EXPERT REVIEWS

Current recommendations and emerging options for the treatment of allergic rhinitis

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Allergic rhinitis (AR) is one of the most common diseases and represents a global health problem, currently affecting up to 30% of the general population, with a continuously increasing prevalence and significant comorbidities and complications. The aim of this review is to provide an update on AR treatment, with a focus on current therapies defined by AR and its impact on asthma guidelines and with a particular emphasis on new and future therapeutic perspectives.

KEYWORDS: allergic rhinitis • drugs • efficacy • immunology • inflammation • safety • therapy

An overview of allergic rhinitis

Allergic rhinitis (AR) is one of the most common diseases and represents a global health problem, currently affecting up to 30% of the general population, but its prevalence is steadily increasing both in children and adults. In addition, symptoms of AR develop before the age of 20 years in 80% of cases, with 40% of those becoming symptomatic by 6 years of age [1–3].

AR is an inflammatory disease of the upper airways, and its symptoms include nasal congestion, rhinorrhea, sneezing and itching. Symptoms can also involve the eyes, ears and throat, including postnasal drip. The pathophysiology of this disorder has been better understood thanks to studies on nasal challenge with specific allergens in animal models and humans. It is now well established that AR is due to an allergic immune response to inhaled allergens [4]. This aberrant reaction involves the release of inflammatory mediators and the activation and recruitment of cells to the nasal mucosa. The first pathogenic process in the development of AR is the sensitization to allergens. In the condition of atopy, sensitization takes place when an inhaled allergen is recognized by the APCs in airway mucosa. It is important to highlight that the allergic sensitization that characterizes AR has a strong genetic component. Atopic individuals have a genetic predisposition to become sensitized to harmless allergens through the development of an altered immune response characterized by IgE production and T helper type 2 lymphocyte (Th_2) activation. On mucosal surfaces, APCs recognize, uptake and present the allergenic peptides to T lymphocytes in draining lymph nodes. Moreover, some APCs produce cytokines such as IL-4 that promote the transformation of naive T helper cells into Th_2 cells [4]. On their side, Th_2 lymphocytes play an important role in the support of the allergic immune response through secretion of several cytokines such as IL-4, IL-5, IL-10 and IL-13; in particular, IL-4 is essential to induce the isotype switching from IgM to IgE class antibodies in B lymphocytes, while IL-5 induces eosinophilic inflammation through stimulation of production, chemotaxis and sustained survival of eosinophils in target tissue [4]. The antibody production in response to re-exposure to the same antigen is due to memory B lymphocytes that proliferate and differentiate into antibody-secreting plasma cells producing high-affinity IgE antibodies. Once produced, IgE molecules are released into the bloodstream and bind to high-affinity receptors for the Fc region of IgE on the surface of tissue mast cells and circulating basophils [4]. Besides this systemic production of IgEs, several studies demonstrate that even the B lymphocytes residing in nasal mucosa are able to locally produce IgEs [5]. This process is considered the molecular basis of localized mucosal allergic disease and could explain the allergic

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Th_2 disease pathway localized in the nasal mucosa of some 'nonallergic' rhinitis subjects despite the absence of systemic responses for atopy [6,7].

Once the patient has become sensitized to an allergen, subsequent exposures trigger a cascade of events that result in the clinical manifestation of AR. In AR, the reaction to an allergen can be divided into two phases: the immediate- or early-phase response and the late-phase response [4]. The early-phase response occurs usually within minutes and results in symptoms mainly mediated by histamine. Nasal itching, sneezing, rhinorrhea and nasal congestion are some of the early-phase symptoms. Late-phase symptoms stem from eosinophils and T-cell mediated cytokines such as IL-4 and IL-5 and can present with rhinorrhea and nasal obstruction [4].

AR is caused by the IgE-mediated sensitization to environmental allergens, such as mites, pollens, domestic animals and moulds. Therefore, the diagnosis of AR is correctly made whenever the nasal symptoms are consistent with a profile of allergic sensitization (which must be documented by skin prick tests and/or the dosage of serum of allergen-specific IgE), both considering the clinical picture and its temporal pattern [8].

