

New Pharmacologic Strategies for Allergic Rhinitis

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Opinion statement

Current treatment guidelines for allergic rhinitis (AR) recommend a stepwise therapeutic approach that combines patient education with specific allergen avoidance, symptomatic pharmacotherapy, and allergen immunotherapy (AIT). The available pharmacological strategies provide suboptimal symptom relief in patients with moderate-to-severe disease who continue to experience symptoms while treated, even on multiple therapies. The development of new symptomatic drugs with improved pharmacokinetics and safety has recently opened new perspective in the field of AR treatment, overcoming current limitations and increasing compliance to therapy. However, the ultimate research goal is beyond symptomatic treatment, and is mainly directed at modifying the immune response to allergens. In this direction, promising advances are expected in the fields of AIT and biological drugs. Significant research efforts are also focused on new therapeutic targets involved in the Th₂-driven pathway inflammation.

Introduction

Allergic rhinitis (AR) represents an inflammatory disorder of the nasal mucosa initiated by an immunoglobulin E (IgE)-driven response to inhaled allergens in sensitized individuals [1]. Currently affecting up to 40 % of the population worldwide including both adults and children, AR represents a global health problem [1, 2••]. AR symptoms include nasal congestion/obstruction, rhinorrhea, itchy nose, and/or sneezing, in a variable degree of severity and duration. Additional

symptoms include ear fullness, itching and tearful eyes, post-nasal drip, and cough. Fatigue, reduced quality of sleep, impaired concentration, and reduced productivity or school performance are all general symptoms associated with AR and if left untreated, it may significantly affect quality of life (QoL) [3]. The disease burden includes also various comorbidities, including asthma; in particular, AR is an independent risk factor for the development of asthma [4].

ARIA guidelines currently recommend a therapeutic approach that combines patient education with specific allergen avoidance, symptomatic pharmacotherapy (mainly H₁-antihistamines and intranasal corticosteroids (INCS)) and allergen immunotherapy (AIT) [1, 5].

Despite the availability of effective therapy, AR continues to be associated with a high clinical and economic burden [6]. An increasing number of patients report a moderate-to-severe disease and persistent symptoms,

and are frequently polysensitized, thus complicating allergen avoidance and requiring ongoing treatment [7]. Moreover, the evolving AR phenotype also recognizes the presence of mixed forms (both allergic and non-allergic rhinitis) and an estimated 10–20 % of patients suffering from severe chronic upper airway disease (SCUAD) [8].

To fill this medical need, new and emerging pharmacologic strategies for AR have shown promising results.

Current treatment

Management strategies for AR require a stepwise approach which may include environmental control, pharmacologic therapies, and AIT [1, 5].

Allergen avoidance

The identification and the subsequent avoidance of known offending allergens, when possible, is one the components of allergy treatment. Unfortunately, complete avoidance is rarely possible, especially for perennial and/or outdoor allergens, and it is still not supported by good evidence [9].

Pharmacologic treatment

Given the IgE-mediated nature of inflammation in AR, current pharmacotherapy aims to improve symptoms by targeting receptors of bioactive mediators or by reducing inflammation. The major pharmacological agents used in management of AR are H₁-antihistamines and INCS. Additional pharmacological treatments include leukotriene receptor antagonists, systemic corticosteroids, anticholinergics, nasal decongestants, and mast cell stabilizers, all used to a lesser extent [1, 10]. The strength of the evidence upon which ARIA treatment recommendations are made is shown in Table 1.

H₁-antihistamines

ARIA guidelines recommend the use of oral and topical second-generation, non-sedating, H₁-antihistamines alone for mild-to-moderate AR and in combination with INCS for moderate-to-severe disease [1, 2••, 11••]. In AR, H₁-antihistamines are particularly effective in reducing rhinorrhea, itching, sneezing, and vasodilation, with little or no effect on nasal congestion [1]. Pharmacological characteristics of second-generation H₁-antihistamines are preferential binding to peripheral H₁-receptors, which results in minimal penetration of the central nervous system; minimal antiserotonergic, anticholinergic, and α -adrenergic blocking activities; and minimal sedative and performance-impairing effects [12]. These features support second-generation H₁-antihistamines as a safe and effective therapeutic option, even for pediatric patients [2••, 11••].

