Pharmacotherapy of Allergic Rhinitis

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Introduction

The primary goal of allergic rhinitis (AR) treatment is to alleviate symptoms, improve quality of life and prevent comorbidities. In addition to allergen avoidance there are several pharmacologic agents available: oral and topical H1-antihistamines, intranasal glucocorticosteroids, leukotriene receptor antagonists, mast cell stabilizers, anticholinergic agents and decongestants.

Medications used for AR are typically administered orally or intranasally. The intranasal route allows for higher concentrations of the drug to be delivered thus minimizing the systemic side effects. However, many patients with AR have an aversion to using nasal spray, and oral medications are typically used in these patients.

Oral H1-Antihistamines

Histamine is an important chemical mediator of allergic inflammation and is released in large quantities from tissue mast cells and basophils upon antigen binding to IgE on the cell surface and crosslinking FceRI (high affinity receptor for IgE) during the early allergic response [1, 2]. Histamine then acts in the nose to cause
vasodilatation and increased vascular permeability, and stimulation of sensory nerves leading to the sensation of itching [1, 2]. This manifests clinically as sneezing, rhinorrhea, and pruritus [2]. There are at least four types of histamine receptors that have been identified. However, the majority of allergic responses are mediated via the H1 receptor [3].

H1-antihistamines are inverse agonists, rather than H1-antagonists, that combine with and stabilize the inactive form of the H1 receptor leading toward a shift in equilibrium to the inactive state [3]. In addition to the inverse agonist effect at the H1 receptor, the newer second-generation agents have both antiallergic and anti-inflammatory properties. They have been shown to inhibit the release of mediators from mast cells and basophils through a direct inhibitory effect on calcium-ion channels [4]. Pretreatment with an H1 antihistamine has been shown to decrease the early response to an allergen challenge through decreasing the levels of proinflammatory cell adhesion molecules, cytokines, mediators such as histamine, leukotrienes, and prostaglandins [4–8].

**First Generation H1-Antihistamines**

The first generation H1 antihistamines such as diphenhydramine, chlorpheniramine, brompheniramine and hydroxyzine are also referred to as the sedating antihistamines. These agents are effective in controlling the rhinorrhea, sneezing and pruritus associated with AR. Unfortunately these agents cross the blood-brain barrier producing undesirable side-effects such as central nervous system depression, sedation leading to impaired performance at home, work and school and cardiotoxicity [9–11]. There are no long-term safety studies on the first generation antihistamines. These agents have poor H1 receptor selectivity and act on muscarinic receptors causing anticholinergic effects such as dry mouth, urinary retention, constipation and tachycardia [9]. The high risk to benefit ratio makes the first generation H1 antihistamines a less attractive therapeutic option and are not recommended as first line therapy in AR.

**Second Generation H1-Antihistamines**

The second generation antihistamines (Table 1), developed in the early 1980s, have improved H1 receptor selectivity, absent or decreased sedation, faster onset and longer duration of action and fewer adverse effects [11, 12]. To date, no clinically significant cardiotoxic effects have been reported for loratadine, desloratadine, fexofenadine, cetirizine and levocetirizine. In general, second generation antihistamines exhibit favorable pharmacokinetics. They have a relatively quick onset of action, near complete absorption, widespread tissue distribution with minimal CNS
penetration unlike first generation antihistamines, and relatively long half-life allowing for once daily dosing [13]. Several controlled trials of second generation H₁ antihistamines have been published and have shown overall relief of symptoms including sneezing, pruritus, rhinorrhea, and conjunctival symptoms, and improved quality of life [2, 14, 15].

**Table 1** Available second generation H₁-antihistamines

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual pediatric daily dosage</th>
<th>Usual adult daily dosage</th>
<th>Sedation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loratadine</td>
<td>2–5 yrs: 5 mg</td>
<td>10 mg</td>
<td>No</td>
</tr>
<tr>
<td>Desloratadine</td>
<td>6–11 mos: 1 mg</td>
<td>5 mg</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>12 mos–5 yrs: 1.25 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6–11 yrs: 2.5 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cetirizine</td>
<td>6–11 mos: 2.5 mg</td>
<td>5–10 mg</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>12 mos–5 yrs: 2.5–5 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fexofenadine</td>
<td>6–11 yrs: 30 mg twice daily</td>
<td>60 mg twice daily; 120 mg</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>12 mos–5 yrs: 55–30 mg</td>
<td>or 180 mg daily</td>
<td></td>
</tr>
<tr>
<td>Levocetirizine</td>
<td>6–11 yrs: 2.5 mg</td>
<td>5 mg</td>
<td>Yes</td>
</tr>
<tr>
<td>Intranasal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azelastine</td>
<td>5–11 yrs: 1 spray twice daily</td>
<td>2 sprays twice daily</td>
<td>Yes</td>
</tr>
<tr>
<td>Olopatadine</td>
<td>&gt;12 yrs: 2 sprays twice daily</td>
<td>2 sprays twice daily</td>
<td>Yes</td>
</tr>
</tbody>
</table>