Traditionally, AR has been categorized as seasonal or perennial, according to the relevant allergen; however, this distinction is not globally applicable, and therefore, it has been revised by the allergic rhinitis and its impact on asthma (ARIA) group. The ARIA guideline provides a global, evidence-based, pragmatic, stepwise approach to treatment of AR and has been updated and evaluated in recent years with grading of recommendations assessment, development and evaluation (GRADE) methodology [8]. The new classification system includes the categories of intermittent and persistent AR, according on duration of symptoms. It further divides AR severity into mild or moderate–severe, according on whether the AR symptoms result in any impairment of daily activities, sleep disturbances and the degree of troublesome of symptoms. Although it is not considered a serious illness, AR can often be a debilitating condition, resulting in considerable health-related and economic consequences [9]. AR is associated with significant morbidity and also affects patients' quality of life, emotional well-being, productivity and cognitive functioning. Many of these issues are related to poor sleep quality and sleep disturbances caused by AR [10]. The health impact of AR is compounded by associated complications and comorbidities including asthma, otitis media, sinusitis, nasal polyps, secondary obstructive sleep apnea (OSA) and sleep disorders [8]. Children with AR are particularly at risk for certain comorbidities and complications. Several studies showed a significant association between AR symptoms and otitis media with effusion (OME) in pediatric patients and concluded that AR may play a role in the pathogenesis of OME, providing a rationale for the evaluation of AR as a factor in the development of OME in children with AR symptoms [11]. AR should be considered also a potential factor in the development of sinusitis and its complications in children; adequate therapy helps to avoid the development of dangerous complications such as orbital complications, including preseptal cellulitis, periostitis and subperiosteal abscess [11]. Nasal congestion and obstruction as a result of AR might contribute to mouth breathing that has been linked to an increased incidence of orthodontic malocclusions and habitual snoring in children. In children with snoring due to AR, OSA may be present and may lead to potential neurobehavioral consequences of OSA, such as excessive daytime sleepiness, impaired vigilance, mood disturbances and cognitive dysfunctions [11].

The link existing between the upper and lower airways has been observed repeatedly in the past, but the concept of 'united airways disease' is a matter of recent years, thanks to the increasingly detailed pathogenic knowledge acquired over the last 15 years [12]. In particular, asthma and AR frequently coexist, with epidemiological data suggesting that up to 80% asthma patients also suffer from AR, and up to 40% of patients with rhinitis also have asthma [13]. AR often precedes the development of asthma in children, and this sequence is commonly called the atopic march [14]. Large studies have found a link between the severity and/or control of both diseases in children and adults; in particular, poor asthma control is linked to moderate–severe rhinitis, which should be identified and treated. Numerous studies have also shown that treatment of AR will improve asthma outcomes [8]. Moreover, AR is considered a relevant and independent risk factor for developing asthma as it often precedes bronchial hyperreactivity [13]. AR has also been linked to 'small airway disease', defined as a reduction in forced expiratory flow at 25–75% of the pulmonary volume and a normal spirometry, which is suggested to be an early marker of bronchial involvement in patients with AR who perceive only nasal symptoms [15]. ARIA document has clearly underlined, throughout these last 10 years, the role of AR as a risk factor for asthma and suggests to always consider bronchial involvement in patients presenting with AR [8].

Current recommendations for the treatment of AR

The cornerstones of AR management are allergen avoidance, drug treatment and allergen immunotherapy (AIT). The first is always indicated, but rarely its outcome is actually effective in the clinical control of symptoms. Drug treatment is mainly based on antihistamines and intranasal corticosteroids (INCSs), the latter offering comparable efficacy to systemic administration while minimizing the known side effects of these agents. However, drugs work on symptoms but not on natural history of AR, which instead is influenced by AIT.

Allergen avoidance

Once allergy testing is complete, the physician may devise a comprehensive program of allergen avoidance.

The lack of hay fever outside the pollen season indicates that complete allergen avoidance can be effective. Unfortunately, complete avoidance is rarely possible, especially for outdoor allergens. The effects of environmental control strategies have been most heavily studied with regard to dust mites and furry pets [8]. Compliance with these measures may be difficult but

will certainly be helpful in many patients with hypersensitivity to these allergens. Avoidance of other rhinitis triggers, such as cigarette smoke, outdoor pollutants, fumes and irritants, is sensible in clinical practice.

Pharmacotherapy

While carefully designed allergen avoidance strategies may reduce symptoms to varying degrees, most patients will still require pharmacotherapy. The major pharmacological agents used in management of AR are H_1 antihistamines and INCSs (Table 1). Sodium cromoglycate, topical anticholinergic agents and topical or oral vasoconstrictors are used to a lesser extent [8].

Anti-H_1 antihistamines

More than 45 H_1 antihistamines are available worldwide, comprising the largest class of medications used in the treatment of allergic diseases. The mechanism of action of this drug class is blockage of H_1 receptors, and some antiallergic activity. H_1-antihistamines downregulate allergic inflammation directly by interfering with histamine action at H_1-receptors on sensory neurons and small blood vessels. They also decrease antigen presentation, expression of proinflammatory cytokines and cell adhesion molecules, and chemotaxis. In a concentration-dependent manner, they inhibit mast cell activation and histamine release [16].

