

EXPERT
REVIEWSFocusing the mechanism
of action to dissect the
different treatments of
respiratory allergy*Expert Rev. Clin. Immunol.* Early online, 1–9 (2015)**Cristoforo Incorvaia¹,
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The treatment of respiratory allergy is based on several drugs with different mechanisms of action, which encompass an effect only on symptoms, limited factors of inflammation or the whole process of inflammation. Dissecting the different treatments by their mechanism of action is relevant for the management of allergic patients. Corticosteroids, administered as nasal sprays in rhinitis or by inhalation devices in asthma, and allergen immunotherapy (AIT) are the most effective treatments for respiratory allergy, achieving the control on inflammation by a number of cellular and molecular mechanisms. What distinguishes corticosteroids from AIT is the duration of clinical outcomes that ends with treatment withdrawal for the former but persists after stopping for AIT, due to its disease-modifying effect.

KEYWORDS: allergen immunotherapy • antiinflammatory action • asthma • corticosteroids • drug treatment
• respiratory allergy • rhinitis • symptomatic effect

Respiratory allergy, clinically expressed as rhinitis or asthma, has a very high prevalence that results in a dramatic impact on social and individual aspects [1–5]. International guidelines are available, indicating the goals of medical treatment, which consist of achieving in each patient the best possible control of the disease and a satisfactory quality of life (QoL) in both rhinitis [2] and asthma [6]. These aims may be pursued by three main interventions: allergen avoidance, pharmacotherapy and allergen-specific immunotherapy. Also, recent data highlighted that regular physical activity provides beneficial effect as a supplementary treatment in patients with asthma and allergies [7].

The approach to avoid the causative allergen would be decisive in therapeutic terms since the complete elimination of the exposure to the allergen abolishes the stimulus to produce specific IgE antibodies and leads to cessation of allergic inflammation and disappearance of symptoms. However, in clinical practice, this approach is often unsatisfactory or impractical for both indoor and outdoor allergens. Avoiding exposure to pollen is almost unfeasible,

although a randomized double-blind study in patients with seasonal allergic rhinitis (AR) reported a possible benefit of the use of nasal filters during exposure to ragweed and grass pollen [8]. Concerning house dust mites, in a Cochrane meta-analysis, the use of acaricides and extensive bedroom-based environmental control programmes was found to be of some benefit in reducing nasal symptoms in mite-allergic patients, while the isolated use of dust-mite-impermeable bedding was not effective [9]. The actual strategy to completely avoid exposure to dust mites is living in high altitude, which is beneficial also in severe asthma [10], but it is obvious that such measure cannot be routinely proposed to mite-allergic patients.

Pharmacotherapy for allergic rhinitis & asthma

In general, pharmacotherapy is considered the cornerstone treatment of AR and asthma. Some drugs are regarded as effective agents for both diseases, as recommended by the Allergic Rhinitis and its Impact on Asthma document [11] and by Global Initiative for Asthma

(GINA) guidelines [6]. This is true for corticosteroids, by topical nasal preparations for AR and inhalation for asthma, for chromones and, to a lesser extent, for leukotriene receptor antagonists (LTRAs), anticholinergics and omalizumab, while antihistamines and nasal decongestants are specific for rhinitis and β 2-agonists are specific for asthma.

Antihistamines

The human histamine H1-receptor is a member of the superfamily of G-protein-coupled receptors. Its gene encodes a 487 amino acid protein with a molecular mass of 55.8 kDa. The histamine H1-receptor, like other G-protein-coupled receptors, may be considered a 'cellular switcher', providing a balance between the inactive or 'off' state and the active or 'on' state [12]. In fact, histamine cross-link sites on transmembrane domains III and V of the histamine H1-receptor to stabilize the receptor in its active conformation, thus resulting in the 'on' position. H1-antihistamines are not structurally related to histamine, thus they do not antagonize the binding of histamine but bind to different sites on the receptor to produce the opposite effect, that defines them as inverse agonists [12].

Antihistamines work on the early-phase symptoms of AR such as itching, sneezing, runny nose and, to a lesser degree, nasal congestion by reducing vascular permeability, mucus secretion and vasodilatation through their competitive binding to histamine H1 receptors. Antihistamines were also shown to act on other receptors, inflammatory cell lines and mediators, this being associated with a number of other anti-inflammatory properties, regulating events such as chemotaxis and survival of eosinophils, expression of adhesion molecules and release of chemokines and Th2-type cytokines from different sources, through receptor-dependent and receptor-independent mechanisms [13].