yrs years; mos months

*Cause sedation at higher than recommended doses

Cetirizine

Cetirizine is rapidly absorbed and achieves peak plasma concentration in ~1 h [3]. In addition to H₁ receptor antagonism, cetirizine was found to inhibit eosinophil chemotaxis during the allergic response and therefore blunted the late-phase reaction [16]. Cetirizine can cause an increased incidence of sedation at its recommended dose in patients aged 12 or older [17]. Cetirizine is classified as mildly-sedating and should not be prescribed to patients whose jobs require high psychomotor skills such as pilots.

Cetirizine has been shown in numerous clinical trials to be more efficacious compared to placebo in the treatment of both seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) [18–23]. Cetirizine significantly improved QOL measures of general health, physical functioning, vitality, social functioning, and emotional and mental health within one week of treatment and continued up to 6 weeks [24].
Levocetirizine

Levocetirizine is the enantiomer of cetirizine. Levocetirizine, like cetirizine, has been shown to inhibit eotaxin-induced transendothelial migration of eosinophils in vitro, thus blunting the late phase response [16]. Levocetirizine shows lower sedating effects in clinical studies than cetirizine [25].

A randomized trial involving >400 patients with SAR found that levocetirizine significantly reduced symptom scores over an 8-week period [26]. A multinational placebo-controlled study found that levocetirizine significantly improved QOL over 6 months of treatment [11]. A large multicenter study in children with SAR and PAR found that 4–6 weeks of treatment with levocetirizine significantly improved symptoms and QOL [27].

Loratadine

Loratadine has been found to blunt the early- and late-phase of allergic reactions [7]. Loratadine is a nonsedating antihistamine, and psychomotor tests confirm its safety at the recommended dosage (10 mg/day) [28]. However, performance studies with higher, off-label loratadine doses of 20 and 40 mg showed significant impairment and sedation in some objective performance tests compared with placebo [29].

Although the placebo controlled studies with loratadine are limited, two studies have shown that loratadine was superior to placebo in the treatment of AR [30, 31].

Desloratadine

Desloratadine, an active metabolite of loratadine, has been shown to inhibit IgE-mediated and non-IgE-mediated release of IL-4 and IL-13 from human basophils in vitro [32]. Like loratadine, desloratadine significantly reduces the symptoms of SAR. However, as in the case of loratadine, somnolence has been noted at higher-than-recommended doses [29].

Two multicenter, randomized, double-blind studies comparing the efficacy of desloratadine to placebo showed a statistically significant reduction in symptoms in patients with SAR over a 2-week study period [33, 34]. Desloratadine rapidly and safely reduced the symptoms of PAR, and its efficacy did not diminish during 4 weeks of treatment [35]. There have been no large clinical trials studying the effect of desloratadine on QOL.
Fexofenadine

Fexofenadine, the active metabolite of terfenadine, is a potent H₁ receptor antagonist that does not display cardiotoxicity like its predecessor [36]. In addition to blocking H₁ receptors, in vitro and in vivo studies have shown that fexofenadine reduces allergic inflammatory responses mediated by mast cells, basophils, epithelial cells, eosinophils and lymphocytes [37]. Fexofenadine has also been shown to demonstrate anti-inflammatory activity through inhibition of ICAM-1 expression on nasal epithelium in vitro [20].

Numerous clinical trials have shown fexofenadine to be more efficacious than placebo for the symptoms of SAR [38–44]. van Cauwenberge et al. [45] conducted a large multinational, double-blinded, placebo-controlled, 2 week trial of fexofenadine (120 mg once a day) versus loratadine (10 mg once a day) in patients with SAR. Individual symptoms were self-assessed and no difference in overall symptom scores was observed between fexofenadine and loratadine. However, fexofenadine significantly improved the individual symptoms of nasal congestion and itchy, watery, red eyes compared with loratadine. Fexofenadine has also been found to decrease work impairment and benefit emotions, sleep and practical problems [43].