Oral H_1 antihistamines have long been a mainstay of therapy for AR; they are more efficacious than chromones and montelukast; however, all these classes of medications are less efficacious than INCSs [8]. Oral H_1 antihistamines are most effective in preventing and relieving sneezing, itching and rhinorrhea that characterize the early response to allergen, with a small beneficial effect on the nasal congestion that characterizes the late allergic response. For this reason, some oral H_1 antihistamines are marketed in fixed-dose combination with the decongestant pseudoephedrine [16,17].

Because they are available in a number of different formulations (i.e., tablets, rapidly dissolving pills and liquids), patient preference may dictate choice of medication.

First-generation H_1 antihistamines have poor receptor H_1 receptor selectivity, and cross blood–brain barrier; their sedative and anticholinergic side effects have restricted their current use. In contrast, second-generation H_1 antihistamines were highly selective for the histamine H_1 receptor, do not cross the blood–brain barrier and have minimal adverse events [16]. For most second-generation H_1-antihistamines, pharmacokinetics have been extensively investigated in healthy adults, patients with impaired hepatic or renal function, and elderly people, children and infants. Their use in patients with AR is supported by hundreds of well-designed, randomized, placebo-controlled trials [8,18]. A number of newer oral H_1 antihistamines have been approved for use in young children, including cetirizine, fexofenadine, loratadine and rupatadine [8,19,20].

Among these novel agents, rupatadine may play an unique role showing a multiple receptor antagonism because its strong antagonist activity toward both histamine H_1 receptors and platelet-activating factor (PAF) receptors. PAF stimulates human mast cell release of proinflammatory mediators and has the capability to attract and activate neutrophils and eosinophils in the nasal mucosa [21]. Thus, rupatadine can provide additional anti-inflammatory effects by means of its dual capacity of blocking histamine and PAF receptors in comparison with other antihistamines [22].

A new H_1 antihistamines, bilastine, has been approved in Europe countries for the symptomatic treatment of allergic rhinoconjunctivitis and urticaria in adults and children older than 12 years. Pharmacological studies have shown that bilastine is highly selective for the H_1 receptor, with no apparent affinity for other receptors. In addition, it has no sedative side effects, no cardiotoxic effects and no hepatic metabolism. In large randomized, placebo-controlled trials (RCTs), bilastine had a favorable safety profile; for this reason, bilastine meets current ARIA criteria for medications used in the treatment of AR [23]. However, research into aspects of pharmacokinetics and efficacy and adverse effect profiles of bilastine in children under 12 years of age is needed as are dose–response assessments and studies planned rigorously with the aim of assessing quality-of-life effects [24].

Important advances in current therapy include improved nasal and ophthalmic H_1 antihistamines with rapid onset of action (in minutes) for AR and allergic conjunctivitis treatment [16]. In patients with seasonal AR, nasal H_1 antihistamines are reported to be as efficacious or more efficacious than oral H_1 antihistamines, particularly for relief of nasal congestion. They improve symptoms in patients who are unresponsive to oral H1-antihistamines and those with vasomotor rhinitis [25]. Finally, promising H_1 antihistamine/glucocorticoid nasal formulations are being investigated.

Intranasal corticosteroids

INCSs represent the gold standard for treating patients presenting with AR for their ability to control nasal symptoms, especially when nasal obstruction is the main symptom, since they show profound effects on the inflammatory process seen in this disease [26]. INCSs block both the acute- and late-phase reactions following allergen challenge as they reduce the level of several inflammatory cytokines that are overexpressed in patients affected by AR. In addition, these drugs are helpful in both reducing the number of APCs and in impairing their processing of antigens. Finally, they are also able to interfere with the migration of basophils and mast cells to the nasal epithelium and with several eosinophil functions [27].

INCSs are recommended as first-line treatment for persistent moderate-to-severe AR [8]. In intermittent AR, treatment with INCSs should be started prophylactically or early in the relevant season, or at the appearance of the symptoms in those cases in which a causative allergen has not been detected.

The use of INCSs has been introduced in order to reduce the systemic effects seen with long-term use of systemic corticosteroids, which frequently resulted in growth retardation in

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Table 1. Pharmacological agents for allergic rhinitis treatment.