H1-antihistamines are classified into two groups: the first-generation antihistamines (chlorpheniramine, diphenhydramine and hydroxyzine) cross the blood-brain barrier and bind the H1-receptors on postsynaptic membranes of histaminergic neurons in the central nervous system causing sedation and impaired mental status, while the second-generation antihistamines (cetirizine, loratadine, levocetirizine, desloratadine, fexofenadine, azelastine, ebastine, olopatadine, levocabastine, bilastine, rupatadine and others) usually do not cross the blood-brain barrier and have fewer sedative effects [14]. In addition, first-generation antihistamines have anticholinergic effect like drying of mucous membrane, urinary retention, constipation and tachycardia, which limit their use.

Antihistamines can be administered on demand but regular treatment is more effective in AR. Continuous treatment requires the better safety profile that can be supplied by the second-generation antihistamines, with a low sedation impact, low-performance impairment and no anticholinergic adverse effects [15]. First-generation antihistamines are no longer recommended for AR due to their potential adverse events [14].

Some of the new antihistamines may affect allergic pathogenesis at different levels, showing multiple receptor

antagonism. This concerns rupatadine, that also exerts an additional anti-platelet activating factor effect [16], clinically expressed by reduction of nasal congestion [17], and bilastine, that also acts on nasal obstruction by its anti-inflammatory activity based on inhibition of IL-4 and TNF- α [18,19]. Also topical antihistamines (azelastine, levocabastine and olopatadine) are efficacious on nasal symptoms such as itch, sneezing, and rhinorrhea with rapid onset of action and have the advantage to deliver the drug into the target organ [20].

Intranasal corticosteroids

Nasal steroids are significantly effective on nasal inflammation and congestion and can be used for the treatment of moderate-to-severe AR both in adults and children. Nasal steroids have a good long-term safety, and the agents developed more recently (like mometasone or fluticasone furoate) showed a very low systemic bioavailability and adverse effects usually limited to nasal dryness or blood-tinged secretions [21,22]. However, in patients with concomitant AR and asthma using both inhaled and intranasal steroids (INS), and thus receiving higher doses, it is recommended to monitor the possible systemic side effects [23]. A meta-analysis of randomized, placebo-controlled trials evaluating the efficacy of mometasone furoate nasal spray in patients with AR compared with placebo confirmed a significant effect for nasal congestion, rhinorrhea, sneezing and nasal itching [24]. A novel type of inhaled topical corticosteroids, such as ciclesonide, that once administered are activated on site, have become available. Ciclesonide is a prodrug metabolized by esterases to desisobutyl ciclesonide (des-CIC), an active metabolite with a 100-fold greater affinity for the glucocorticoid receptor [25]. Ciclesonide has demonstrated a targeted activation in the nose and consequently minimal systemic adverse effects, showing a significant efficacy [26]. A favorable effect on asthma symptoms of nasal steroids has also been suggested. Considering the immunological and pathogenic relationship between AR and asthma, it can be hypothesized that reducing inflammation in the upper airway may improve asthma outcome. A meta-analysis evaluated asthma-specific outcomes from randomized, controlled studies on INS in patients with AR, including studies that compared INS with placebo, INS plus orally inhaled corticosteroids to orally inhaled corticosteroids alone, and nasally inhaled corticosteroids to placebo [27]. The subgroup of studies comparing INS to placebo had significant improvements in forced expiratory volume in 1 s, bronchial challenge, asthma symptom scores and use of rescue medication. Nasal inhalation of corticosteroids significantly improved morning and evening peak expiratory flow. Instead, there were no significant changes in asthma outcomes with the addition of INS to orally ICSs.

Combination of topical antihistamine & corticosteroid

Recently, the new approach of combining the topical antihistamine azelastine hydrochloride and the corticosteroid

fluticasone propionate was introduced. In a randomized, double-blind, placebo-controlled trial on patients with seasonal AR, this combination significantly reduced all nasal symptoms, improving the total nasal symptom score by 39% beyond the contribution of fluticasone alone [28]. Other trials versus first-line therapies showed that the combination was twice as effective as azelastine or fluticasone alone, that patients treated with the combination had clinically relevant responses (such as halving of nasal symptom burden) and that the efficacy was sustained long-term compared with fluticasone alone (up to 52 weeks) in chronic rhinitis patients, with 70% of patients becoming symptom free after 1-month treatment [29,30]. This suggests a positioning of such product as first-line treatment for moderate-to-severe AR patients, the majority of whom are uncontrolled by available drugs.