Fexofenadine is a substrate for P-glycoprotein (P-gp), which is a membrane-bound transporter that inhibits absorption and promotes excretion [46]. Grapefruit juice has been found in vitro to inhibit P-gp activity and when consumed with grapefruit juice, the plasma concentration of fexofenadine can be decreased by up to 40% [47]. Conversely, when fexofenadine is taken in conjunction with ketoconazole and erythromycin, plasma levels may be increased, thus increasing the potential for adverse effects [48]. It is important to note that no serious adverse effects attributable to drug interactions with this second generation H₁ antihistamine have been reported.

Intranasal H₁-Antihistamines

Topical second generation H₁-antihistamines (Table 1) are considered to be similar in efficacy to oral H₁ antihistamines and are also considered as first-line therapy for mild-moderate AR [9, 11].

Azelastine

Dose-ranging trials have shown a therapeutic onset of action within 3 h after initial dosing and persistence of efficacy over a 12-h interval. The most common side effects seen with azelastine at the recommended dose of two sprays per nostril twice a day, are bitter taste (19.7% vs. 0.6% placebo) and sedation (11.5% vs. 5.4% placebo) [49,50]. Studies have shown that azelastine improved all symptoms in SAR and PAR including ocular symptoms, and can also reduce nasal congestion [9, 11, 51].
Azelastine has demonstrated efficacy in SAR [52–54], and in recent studies azelastine appears to be slightly superior to cetirizine [55], desloratadine [56], and fexofenadine [49] in its ability to reduce total nasal symptoms scores, including nasal congestion. An older study, however, did not find that azelastine was superior to cetirizine in seasonal AR [57].

**Olopatadine**

Olopatadine nasal spray provided reductions in total nasal symptom scores at 30 min compared to placebo and maintained an effect for at least 12 h after dosing [58]. A multicenter, randomized, double-blind SAR study comparing olopatadine to placebo nasal spray found that olopatadine was an effective antiallergy medication that significantly improved the QOL of patients suffering from SAR [59]. Olopatadine nasal spray (0.4% and 0.6%) provided statistically significant improvements in AR symptoms compared with placebo regarding TNSSs and in quality-of-life variables in patients with SAR [60]. Olopatadine nasal spray administered twice daily was safe and well tolerated in adolescents and adults. Olopatadine was also found to be superior to placebo spray and mometasone furoate in reducing allergy symptoms associated with SAR [61].

**Intranasal Corticosteroids**

Intranasal corticosteroids (INS; Table 2) are recommended as first-line therapy for moderate-severe AR [62]. Corticosteroids target the inflammatory mechanism of the early and late phase allergic processes and are therefore effective in treating most symptoms of AR including: congestion; sneezing; rhinorrhea and nasal pruritus [9, 11, 62].

<table>
<thead>
<tr>
<th>Available intranasal corticosteroids</th>
<th>Usual pediatric daily dosage</th>
<th>Usual adult daily dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Triamcinolone acetonide</strong></td>
<td>2–5 yrs: 1 spray/nostril daily</td>
<td>1–2 sprays/nostril daily</td>
</tr>
<tr>
<td></td>
<td>6–12 yrs: 1–2 sprays/nostril daily</td>
<td>2–4 sprays/nostril daily</td>
</tr>
<tr>
<td><strong>Budesonide</strong></td>
<td>6–11 yrs: 2 sprays/nostril daily</td>
<td>2 sprays/nostril daily</td>
</tr>
<tr>
<td><strong>Fluticasone propionate</strong></td>
<td>6–12 yrs: 1–2 sprays/nostril daily</td>
<td>1–4 sprays/nostril daily</td>
</tr>
<tr>
<td><strong>Mometasone furoate</strong></td>
<td>≥4 yrs: 1–2 sprays/nostril daily</td>
<td>2 sprays/nostril daily</td>
</tr>
<tr>
<td><strong>Flunisolide</strong></td>
<td>6–12 yrs: 1 spray/nostril daily</td>
<td>2 sprays/nostril daily</td>
</tr>
<tr>
<td><strong>Fluticasone furoate</strong></td>
<td>6–14 yrs: 2 sprays/nostril twice daily</td>
<td>2 sprays/nostril twice-three times daily</td>
</tr>
<tr>
<td><strong>Ciclesonide</strong></td>
<td>&gt;2–11 yrs: 1–2 sprays/nostril daily</td>
<td>2 sprays/nostril daily</td>
</tr>
<tr>
<td><strong>Budesonide dipropionate</strong></td>
<td>≥12 yrs: 2 sprays/nostril daily</td>
<td>2 sprays/nostril daily</td>
</tr>
</tbody>
</table>