Name	Generic name	Name	Generic name
Antihistamines		Leukotriene antagonists	
Oral H_1 antihistamines	*First generation*		Montelukast
	Chlorphenyramine		Pranlukast
	Clemastine		Zafirlukast
	Dimethindene maleate	Local cromones (intranasal and intraocular)	
	Hydroxyzine		Cromoglycate
	Ketotifen		Nedocromil
	Oxatomine	Oral decongestants	
	Second generation		Ephedrine
	Acrivastine		Phenylephrine
	Azelastine		Phenyl-propanolamine
	Cetirizine		Pseudoephedrine
	Desloratadine	Intranasal decongestants	
	Ebastine		Oxymethazoline
	Fexofenadine		Xylomethazoline
	Levocetirizine	Intranasal anticholinergics	
	Loratadine		Ipratropium
	Mequitazine		
	Mizolastine		
	Rupatadine		
Local H_1 antihistamines (intranasal and intraocular)	Azelastine		
	Levocabastine		
	Olopatadine		
Corticosteroids			
Intranasal corticosteroids	Beclomethasone dipropionate		
	Budesonide		
	Ciclesonide		
	Flunisonide		
	Fluticasone propionate		
	Fluticasone furoate		
	Mometasone furoate		
	Triamcinolone acetonide		
Oral/IM corticosteroids	Dexamethasone		
	Hydrocortisone		
	Methylprednisolone		
	Prednisolone		
	Prednisone		
	Triamcinolone		

children and adolescents. A large number of studies have established that there are no differences in efficacy between all of the available compounds [28], and most (including beclomethasone dipropionate, budesonide, mometasone furoate and fluticasone propionate and furoate) have been shown to have no significant effects on linear growth velocity in young children [29]. These, and other second-generation INCSs, are strongly preferred over first-generation corticosteroids (e.g., dexamethasone) owing to their superior tolerability profiles [26].

The new association of azelastine and fluticasone nasal spray, approved by the US FDA in 2012 for patients older than 12 years of age, may provide a substantial therapeutic benefit for patients with seasonal AR compared with therapy with either agent alone, as indicated by the newest ARIA guidelines as well [8,30,31].

In general, the newer INCSs appear to be well tolerated and the evidence suggests that any associated risks appear to be limited and transient, and that these are outweighed by the benefits. INCSs are thus extremely effective and have an excellent profile of safety and tolerability [32–34]. Owing to their good anti-inflammatory activity, poor systemic absorption (~1%) and first-pass hepatic metabolism, second-generation INCSs are usually considered as the best choice. Although some concerns have persisted about the systemic adverse effects of these agents, very little clinical evidence suggested that they are connected with growth suppression in children or inhibition of hypothalamic–pituitary–adrenal axis function in adults and children despite differences in lipophilicity and bioavailability among the different agents [35–37]. Similarly, the use of INCSs at recommended dosed is not related to histopathological nasal changes during long-term use, elevation of intraocular pressure to clinically relevant levels, a reduction in bone mineral density or the onset of osteoporosis. The incidence of septal perforation with INCSs is rare and often related to an incorrect use of the device. However, individuals may differ their susceptibility to the systemic adverse effects of INCSs, and different CS formulations and delivery systems may have different effects, particularly in patients receiving concomitant treatment for AR and asthma [38].

About their use in pregnant women with AR, there is always the concern for adverse effects especially to the unborn fetus, particularly cleft lip and palate development. Thus far, there have not been any reported teratogenic effects. Overall, there are not enough studies to support any definitive conclusion regarding the use of these agents in pregnancy. Therefore, careful risk–benefit analysis is recommended for mother and fetus when considering the use of INCSs for the treatment of AR in pregnant women. Of INCSs, budesonide is the only category B drug [8].

Patient education regarding how to use these drugs should be highlighted. The correct method to administer a dose can vary from drug to drug and its delivery system. Patients should also be reminded that this medication can take some time to reach a level of maximal benefit, usually on the order of several days [8].

Intramuscular & oral corticosteroids

Intramuscular corticosteroid injections must be avoided because their use is associated with potentially severe adverse events such as systemic side effects and subcutaneous and muscular necrosis. A short course of oral corticosteroids is only possibly suggested in patients with AR and moderate-to-severe nasal and/or ocular symptoms that are not controlled with other treatments, with the exception of children, pregnant women and patients with known contraindications [8].