Nasal decongestants

Nasal decongestants such as ephedrine, pseudoephedrine and xylometazoline are potent vasoconstrictors that are very effective on nasal congestion also with fast onset of action. In a placebo-controlled study, a single dose of pseudoephedrine but not of phenylephrine resulted in significant improvement in measures of nasal congestion [31]. Their mechanism of action is related to the activation of α -adrenergic receptor that results in vasoconstriction in the nasal mucosa. If administered orally, they are burdened by several contraindications and side effects (such as insomnia, headache, tachycardia, hypertension and nervousness). Combination of oral antihistamine and decongestant is available, such as cetirizine/pseudoephedrine, that was reported to be significantly more effective than each drug given alone at reducing mean total symptom scores for seasonal or perennial AR [32]. Still, the tolerability issue remains. Nasal decongestants spray must be used only for short-term treatment because they can cause rhinitis medicamentosa and rebound congestion following prolonged use [33].

Mast cell stabilizers

Stabilization of the mast cell membrane reduces the synthesis and release of mediators such as histamine and leukotrienes by mast cells after the binding of IgE antibodies to the FcRI receptor. In patients with AR, intranasal chromones, including sodium chromoglycate and nedocromil, are able to inhibit both the early and the late phase of the allergic reaction and to reduce nasal symptoms. The need of repeated applications (three to four times daily) is a main limitation due to the low patient's compliance, and the effect on AR symptoms is weaker than the other drugs [34]. In the treatment of asthma, chromones are mainly suggested in children because of the concern of side effect of inhaled corticosteroids (ICSs), but two Cochrane meta-analyses on sodium chromoglycate [35] and nedocromil [36] concluded that there is insufficient evidence on their clinical efficacy in childhood asthma.

Inhaled corticosteroids for asthma

According to the GINA guidelines [6], ICS, at increasing dosage according to the severity step, are the mainstay of drug treatment. When asthma is not controlled by low-to-medium dose ICS monotherapy, adding a long-acting β_2 -agonist (LABA) or a LTRA is recommended [37]. Corticosteroids act by anti-inflammatory mechanisms, based on the capacity to modify multiple signal transduction pathways, including suppressing the actions of proinflammatory transcription factors, such as NF- κ B and activator protein 1, enhancing the activity of anti-inflammatory cytokines, including inhibitory molecule for NF- κ B1, IL-10 and IL-12, and switching off the activated inflammatory genes through inhibition of histone acetyltransferase (HAT) and recruitment of histone deacetylases activity (HDACs) to the inflammatory gene transcriptional complex [38]. In particular, in lung inflammation, there is an increased expression of multiple inflammatory genes that is regulated by acetylation of core histones through the action of coactivators with intrinsic HAT activity. Corticosteroids switch off inflammatory genes in asthma through the inhibition of HAT activity and by the recruitment of HDAC2 to the activated inflammatory gene complex [39]. Moreover, corticosteroids activate a number of anti-inflammatory genes and increase the degradation of mRNA that encode some inflammatory proteins. This broad array of actions may account for the striking effectiveness of corticosteroids in complex inflammatory diseases such as asthma and the difficulty in finding alternative anti-inflammatory drugs of comparable efficacy. Pharmacological characteristics that could theoretically optimize ICS effectiveness include a low oral and a high pulmonary bioavailability, high receptor-binding affinity, high protein-binding capacity and a long pulmonary retention time. ICSs differ in terms of their specific pharmacological profiles, and variation in potency among the available ICSs is related to specific differences in pharmacokinetic and pharmacodynamic properties. From a clinical point of view, Adams and Jones overviewed the findings from a number of Cochrane systematic reviews concerning the relative benefits of different doses of beclomethasone dipropionate, budesonide and fluticasone propionate when used to treat children and adults. All ICSs demonstrated a dose-response relationship for efficacy measures, low-to-moderate dose range of each drug showing most of the benefit in mild-to-moderate severity asthma [40]. High doses, corresponding to >1000 mcg/day of beclomethasone or equivalent, are indicated in patients with severe asthma [6].

