue KH, Sun HL, Lu KH, et al. A trial of adding *Lactobacillus johnsonii* EM1 to levocetirizine for treatment of perennial allergic rhinitis in children aged 7–12 years. *Int J Pediatr Otorhinolaryngol.* 2012;76:994–1001.
77. Strachan DP. Hay fever, hygiene, and household size. *BMJ.* 1989;299:1259–60.
78. Wheeler JG, Bogle ML, Shema SJ, et al. Impact of dietary yogurt on immune function. *Am J Med Sci.* 1997;313:120–3.
79. Pessi T, Sütas Y, Hurme M, et al. Interleukin-10 generation in atopic children following oral *Lactobacillus rhamnosus* GG. *Clin Exp Allergy.* 2000;30:1804–8.
80. Smits HH, Engering A, van der Kleij D, et al. Selective probiotic bacteria induce IL-10-producing regulatory T cells in vitro by modulating dendritic cell function through dendritic cell-specific intercellular adhesion molecule 3-grabbing nonintegrin. *J Allergy Clin Immunol.* 2005;115:1260–7.
81. Di Giacinto C, Marinaro M, Sanchez M, et al. Probiotics ameliorate recurrent Th1-mediated murine colitis by inducing IL-10 and IL-10-dependent TGF-beta-bearing regulatory cells. *J Immunol.* 2005;174:3237–46.
82. Lammers KM, Brigidi P, Vitali B, et al. Immunomodulatory effects of probiotic bacteria DNA: IL-1 and IL-10 response in human peripheral blood mononuclear cells. *FEMS Immunol Med Microbiol.* 2003;38:165–72.
83. Singh A, Hacini-Rachinel F, Gosoniu ML, et al. Immune-modulatory effect of probiotic *Bifidobacterium lactis* NCC2818 in individuals suffering from seasonal allergic rhinitis to grass pollen: an exploratory, randomized, placebo-controlled clinical trial. *Eur J Clin Nutr.* 2013;67:161–7.
84. Böhm M, Avgitidou G, El Hassan E, et al. Liposomes: a new non-pharmacological therapy concept for seasonal-allergic-rhinoconjunctivitis. *Eur Arch Otorhinolaryngol.* 2012;269:495–502.
85. Sayed R, Abou-Elhamd K, Abdel-Kader M, et al. Study of surfactant level in cases of primary atrophic rhinitis. *J Laryngol Otol.* 2000;114:254–9.
86. Yarosh D. Topical application of liposomes. *J Photochem Photobiol B.* 1990;6:445–9.
87. D'Amato G, Liccardi G, Salzillo A, et al. Nasal filters in prevention of seasonal rhinitis induced by allergenic pollen grains. Open clinical study. *Eur Ann Allergy Clin Immunol.* 2012;44:83–5.
88. Marchisio P, Varricchio A, Baggi E, et al. Hypertonic saline is more effective than normal saline in seasonal allergic rhinitis in children. *Int J Immunopathol Pharmacol.* 2012;25:721–30.
89. Rabago D, Zgierska A. Saline nasal irrigation for upper respiratory conditions. *Am Fam Physician.* 2009;80:1117–9.
90. Parsons DS. Chronic sinusitis: a medical or surgical disease? *Otolaryngol Clin North Am.* 1996;29:1–9.
91. Gupta R, Sheikh A, Strachan DP, et al. Increasing hospital admissions for systemic allergic disorders in England: analysis of national admissions data. *BMJ.* 2003;327:1142–3.
92. Strannegard O, Strannegard IL. The causes of the increasing prevalence of allergy: is atopy a microbial deprivation disorder? *Allergy.* 2001;56:91–102.
93. Gründling C, Schimetta W, Frass M. Real-life effect of classical homeopathy in the treatment of allergies: a multicenter prospective observational study. *Wien Klin Wochenschr.* 2012;124:11–7.
94. Choi SM, Park JE, Li SS, et al. A multicenter, randomized, controlled trial testing the effects of acupuncture on allergic rhinitis. *Allergy.* 2013;68:365–74.
95. Reinhold T, Roll S, Willich SN, et al. Cost-effectiveness for acupuncture in seasonal allergic rhinitis: economic results of the ACUS AR trial. *Ann Allergy Asthma Immunol.* 2013;111:56–63.