Decongestants

Decongestants (e.g., ephedrine and pseudoephedrine) are frequently used for symptomatic relief of nasal symptoms; as vasoconstrictor agents, they act only on nasal congestion. Their use is conditionally suggested only as a very short intranasal course (not longer than 5 days and preferably shorter) while coadministering other drugs; their overuse has been recently reported in half of the individuals self-medicating persistent rhinitis [39], with consequent induction of a rebound of nasal congestion ('rhinitis *medicamentosa*'). Intranasal decongestants should not be used in preschool children [3]. The use of oral decongestants is associated with serious side effects, as insomnia, headache and palpitations, limiting their use. Furthermore, these agents are contraindicated in patients with hypertension and coronary artery disease [8].

Chromones & anticholinergics

The use of intranasal chromones and anticholinergics, while being effective and well tolerated, is conditioned by the need for multiple administration daily that reduces patient adherence and limits their application [8].

Saline nasal irrigation

The use of saline nasal irrigation as an adjunctive therapy for upper respiratory conditions, including AR, has been recommended both for adults and children, allowing a better control of symptoms and improving quality of life [40–42].

Leukotriene inhibitors

Leukotriene inhibitors target potent inflammatory mediators by competitively blocking the binding of cysteinyl leukotrienes to end-organ receptors. Montelukast is the only leukotriene inhibitor that is FDA-approved for AR in adults and children. Its safety profile is optimal, even in pregnancy (FDA risk category B) [8]. Studies have demonstrated clinical efficacy of montelukast in reducing all of the symptoms of AR, including nasal congestion, although its effects were inferior to antihistamines INCSs [8,43–46].

For this reason, combination therapy with oral H_1 antihistamines or INCSs is a more effective strategy than monotherapy in the treatment of AR [6]. Because montelukast is also effective in reducing bronchial symptoms in asthmatic patients, this agent is a reasonable choice for patients with concurrent asthma and AR [8,47].

Disease costs and the economic value of disease management strategies are a current issue [9]. The cost-of-illness literature on AR is limited to few data, mainly derived from the USA. A systematic review of the pharmacoeconomic literature on

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pharmacotherapy of AR assessed a substantial economic burden on society, with indirect costs of productivity loss being larger than the direct healthcare costs. About the economic value of different pharmacotherapeutic approaches to the management of AR, there is some evidence supporting the cost-effectiveness of levocetirizine as compared with placebo [48]. European studies are required to collect primary data on healthcare resource utilization and costs associated with the different forms of AR.

Allergen immunotherapy

AIT, defined as a prolonged process of repeated administration of extracts of allergens, by subcutaneous or sublingual routes, to patients with a demonstrable allergic disease for the purpose of reducing symptoms, is a recognized intervention in patients not responding to standard pharmacotherapy or in whom pharmacotherapy is contraindicated [8]. The effectiveness of subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) in treatment of patients suffering from AR has been evaluated in a number of randomized-controlled trials, systematic reviews and meta-analyses conducted over the past few decades, both showing clinical evidence of disease modification by decreasing new sensitizations in individuals who were monosensitized, by reducing the development of asthma in patients with AR, and by inducing clinical improvement that persists for years after discontinuation of a successful course of treatment. In addition, AIT can change the course of allergic disease and induce allergen-specific immune tolerance [49]. Recent data reported the efficacy of SCIT also in children with allergies to pollen and house dust mite [11]. Currently, there is a growing interest in evaluating comparative effectiveness of SCIT versus SLIT to identify whether one form of immunotherapy is better than the other. When each is compared with placebo, results of meta-analyses suggest greater efficacy of SCIT [50,51].

Recently, the European Academy of Allergy and Clinical Immunology edited an important position paper on pediatric rhinitis, providing several evidence-based insights on diagnostic and therapeutic aspects. In this paper, SLIT is presented as an effective treatment for grass pollens and house dust mite AR, labeling the force of this statement as grade A, according to the system for grading clinical recommendation in evidence-based guidelines [3].

In controlled clinical trials, SLIT appears to be safe than SCIT, and its side effects are generally mild, limited to the first doses and usually restricted to the upper airways and gastrointestinal tract. Systemic reactions do occasionally occur with SLIT but much less frequently than with SCIT, and, to date, no fatal or near-fatal reactions have been reported [49]. SCIT is generally well tolerated, even in children, but it has to be administered by trained staff and full resuscitation facilities must be available because it is associated with systemic reactions [52].

Cost-effectiveness of AIT for respiratory allergy has been recently evaluated; the available data support the cost-effectiveness of immunotherapy as compared with pharmacotherapy for allergic rhinoconjunctivitis, SCIT as compared with pharmacotherapy for AR and immunotherapy as compared with pharmacotherapy for AR and asthma [53]. More studies are needed for economic evaluations based on high-quality prospective and long-term clinical studies comparing immunotherapy with pharmacotherapy in real-life practice and comparing SLIT with SCIT.