Systemic corticosteroids

GINA guidelines recommend oral corticosteroids, with 5- to 7-day courses, only in asthma exacerbations or in the step 5 of the disease that is not controlled by maximum treatment [6]. Due to the well-known systemic side effects of corticosteroids, such courses should not be performed >2 times per year. In

AR, oral corticosteroids could be administered as rescue therapy only in patients having severe symptoms, in particular nasal obstruction, not controlled by other treatments. Intramuscular corticosteroids should be avoided [11].

Leukotriene receptor antagonists

Leukotriene B₄ (LTB₄), and cysteinyl leukotrienes, including leukotriene C₄ (LTC₄), D₄ (LTD₄) and E₄ (LTE₄), are a group of arachidonic acid-derived lipid endogenous inflammatory mediators clearly involved in airway inflammation and certain clinical features of asthma. Recent evidence indicates that leukotriene B₄ is particularly important in the development of asthma and that cysteinyl leukotrienes are key mediators of the airway remodeling process [41]. According to a systematic review, LTRAs as monotherapy are less effective than ICS [42], but their addition to treatment may result in a steroid-sparing effect [6]. In patients with AR, elevated levels of leukotriene following challenge with the specific allergen have been shown [43]. LTRAs, such as montelukast, zafirlukast and pranlukast, act against cysteinyl leukotrienes, while LTB₄ antagonists are not yet available. LTRAs are useful also in the treatment of AR, showing a favorable safety and tolerability profile. In controlled trials in children, montelukast was associated to generally mild and transient side effects, which had a rate comparable with placebo [44]. The efficacy of LTRAs in AR has been shown to be similar to that of the antihistamine loratadine in controlled clinical trials, but it seems to be lower than the intranasal corticosteroid fluticasone propionate [45]. Adding LTRAs (such as montelukast) to a second-generation antihistamine may generate an added benefit for AR and also provides a better protection against seasonal impairment in lung function [46].

Anticholinergics

Acetylcholine, through the muscarinic receptor, exerts various physiologic functions relevant in asthma, which include airway muscle tone and mucus gland secretion. These activities are the basis for the use of muscarinic receptors antagonists in the treatment of asthma [47]. Short-acting antimuscarinic agents may be effective alone or in combination with short-acting β -agonists for the relief of acute broncho-constriction. Long-acting antimuscarinic antagonists (LAMA) have emerged as useful in the long-term bronchodilator treatment. LAMA have an important role in the treatment of chronic obstructive pulmonary disease, with clinically significant effects in lung function and other efficacy outcomes, such as exacerbations, health-related QoL, dyspnea, rescue medication use and nighttime/early morning symptoms [48]. Their bronchodilator effect was recently considered also in asthma, in which the use of the LAMA tiotropium in the maintenance therapy of asthma was shown to be effective in some patients with moderate-to-severe asthma who are uncontrolled by combination therapy with ICS and

LABA [49], this being recognized in the update of GINA guidelines [6]. Concerning the use in AR, cholinergic stimulation of nasal glands induces watery secretion. Intranasal anticholinergics are effective in reducing rhinorrhea with minimal side effects, but they have no effects on all the other nasal symptoms. Ipratropium bromide was found as effective as beclomethasone dipropionate in the control of rhinorrhea in children with perennial AR [50].

β 2-Agonists

Short-acting β 2-agonists (SABA) and LABAs are largely used, the former (including salbutamol, fenoterol and terbutaline) as rescue medications and the latter (including formoterol and salmeterol) as maintenance therapy, in the treatment of asthma because of their bronchodilator and bronchoprotective effects. Both types of β 2-agonists are effective bronchodilators due to their ability to relax airway smooth muscle (ASM) by binding to the active site of β 2-adrenoceptors on ASM, which drives a cascade resulting in a number of events contributing to its relaxation [51]. However, the use of these drugs in asthma without ICS has generated some controversy because of their association with increased mortality [52]. Ongoing pharmacogenetics studies might prove useful to assess the variation in response to both SABAs and LABAs that has been observed in patients with polymorphisms in the β 2 adrenoceptor gene (ADRB2) [53]. By assessing the ADRB2 genotype, it could be possible to predict the responsiveness to chronic administration of β 2-agonists. Currently, the GINA guidelines recommend ICS as first-line treatment, reducing the protracted use of β 2-agonists [6].