*yr* years; *mos* months; *HFA* hydrofluoroalkane
INS Compared with Placebo

When INS are compared to placebo, this treatment group shows improvement in all parameters examined. A randomized, double blind, 3-week study of 429 patients, 12 years and older with AR who were treated with triamcinolone acetonide 220 µg/day showed a significant decrease in nasal congestion, discharge and sneezing compared to placebo [63]. In placebo-controlled, double blind studies of fluticasone propionate (100 µg twice daily or 200 µg/day), fluticasone propionate was significantly more effective than placebo in improving nasal and ocular symptoms and increasing the number of symptom free days [64]. A double blind, placebo controlled, randomized study of patients with AR comparing mometasone furoate versus placebo showed a significant decrease with mometasone furoate in total symptom scores, total nasal scores and individual nasal symptoms [65]. Fluticasone furoate (110 µg/day), was recently found to significantly improve nasal congestion, itching, rhinorrhea, and sneezing over a 2-week period when compared to placebo in children and adults greater than 12 years [66]. Ciclesonide for intranasal use is formulated in a hypotonic suspension, which has been shown in preclinical in vivo models to provide enhanced tissue uptake when compared with a traditional isotonic formulation [67]. In addition, the intranasal formulation of ciclesonide is preserved with potassium sorbate rather than benzalkonium chloride, which is used in many INSs. Benzalkonium chloride is believed to interfere with mucociliary transport and can lead to the development of hypersensitivity, rhinitis medicamentosa, and neutrophil dysfunction, though there are no clinical studies showing significant adverse effects in humans [68, 69]. Ciclesonide is administered as an inactive parent compound that is metabolized by endogenous esterases in the upper and lower airways to the pharmacologically active metabolite desisobutyrylciclesonide. A recent clinical study evaluated the efficacy of 200 µg of ciclesonide nasal spray administered once daily compared with that of placebo on nasal symptoms and signs of AR in adults and adolescents with SAR over a 28-day period. Intranasal ciclesonide was found to be superior to placebo in relieving nasal congestion, rhinorrhea, sneezing and itching [70].

Comparison of Individual INS

Several studies have compared individual INS and it appears that there is no clinically significant difference in the efficacy of various INS. Welsh et al. compared beclomethasone dipropionate, 168 µg twice daily, versus flunisolide propionate, 100 µg twice daily, in patients with SAR and found the two drugs to be equally effective [71]. Similarly, trials comparing beclomethasone, flunisolide, triamcinolone and budesonide in patient with AR found them to be equally effective [72]. Beclomethasone dipropionate and fluticasone propionate have been compared in multiple trials. A two week study in patients with SAR found beclomethasone dipropionate to be as effective as fluticasone propionate [73]. A 3-week study in
patients with PAR found that beclomethasone and fluticasone propionate were equally effective [74]. Conversely, a 12-month study in patients with PAR found fluticasone propionate to be superior to beclomethasone dipropionate [75].

Onset of action of individual INS may differ. Recent studies suggest that fluticasone propionate, budesonide, mometasone and triamcinolone show clinical benefit within 1–2 days [71, 76–78], whereas fluticasone furoate showed benefit within 8 h of administration [66]. Jen et al. [76] demonstrated that fluticasone propionate nasal spray was more effective than placebo within 12 h of treatment, although peak efficacy took several days to obtain. Similarly, one dose of triamcinolone acetonide provided symptom relief in patients with AR within 12 h of administration [78]. Mometasone furoate was found to provide relief of AR symptoms within 12 h [77] and budesonide was demonstrated to act within 3 h of administration, although maximum efficacy occurred within days to weeks [78].

**INS Compared with Oral H\textsubscript{1} Antihistamines**

A meta-analysis of 16 studies involving 2267 subjects (ages 12–75 years) with AR showed that INS produced significantly greater improvement with total nasal symptoms compared to oral H\textsubscript{1} antihistamines [79]. Significant findings from this meta-analysis include: INS produced significantly greater relief of nasal congestion, decreased nasal discharge, and decreased nasal pruritus than oral H\textsubscript{1} antihistamines. Two studies from this meta-analysis demonstrated that INS showed a modest but significant decrease in post-nasal drip compared to oral H\textsubscript{1} antihistamines. However, there was no difference in ocular symptoms.