Topical formulation of second-generation antihistamines, including intranasal and intraocular antihistamines, can be utilized on an as needed basis given their fast onset of action. Topical administration has the advantage to provide

Table 1. Strength of evidence for current pharmacological treatment in AR. Adapted by [1]

	Intermittent AR		Persistent AR	
	Adults	Children	Adults	Children
H1-antihistamines				
Oral	A	A	A	A
Intranasal	A	A	A	A
Intraocular	A	A	B	B
Intranasal corticosteroids	A	A	A	A
Oral steroids	A	B	B	B
Leukotriene receptor antagonists	A	A	A	A
Cromones				
Intranasal	A	A	A	B
Intraocular	A	A	B	B
Intranasal decongestant	C	C ^a	C	C ^a
Anticholinergic			A	A
A At least one randomized controlled trial, B at least one study or extrapolated from randomized controlled trial, C nonexperimental descriptive studies				
^a Age >12 years				

specific symptom relief and limit escalation in systemic therapy to control nasal and ocular symptoms [10, 11••].

Intranasal corticosteroids

INCS are recommended as first-line treatment for moderate-to-severe AR [1, 2••, 11••]. INCS represent the most effective medication class for the treatment of AR and are useful in relieving symptoms of nasal pruritus, rhinorrhea, sneezing, and congestion, addressing the inflammatory component of the disease [13, 14]. They also control the ocular symptoms of rhinoconjunctivitis [11••].

A number of glucocorticoid compounds are available for intranasal use in both aerosol and aqueous formulations and they are all generally well tolerated [15]. A large number of studies have established that there are no relevant differences in efficacy between all of the available compounds [16]. In pediatric patients, the most commonly cited parental concerns are possible side effects due to systemic absorption including suppressed growth and hypothalamic-pituitary-adrenal (HPA) axis suppression. Most of INCS compounds studied in pediatric patients have not demonstrated any adverse effects on cortisol levels, the HPA axis, or linear growth velocity in young children [17]. The newer once-daily products are strongly preferred over first-generation corticosteroids (e.g., dexamethasone), owing to their good anti-inflammatory activity targeting active agents directly onto the nasal mucosa, limited bioavailability (to less than 1 %, due to inactivation of swallowed portion by first pass metabolism), and increased lipophilicity [18].

Leukotriene receptor antagonists

Currently, leukotrienes inhibitors are recommended as add-on therapy of AR; in particular, montelukast is the only leukotriene inhibitor that is Food and Drug Administration (FDA) approved for AR in adults and children [11••]. Although it has inferior efficacy compared to H₁-antihistamines and INCS, montelukast has been reported to relieve all of the symptoms of AR, including nasal congestion [19–21]. For this reason, combination therapy with oral H₁ antihistamines or INCSs is a more effective strategy than monotherapy in the treatment of AR [1, 2••, 11••]. Because it is also effective in reducing bronchial symptoms in asthmatic patients, this agent is a reasonable choice for patients with concurrent asthma and AR [2••, 11••].

Other therapies

Additional drug treatment options include oral and nasal decongestants, nasal anticholinergics, cromones, and systemic corticosteroids [1]. Because of adverse effects, only a short course of nasal decongestants or oral steroids may be recommended in patients with persistent nasal obstruction despite INCS. In patients with persisting rhinorrhea, add-on topical anticholinergics are the treatment of choice. Finally, nasal cromones may be an alternative choice in small children and in pregnancy [11••, 22].

Allergen immunotherapy

Allergen immunotherapy is an immune-mediated biological treatment, inducing a long-lasting immunological and clinical tolerance toward the causal allergen. AIT acts by modifying Th₂-driven responses through different mechanisms, including through increased IgG4 blocking antibodies and increased production of T regulatory (CD4⁺ Foxp3⁺) cells that produce immunomodulatory cytokines (IL-10 and transforming growth factor [TGF]- β) [23, 24].

AIT is indicated for the treatment of moderate-to-severe intermittent or persistent symptoms of AR, especially in those who do not respond well to pharmacotherapy [1, 2••, 11••]. Subcutaneous injection (SCIT) has been the predominant method of administration. Over the last two decades, sublingual application (SLIT) of the extracts has increased and is now the dominant approach in several European countries. SLIT can be differentiated into SLIT drops and SLIT tablets [25••]. 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 [26]. 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 [27].

Recent systematic reviews have consistently shown that both SCIT and SLIT provide effective treatment for AR, results by improving nasal and ocular symptoms and by reducing medication need [24, 26, 28–31]. AIT also improves the QoL, prevents the progression of AR to asthma, and reduces new sensitizations. In contrast to pharmacotherapy, the clinical benefits of AIT appear to be sustained after cessation of treatment [23, 24]. Being the only disease-

modifying treatment for AR, AIT also owns a clear pharmacoeconomic advantage over other therapies in terms of cost-effectiveness [24].

Emerging therapies

The development of new symptomatic drugs with improved pharmacokinetics and safety has recently opened new perspective in the field of AR treatment, overcoming current limitations and increasing compliance to therapy. However, the ultimate research goal is beyond symptomatic treatment, and is mainly directed at modifying the immune response to allergens. In this direction, promising advances are expected in the fields of AIT and biological drugs. Significant research efforts are also focused on new therapeutic targets involved in the Th₂ pathway inflammation. Emerging therapies for AR are summarized in Table 2.