Omalizumab

Omalizumab is a recombinant humanized anti-IgE antibody that blocks the interaction of IgE with mast cells and basophils, which is approved for the treatment of severe persistent allergic asthma. A large number of trials showed that omalizumab is very effective in patients with severe allergic asthma and also has a good safety profile and pharmacoeconomic advantage due to a reduction in the number of hospitalizations for asthma attacks [54,55]. IgE plays a central role in the pathogenesis of AR, so in addition to asthma, its efficacy has been evaluated in patients with AR. In a large controlled trial on 536 patients with seasonal ragweed-induced AR randomized to receive omalizumab at different doses or placebo, a dose-dependent clinical benefit was reported [56]. Also in patients with perennial AR, omalizumab has been shown to improve symptoms with a parallel reduction in use of antihistamines compared with placebo [57]. A recent systematic review found that omalizumab is statistically significantly associated with nasal symptoms relief, decreased rescue medication use and improvement of QoL in patients with AR inadequately controlled by conventional treatment [58].

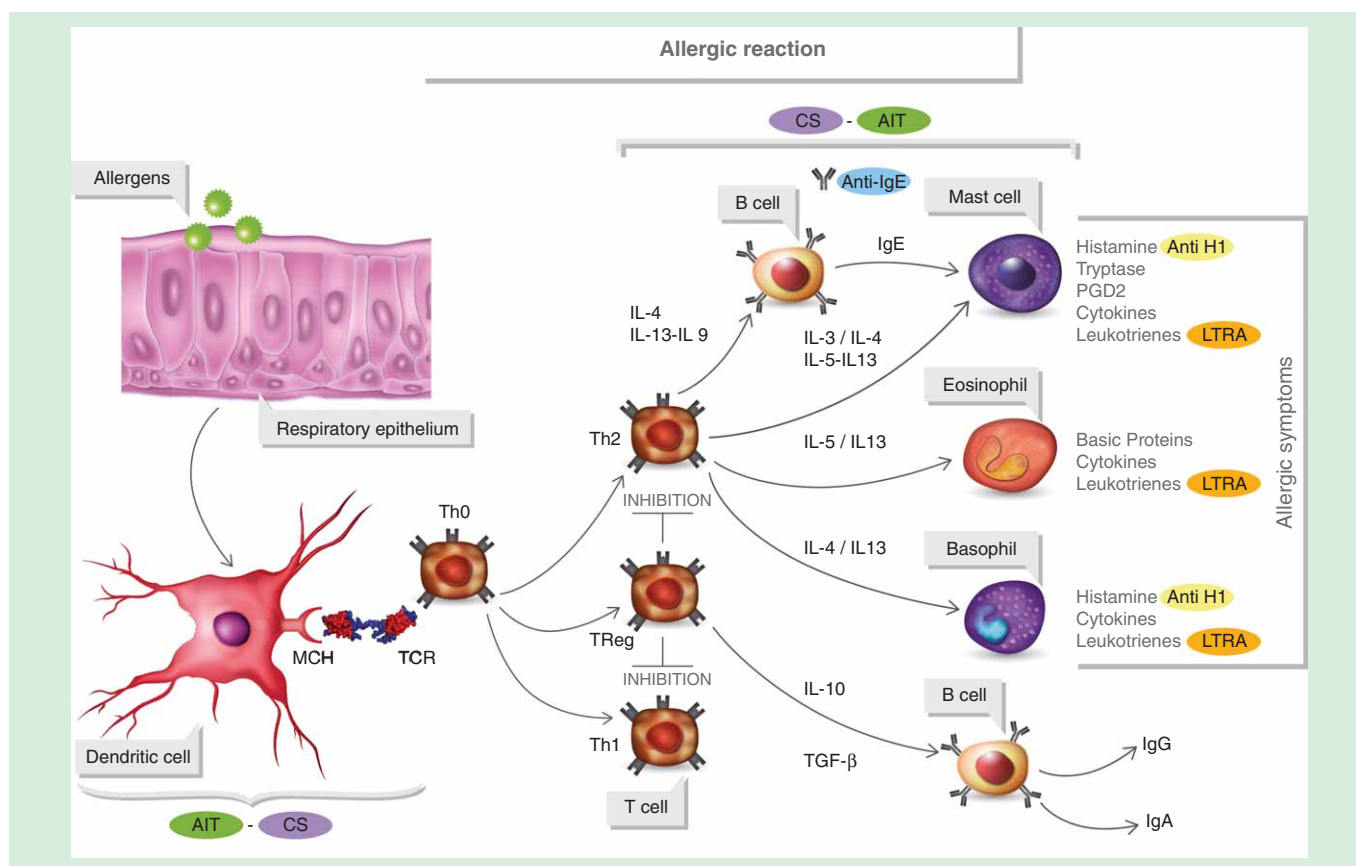


Figure 1. Overview on the mechanisms of action of the different drugs in respiratory allergy.