Research in immunotherapy continues in several directions. Standardization of allergen extracts to make available products with consistent potency has dramatically increased the reliability of commercially available extracts. Studies have demonstrated the safety and efficacy of shortening the dose escalation phase with schedules for rush and ultra-rush immunotherapy [49]. Investigators have also been studying adjuvants to improve efficacy of immunotherapy as well as modified allergens, either through chemical manipulation producing allergoids or directly producing recombinant proteins or significant peptides, to reduce the risk of serious reactions to immunotherapy. Other routes of administering allergen extracts are also being studied, as well as the use of immunotherapy for other allergic diseases such as food allergy. The addition of omalizumab or Toll-like receptor (TLR) agonists to standard SCIT has been evaluated with promising results [54].

Emerging options for the treatment of AR

New insights in current therapies

As mentioned before, oral H_1 receptor antagonists are currently the first line of treatment for acute symptomatic relief of AR, positively affecting all symptoms, expect nasal obstruction. Distribution of histamine receptors other than H_1, in particular of type H_3, has been recently demonstrated in human nasal tissue in close proximity of H_1 receptors. Thus, clinical studies of H_3 antihistamines with enhanced decongestant effects have been conducted in patients with AR. A potent H_3 receptor antagonist (PF-03654746) with significant selectivity for the H_3 receptor over the H_1, H_2 and H_4 receptors has been shown to reduce allergen-induced nasal symptoms, including obstruction, in combination with an oral H_1 receptor antagonist (fexofenadine) [55]. Another novel selective H_3-receptor antagonist (JNJ-39220675) despite reducing nasal congestion in patients with allergen-induced AR showed a limited potential anti-inflammatory effect [56].

Additional novel compounds being studied include H_4 antihistamines with anti-inflammatory effects in AR, atopic dermatitis and other diseases [16]. Histamine receptor antagonism might be a novel therapeutic strategy to further explore in patients with AR.

Compelling evidences, arising from recent studies, have shown that preseasonal prophylactic treatment of AR with H_1 antihistamines is effective in suppressing nasal symptoms and expression of histamine H_1 receptor gene expression in the nasal mucosa of patients with pollinosis; these preliminary results need to be further investigated [57].

INCSs are only available on aqueous formulations and their use may be challenging in certain patient populations, including children and adolescents, who complain certain sensory perceptions such as the 'wet feeling in the nose' and the 'dripping down the throat' associated with aqueous nasal sprays. Recently, two

dry intranasal formulations of corticosteroids received FDA approval, beclomethasone and ciclesonide [58,59]. A nonaqueous hydrofluoroalkane-propelled beclomethasone dipropionate nasal aerosol with an established efficacy and safety profile has been approved to treat the nasal symptoms associated with AR both in adult and adolescent patients [60]. Ciclesonide is currently available for asthma therapy, but its efficacy and safety have been demonstrated also in patients with AR [61–64], having the potential to be a valuable new treatment option.

New therapeutic options in the field of immunotherapy are in progress. As mentioned before, standardization of allergen extracts, as well as the availability of modified allergens or in combination with adjuvants as TLR agonists, has allowed to improve the therapeutic efficacy, reducing the risks associated with immunotherapy [54]. The use of omalizumab before starting AIT improved the safety of SCIT by reducing systemic allergic reactions, also relieving allergic airway inflammation and leading to decreased symptoms [54]. Furthermore, in order to improve the target allergen to treat, many steps forward have been made thanks to the current availability of microarrayed recombinant allergens for diagnostic tests. Mostly in patients sensitized to profilins and other cross-reacting molecules, component-resolved diagnosis might modify AIT prescription by improving the identification of the disease-eliciting allergen sources, especially pollens [65]. Finally, in addition to SCIT and SLIT, alternative methods of delivery such as nasal, intralymphatic or epicutaneous are still being studied [54].

Anti-IgE

Omalizumab has been reported to be effective for the treatment of patients with seasonal and persistent AR. Many clinical trials have demonstrated that omalizumab improved symptoms, quality of life and rescue medications needed in patients with AR [66,67]. A meta-analysis of randomized clinical trials assessed the efficacy and safety of omalizumab in patients with poorly controlled AR. A statistically significant reduction in the daily nasal symptom severity score and in daily nasal rescue medication score was observed [68]. According to this evidence, omalizumab may provide a new treatment strategy for AR. In particular, omalizumab may benefit patients with moderate–severe AR with proven allergen-specific antibodies who have no sufficient response to recommended medications. Moreover, treatment with omalizumab would be beneficial in patients with comorbid AR and asthma [8,69]. The recently published European Academy of Allergy and Clinical Immunology position paper on pediatric rhinitis considers omalizumab as a possible treatment for patients with AR and moderate-to-severe asthma, when other recommended therapies are ineffective [3]. However, the use of omalizumab for the treatment of AR has not been approved by the FDA and the high cost limits its chronic application for persistent AR.