New and investigational pharmacotherapy

Intranasal combination therapy

A new AR treatment is a novel intranasal formulation of a topical H₁-antihistamine (azelastine hydrochloride) and a corticosteroid (fluticasone propionate) combined in a single device (MP29-02, WHO ATC R01AD58). Taking advantage of two active agents from different drug classes with overlapping and

Table 2. Emerging therapies for AR. Adapted from [10]

Compound	Class and mechanism of action	Stage of development in allergic rhinitis
Azelastine hydrochloride + Fluticasone propionate (MP-2902)	Histamine H ₁ receptor antagonist/Corticosteroid	Commercialized
Mometasone furoate + Levocabastine hydrochloride (CKD-342)	Histamine H ₁ receptor antagonist/Corticosteroid	Phase III
SQ HDM SLIT tablet	SLIT Tablets of HDM Allergen Extracts	Phase III
STG320	SLIT Tablets of HDM Allergen Extracts	Phase III
Asapirant	Prostaglandin D ₂ antagonist	Phase III
PF-03654746	Histamine H ₃ receptor antagonist	Phase II
PF-03654764	Histamine H ₃ receptor antagonist	Phase II
GSK835726	Histamine H ₁ /H ₃ receptor antagonist	Phase II
GSK1004723	Histamine H ₁ /H ₃ receptor antagonist	Phase II
AZD8848	TLR agonist	Phase II
Omalizumab	Humanized anti-IgE monoclonal antibody	Phase II (commercialized for asthma)

HDM house dust mites, *SLIT* sublingual immunotherapy, *TLR* Toll-like receptor

complementary modes of action [32, 33], MP29-02 acts on both the early and late allergic responses, including (among others) also an inhibitory effect on mast-cell degranulation and owns the potential of covering all the symptoms of AR [32]. The evidence of efficacy and safety of MP29-02 have been established in controlled clinical trials as well as in real-life studies, showing a rapid onset of action and a potent anti-inflammatory effect combined a good tolerability profile [33–37]. Moreover, MP29-02 exceeded for the first time the efficacy of an intranasal corticosteroid (fluticasone propionate) alone, representing a promising step beyond over the current first-line therapy of AR [35, 36].

Being approved by the Food and Drug Administration (FDA) in 2012 and by European Medicines Agency (EMA) in 2013 for adults and children 12 years of age and older, MP29-02 is currently indicated for the relief of symptoms of moderate-to-severe seasonal and perennial AR, if monotherapy with either intranasal H₁-antihistamines or INCS alone is not considered sufficient [38]. In 2015, FDA approved the use of MP29-02 for the relief of symptoms of seasonal AR in patients 6–11 years of age who require treatment with both components [39]. However, long-term follow-up studies both in adults and children are still lacking.

In the wake of these promising findings, another fixed-dose combination therapy of mometasone furoate and levocabastine hydrochloride (CKD-342) is currently under investigation in a phase III clinical trial (NCT02498509) for the treatment of perennial AR [40].

New antihistamines

The evidence of histamine receptors of type H₃ in human nasal tissue, in close proximity of H₁ receptors, has disclosed their potential applications in AR treatment [41]. Specifically modulating vascular contractility, the H₃ receptor blockade might have an advantage in targeting nasal congestion with a superior safety and efficacy profile to the currently available oral decongestants, administered with or without H₁-antihistamines [10].

The potential of several H₃ antihistamines (oral PF-03654746 and PF-03654764, intranasal GSK1004723, and oral GSK835726) has been recently tested [42–45]; only PF-03654746, a highly selectively potent H₃ receptor antagonist, was effective in reducing allergen-induced nasal symptoms, including nasal congestion, in combination with fexofenadine [42].

Anti-IgE therapy

Omalizumab is an IgE inhibiting recombinant humanized monoclonal antibody, currently approved for the treatment of uncontrolled allergic asthma and chronic spontaneous urticaria [46]. It acts specifically binding serum-free IgE and preventing binding of IgE with its high-affinity FcεRI receptors on mast cells, basophils, antigen-presenting cells, and other inflammatory cells [47]. The reduction of free IgE levels is followed by the downregulation of FcεRI expression on inflammatory cells; in particular, the reduction of receptor density on dendritic cells may lead to a diminished allergen presentation to T cells and attenuation in the Th₂-mediated allergic pathway [48, 49]. Thanks to these effects, omalizumab decreases pro-inflammatory mediator release, thus globally reducing allergic inflammation [50].