AIT: Allergen immunotherapy; CS: Corticosteroids; LTRA: Leukotriene receptor antagonists.

Specific allergen immunotherapy

Specific allergen immunotherapy (AIT) is the only disease-modifying treatment for AR considering its ability to alter the Th2-biased immune response, while the pharmacotherapy acts only on symptoms [59,60]. The capacity of AIT to improve the symptoms of respiratory allergy and decrease the consumption of drugs is clearly shown by meta-analyses that included a large number of randomized, double-blind, placebo-controlled trials [61]. The clinical effects of AIT persist, due to the modification of the immunological response to the administered allergen, also after discontinuation of treatment [62]. AIT also reduces the risk of asthma onset, as reported in children with seasonal AR treated with or without AIT in a 10-year follow-up [63]. This group of patients was investigated 7 years after the conclusion of a 3-year course of subcutaneous immunotherapy (SCIT) with standardized allergen extracts of grass and/or birch or only with drugs, respectively. As evaluated by clinical symptoms of asthma, significantly less actively treated subjects had developed asthma 10 years after starting SCIT. Currently, two routes of administration of AIT are available, the classical SCIT and sublingual immunotherapy (SLIT), with the allergen kept under the tongue for one to 2 min and then swallowed. SLIT was first

accepted as a viable alternative to SCIT in the 1998 WHO position paper [64], and then analyzed in a dedicated document of the World Allergy Organization [65]. As far as the superiority of one route of administration over the other is concerned, a recent systematic review performed an indirect comparison (only one study of direct comparison met the inclusion criteria) of SCIT versus SLIT in seasonal AR. A trend toward favoring SCIT for symptoms and medication scores was observed, but superiority of one mode of administration over the other could not be reliably demonstrated [66]. Instead, the issue of safety, and particularly the possible occurrence of severe systemic reactions, still remains a drawback for SCIT, making needed a medical supervision [67]. However, most severe reactions are associated with errors in administration, and it was reported that when SCIT is performed following the recommendations on safety, systemic reactions are quite rare [68]. Of interest, the combined treatment using omalizumab and SCIT has shown advantages in terms of better safety, decreasing the risk of anaphylactic reactions to rush immunotherapy and the numbers of adverse events [69] and improved efficacy. In fact, an additional benefit with administration of both omalizumab and SCIT compared with SCIT alone was reported in

patients with seasonal AR with polysensitization [70] or with comorbid seasonal asthma [71]. The safety profile of SLIT is better than that of SCIT, the common side effects being local reactions in the mouth, while systemic reactions are very rare [72,73]. Such good safety allows the administration of the treatment at home and makes SLIT less time-consuming than SCIT. There is evidence suggesting that also for SLIT, as for SCIT, clinical benefits persist after the discontinuation [74,75].

Ultimately, the factors influencing the choice of SCIT or SLIT in single patients are the evidence of efficacy for the available products, the safety profile and the patients' preference. Concerning the latter, a recent study reported that when patients with seasonal allergy are informed on the characteristics of SLIT and SCIT, if based on a short course of injections, their preference may not be dominantly orientated toward SLIT. In fact, of the 145 patients included in the study, 72 chose the short course of SCIT and 73 chose SLIT [76].