Future therapies currently under investigation

TLR-mediated signaling induces proinflammatory responses and can both suppress and exacerbate allergic responses in the airways. TLR targeting may arrest the disease progression of an allergic response either by induction of tolerance to allergens and/or by redirecting the immune response away from the airways. As mentioned before, TLR agonists, such as TLR4 and TRL9, have been widely employed as adjuvants in some SCIT formulations, showing strong immunomodulatory effects [70]. Intranasal administration of TLR7 agonist (AZD8848) and TLR8 agonist (VTX-1463) has revealed efficacy in the relief of symptoms in AR patients. Indeed, most of our knowledge regarding TLRs agonists/antagonists are from experimental studies, even if the first results hold considerable promise [70].

Suplatast tosilate is a novel immunomodulatory compound actually available in Japan, acting as antiallergic-selective Th2 cytokine inhibitor. Its mechanism of action is currently under investigation, even if recent studies highlighted an inhibitory role on the GATA-3/IL-5 signaling pathway [71].

Unmet clinical needs for current pharmacotherapy of AR are related to the fact that many patients may still suffer some residual symptoms despite best available treatment. It has been hypothesized that residual symptoms could be due to allergic mediators directly affecting nasal neuronal hyperresponsiveness by activation of the ion channel transient receptor potential vanilloid 1 (TRPV1), which is considered a mediator of itch in AR. Unfortunately, a highly selective and potent intranasal formulation of a TRPV1 antagonist (SB-705498) failed to demonstrate its clinical efficacy, suggesting a redundant mechanism of action for this class of compounds [72].

Interest in inflammation after allergen exposure has recently shifted attention on different mediators than histamine and leukotrienes. Prostaglandin D_2 (PGD2), an arachidonic acid metabolite, has proinflammatory effects through interactions with the chemoattractant receptor homologous molecule on TH_2 cells (CRTH2), a 7-transmembrane type G protein–coupled receptor selectively expressed on TH_2 cells, T cytotoxic type 2 cells, eosinophils and basophils. CRTH2 mediates chemotactic activity by recruiting and activating TH_2 lymphocytes and eosinophils and therefore it plays an important role in AR. A recent preliminary trial demonstrated the efficacy of oral CRTH2 antagonist (BI 671800) as a treatment for seasonal AR with a favorable safety profile [73]. Another CRTH2 antagonist, named OC000459, has been not only demonstrated to promote nasal and ocular symptoms in allergic subjects exposed to grass pollen, but also to reduce airway inflammation and improve lung function in moderate persistent asthma [74].

There is evidence that adenosine plays a role in the pathogenesis of asthma and rhinitis. Elevated levels of adenosine have been found in bronchoalveolar lavage fluid and exhaled breath condensate of patients with allergic asthma. Increased formation of adenosine can also occur in chronically inflamed upper airways as recently observed in exhaled breath condensates from patients with AR. Unfortunately, no recent studies are available regarding selective agonist or antagonist for adenosine receptor subtypes, even if they may represent valuable targets for drug development in AR [75].

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No progress has also been made with regard to other promising molecules, such as rofleponide palmitate, β-tryptase and phosphodiesterase-4 inhibitors [76].

IL-17 and IL-23 are both cytokines predominantly involved in Th17 cells pathway; they have currently been associated with the development of various inflammatory diseases, such as psoriasis, arthritis and inflammatory bowel disease. It has been recently established a more pronounced pathogenic role for IL-23 only in a mouse model of AR, but their immunomodulatory effect in the pathogenesis of allergic diseases is still controversial [77].

Epidemiological studies and recent experimental research support the idea that microbial stimulation of the immune system can influence development of tolerance to innocuous allergens [78]. In several *in vitro* and *in vivo* studies, it is reported that probiotics can determine a wide array of immune effects potentially in contrast with the atopic constitution. *Bifidobacteria* and *Lactobacilli*, which induce immunoregulatory mechanisms in the host, ameliorate aberrant immune responses in the setting of allergy [79]. Deficient exposure to these microbes might explain the increase in immunological disorders. The mechanisms of action of probiotics in respiratory allergy have been extensively described [80]. In particular, it has been demonstrated that probiotics trigger the production of IFN-γ by blood leukocytes [80]. Moreover, ingestion of probiotics enhance IL-12 production by blood lymphocytes after stimulation of T-cell mitogens [80]. All these effects lead to a higher Th_1/Th_2 ratio [80], promoting the shift to Th_1-type immunity, thus favoring the suppression of Th_2-induced allergic inflammation [79,80]. All these data make the gastrointestinal microbiota composition of particular interest as it provides a major source of immune stimulation and that seems to be a prerequisite for the development of oral tolerance.