Several randomized controlled trials reported the therapeutic efficacy of omalizumab in AR, alone or in combination with AIT, both in adults and children [51–61]. A recent systematic review and meta-analysis of all these trials showed that treatment with omalizumab provides a significant clinical improvement (in daily nasal symptom severity score) and a reduction of rescue medication use compared with placebo, with a good safety profile [62••]. Despite holding good potential for the treatment of AR, in particular for patients with difficult-to-treat moderate-to-severe AR with or without comorbid severe asthma, omalizumab has not been approved due to its high cost.

The validated approach of targeting and modulating IgE inflammatory pathway has stimulated the production of several new anti-IgE antibodies: ligelizumab and MEDI4212, with higher affinity FcεRI receptors than omalizumab; XmAb 7195, with the ability to simultaneously sequester free IgE, suppress B cell differentiation into IgE-secreting plasma cells, and clear IgE from circulation via high FcγRIIb binding; and the latest anti-CεmX, owing the potential to directly targeting IgE-expressing B lymphocytes, are currently at early stage of clinical development [63–65].

Advances in allergen immunotherapy

Following a body of evidence of efficacy and safety both in adults and children, standardized SLIT tablets for grass pollen allergy have recently gained the title of pharmacological treatment [25••]. In this context, several trials have recently evaluated the efficacy and safety of house dust mite (HDM) SLIT tablets, leading to the approval of two different products in Europe and Australia [66–69]. While safety profile has already been assessed in both adults and children [69], efficacy of HDM tablets in pediatric population with AR is still lacking.

In order to improve the efficacy and safety of AIT, novel strategies are currently under investigation and include bypassing IgE binding and targeting allergen-specific T and B cells through different approaches [24].

The use of hypoallergenic recombinant allergen derivatives and synthetic peptide immuno-regulatory epitopes (SPIREs) are aimed to both reduce vaccine allergenicity and improve immunogenicity of SCIT [70]. SPIREs are a new class of product of AIT designed to directly bind to MHC II class molecules and upregulate Treg cells without causing the cross-linkage of IgE [71]. SPIREs for cat, HDM, grass, and ragweed are currently undergoing phase 2 clinical trials with promising results in AR subjects [70, 72, 73], while other allergens as birch, Japanese cedar, and *Alternaria alternata* are still in preclinical development [70]. Coupling allergens to stimulators of the innate immune response, as Toll-like receptors (TLRs), also showed promising insights. In particular, TLR4 (monophosphoryl lipid A) and TLR9 (CpG oligonucleotide) have been employed as adjuvants in some SCIT formulations, given their strong immunomodulatory effects [74]. Allergen complexed to viral and bacterial DNAs sequences or coupled to DNA rich in nonmethylated CG motifs (CpG) have been demonstrated to be highly immunogenic, acting to powerful Th₁ inducers through TLRs pathways [75]; this novel experimental approach recently demonstrated a beneficial impact on allergic symptoms, representing an interesting therapeutic strategy in AIT [76]. As mentioned before, immunological and clinical effects of combining SCIT treatment

with omalizumab resulted in an improved safety profile and better efficacy of SCIT with adequate AR symptom control [62••].

Finally, new routes of administration, including epicutaneous and intra-lymphatic administration, are under active investigation [77•].

Other therapeutic targets

Prostaglandin D₂ (PGD₂) is recognized as an important lipid mediator in the pathogenesis of allergic inflammation such as observed in AR or asthma. The PGD₂ receptor, CRTH2, is expressed on basophils, eosinophils, and Th₂ lymphocytes and mediates chemotactic activity [78]. In recent experimental studies, the antagonist blockade of CRTH2 attenuated the development of nasal inflammation in allergen-induced AR models in mice [79–81]. These results suggest that targeting CRTH2 with a specific antagonist potentially may have benefits in AR.

Conclusions

The recommended stepwise therapeutic approach of AR combines patient education with specific allergen avoidance, symptomatic pharmacotherapy, and AIT. Current pharmacological strategies have been demonstrated to provide suboptimal symptom relief in patients with moderate-to-severe disease and with mixed phenotypes. The latest therapeutic innovation in the field of AR treatment aim to overcome the limitations of available standard pharmacological treatment. New insights into current therapy have been provided with the development of new AR drug class, a novel intranasal formulation of a topical H₁-antihistamine, and a corticosteroid combined in a single device with improved efficacy and safety, even in pediatric population. Recent evidence support its position as a drug of choice for AR more difficult-to-treat cases. However, the ultimate research goal is mainly directed at modifying the immune response to allergens and prevent the progression of AR toward asthma. In this direction, new AIT formulation and new drugs that target IgE and the molecules involved in the Th₂-mediated pathways of allergic inflammation hold good potential as new therapeutic targets.

Compliance with Ethical Standards

Conflict of Interest

Amelia Licari declares that she has no conflict of interest. Gianluigi Marseglia declares that he has no conflict of interest. Giorgio Ciprandi declares that he has 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.

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