Expert commentary & five-year view

A large array of drugs is available to treat respiratory allergy. As summarized in FIGURE 1, part of them are aimed at working solely on symptoms, this being the case for nasal decongestants for AR or bronchodilators for asthma. Some drugs act on specific inflammatory mechanisms, such as antihistamines for histamine-mediated inflammation in AR, LTRAs for leukotriene-mediated inflammation in both asthma and AR, or omalizumab for the IgE-mediated cascade. Only corticosteroids and AIT possess a broad anti-inflammatory action. The former achieve control on inflammation by the capacity to modify multiple signal transduction pathways, including the transactivation pathway and the transrepression pathway, to exert regulatory functions by inducing regulatory cytokines and forkhead box P3 (FoxP3(+)) regulatory T cells, to inhibit proinflammatory transcription factors, and to switch off the activated inflammatory genes through inhibition of HAT [38,77]. AIT, including both SCIT and SLIT, has been demonstrated to act by several cellular and molecular mechanisms, such as the allergen-specific suppressive capacities of both inducible subsets of CD4(+) CD25(+) FoxP3(+) T-regulatory, TGF- β and IL-10-secreting T-regulatory cells in peripheral blood, suppression of eosinophils, mast cells, and basophils, and antibody isotype change from IgE to IgG4 [78,79]. It is apparent that corticosteroids and AIT share some anti-inflammatory mechanisms, but the clinical impact (CI) is clearly different. In fact, the efficacy of INS or ICSs ends with treatment, as clearly showed in the study by Guilbert *et al.*, who reported that in children at high risk for asthma, 2 years of inhaled-corticosteroid therapy did not change the development

of asthma symptoms or lung function during a third, treatment-free year, leading the authors to conclude that corticosteroids have no disease-modifying effect [80]. Instead, the disease-modifying effect of AIT is supported by a number of studies, as recently reviewed by Passalacqua [81]. Concerning the effects of the different drugs on seasonal AR symptoms, an interesting approach was introduced by Devillier *et al.*, who calculated for each treatment the relative CI, on the basis of the post-treatment or season-long nasal or total symptom scores with active treatment compared with placebo reported in 28 trials [82]. The weighted mean (range) relative CIs were -23.5% (-7-54%) for nasal corticosteroids, -15.0% (-3-26%) for antihistamines, -17.1% (-15-20%) for the combination azelastine/fluticasone propionate, -6.5% (-3-10%) for montelukast, -29.6% (-23-37%) for five-grass pollen SLIT tablets and -19.2% (-6-29%) for timothy pollen SLIT tablets. Of note, the outcome of azelastine/fluticasone propionate, as assessed by CI, was lower than the efficacy reported in specific studies on this combination [28-30]. However, this kind of analysis warrants to be extended to the other clinical forms of respiratory allergy, as perennial AR and seasonal and perennial asthma, to provide to the physician evidence-based data to choose the appropriate treatment. The perspective for new drugs in the next years includes for AR the introduction of further combinations of topical corticosteroids and antihistamines, as well as the investigation on H3 and H4 receptor antagonists [20]. For asthma, a promising pathway concerns biologic agents targeting pivotal cytokines involved in bronchial inflammation. Such agents include the monoclonal antibody anti-IL5 mepolizumab, the anti-IL4Ra dupilumab, the anti-IL13 lebrikizumab and the anti-IL 17Ra brodalumab [83]. For both AR and asthma, compounds targeting Toll-like receptors, which are pattern recognition receptors known as the ancient 'gatekeepers' of the immune system [84], have been found to suppress airway inflammation, eosinophilia and airway hyper-responsiveness in various experimental models. Agonists of Toll-like receptors may be also used as adjuvants to enhance the efficacy of AIT. Finally, the ongoing qualitative refinement of allergen preparations for AIT is likely to further improve the effectiveness of this treatment [85].

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Key issues

- The treatment of respiratory allergy is based on several drugs with different mechanisms of action that encompass an effect only on symptoms, limited factors of inflammation or the whole process of inflammation.
- Dissecting the different treatments by their mechanism of action is a critical point when prescribing the most appropriate treatment.
- Nasal decongestants in rhinitis and bronchodilators (including β_2 -agonists and muscarinic antagonists) in asthma have only symptomatic effect, while antihistamines, leukotriene receptor antagonists and the anti-IgE antibody omalizumab target specific components of inflammation.
- Corticosteroids and allergen immunotherapy (AIT) exert a larger anti-inflammatory action. Corticosteroids, administered as nasal sprays in rhinitis or by inhalation devices in asthma, are the most effective drugs in respiratory allergy, achieving the control on inflammation by a number of cellular and molecular mechanisms, some of them, such as the induction of regulatory T cells, shared with AIT.
- What distinguishes corticosteroids from AIT is the duration of clinical outcomes that ends with treatment withdrawal for the former, while persisting also after stopping for AIT, due to its disease-modifying effect.

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