A meta-analysis described the results of 12 randomized clinical trials with probiotics in AR [81], showing some improvements in clinical symptoms and in quality of life, and suggesting a beneficial effect of the consumption of specific probiotic strains belonging to the *Lactobacillus casei*, *Bifidobacterium longum*, *Bifidobacterium lactis* or *Lactobacillus paracasei* species [82]. Although immunological changes on allergic inflammation of nasal mucosa in individuals affected by AR have been demonstrated after probiotic supplementation, the evidence of a beneficial effect of probiotics on allergic respiratory symptoms is still conflicting and their routine use as an additive therapy in patients with AR cannot be recommended [83–85].

Mucosal barrier disorders play an important role in the pathogenic mechanism of the AR. A new nonpharmacological approach for its treatment uses liposomes, which consist of phospholipids that make up 75% of the protective nasal surfactant layer. A number of recent studies practically demonstrate that the symptoms of seasonal AR are effectively reduced by nasal application of liposomes with efficacy comparable to the established cromoglycate combination therapy. Further studies need to confirm their role as a comparable alternative to pharmacological treatment [86].

Finally, some preliminary findings of a beneficial effect of glycirrhetic acid in the treatment of AR in children have been recently reported in literature and need to be further investigated [87].

Conclusion

AR represents today a global health problem, currently affecting up to 30% of the general population, with a continuously increasing prevalence and significant comorbidities and complications. Clinical practice guidelines have been implemented over the past 15 years, better improving the care of patients with AR and offering a wide array of pharmacotherapeutic options with relatively safe side effect profiles for the management of AR. Many steps forward have also been made to improve outcome in the pediatric population.

Expert commentary

Establishing a correct diagnosis is crucial to increasing the degree of successful outcome of AR. Existing test modalities (skin testing and ImmunoCAP-specific IgE blood test) provided a significant improvement to diagnose allergy. The current availability of microarrayed recombinant allergens for diagnostic testing is likely to change not only the diagnostic landscape but also the therapeutic one, especially in the field of immunotherapy.

The concept of 'united airways disease' is a cornerstone of ARIA guidelines and has relevant implications for the diagnostic and therapeutic management of respiratory allergy, especially AR and asthma. ARIA document has clearly underlined, throughout these last 10 years, the role of AR as a risk factor for asthma and suggests to always consider bronchial involvement in patients presenting with AR. On the other hand, even the Global Initiative for Asthma (GINA) advises to evaluate asthmatic patients for nasal involvement as well. In clinical practice, therefore, it should be now clear that, when evaluating a patient presenting with AR, doctors should perform respiratory function test or at least pose questions to evaluate a possible concomitant bronchial involvement; on the other hand, patients suffering from asthma should always receive a nasal treatment as well.

Despite considerable progress in therapeutics, to date, the mainstay of current treatment strategies of AR includes allergen avoidance, pharmacotherapy and allergen-specific immunotherapy, as defined by ARIA guidelines for both adults and children. Although they should be considered as a guide, physicians need to tailor these general recommendations to individual patients given their differences in environments (local circumstances, population characteristics and healthcare system regulations) and in responses to allergens and medications.

Five-year view

The current scientific research is aimed at identifying new therapeutic targets with the purpose of modifying the immune response to allergens. In this direction are designed the studies on immunotherapy and biological drugs, such as omalizumab. Understanding of inflammatory mechanisms is very promising,

but further studies are needed to confirm these early experiences and to translate them in clinical practice.

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Key issues

- The prevalence of allergic rhinitis (AR) is increasing both in adult and pediatric populations and is associated with significant morbidity, comorbidities and complications.
- A close structural and functional relationship has been demonstrated between the upper and lower airways, with profound implications in clinical and therapeutic.
- Current knowledge suggests an integrated therapeutic approach toward AR and asthma.
- The mainstay of current treatment strategies of AR includes allergen avoidance, pharmacotherapy and allergen-specific immunotherapy, as defined by AR and its impact on asthma guidelines.
- New formulations of available drugs, recently discovered molecules, immunological targets are currently under investigation and represent a new frontier in allergy management.

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