**Adverse Effects of INS**

The goal for an ideal AR therapy is an INS with a high therapeutic ratio (i.e., high efficacy, good tolerability, and low systemic bioavailability) [80, 81]. The systemic bioavailability of an INS is related to its deposition in the nasal cavity, followed by mucociliary clearance to the throat and, eventually, to the gastrointestinal tract; absorption from the mucosal surface can contribute up to 50% systemic bioavailability of the INS [80, 82].

The most common local side effects of INS, reported by 2–10% of patients, include burning, irritation, and drying. There have also been a few reported cases of nasal septal perforation [80, 83, 84]. Epistaxis, due to drying or thinning of the nasal mucosa, is another common local side effect associated with the use of INS and occurs in 17–23% of patients treated with INS and in 10–15% of patients treated with placebo in clinical trials [80, 85]. Interestingly, the incidences of epistaxis reported with placebo in clinical trials of INS are high as well; therefore, the physical trauma caused by the nasal spray application device, as well as the
formulation additives, most likely also contribute to epistaxis [80,85]. To minimize epistaxis patients should be instructed on the proper technique for administration, which is to direct the spray away from the septum.

Systemic exposure of INS occurs because of direct absorption of INS from the nasal mucosa as well as runoff down to the gastrointestinal tract [80]. The major effect of corticosteroids on the hypothalamic-pituitary-adrenal (HPA) axis is the negative feedback effect caused by suppression of corticotrophin-releasing hormone and adrenocorticotropic hormone (ACTH) levels, leading to lower cortisol secretion and eventual atrophy of the adrenal cortex [80]. The majority of second-generation INS have little effect on HPA-axis function [80]. In pediatric patients with AR, treatment with fluticasone propionate 200 µg/day for 6 weeks did not suppress 12-h urine cortisol levels [86]. However, in another study of pediatric patients with PAR, intranasal fluticasone propionate 200 µg/day suppressed 12-h urine cortisol compared with placebo, whereas intranasal triamcinolone acetonide 110 µg/day did not [87]. Similarly, treatment with fluticasone propionate 200 µg/day for 4 days suppressed 12-h urinary-free cortisol secretion, whereas treatment with triamcinolone acetonide 220 µg/day or beclomethasone dipropionate 336 µg/day did not suppress cortisol levels [88]. In contrast, treatment with budesonide or mometasone furoate, each at a daily dose of 200 µg, or triamcinolone acetonide at a daily dose of 220 µg for 5 days did not have any suppressive effect on morning, 12-h, or 24-h plasma cortisol levels or on 12- and 24-h urinary free cortisol levels [89]. Finally, in children with PAR, treatment with intranasal budesonide 400 µg/day for 1 year and an aqueous suspension of budesonide 400 µg/day for an additional 6 months did not suppress morning plasma and 24-h urinary-free cortisol levels during the first and second year of treatment [90].

Effects of INS on the HPA axis are influenced by the frequency of drug administration. Once-daily administration of INS would have a negligible effect on the HPA axis [91]. A once-daily morning dosing regimen is very important in prepubertal children, in whom growth hormone secretion is pulsatile and nocturnal, with initiation of pulses corresponding to the normal late-evening low levels of plasma cortisol [80,91]. Absorption of exogenous corticosteroid at this time from a twice-daily regimen could have a suppressive effect on growth hormone release [80]. Consistent with this observation, randomized, parallel-group, short-term studies of intranasal budesonide 200 µg given twice daily to 44 children with AR caused significant suppression of lower-leg growth [92], whereas in another double-blind, parallel-group study of 38 children, budesonide 200 µg or 400 µg given once daily in the morning did not suppress lower-leg growth [93].

Inhaled corticosteroids have been shown to have significant effects on eyes resulting in glaucoma and subcapsular cataracts and on bone [94]. However, enough data are not available on the effects of INS on eyes or bone to draw a definitive conclusion [80]. A retrospective chart review study of 12 patients showed that INS use resulted in an increase in intraocular pressure and a significant reduction in intraocular pressure was observed after discontinuation [95]. In another study, similar effects on intraocular pressure were observed with intranasal or inhaled beclomethasone dipropionate [96].
In summary, currently available INS are effective and safe for the treatment of AR. However, the risk of side effects may be increased by high doses or prolonged exposure to more potent INS, especially in younger or older patients. Furthermore, there is a risk of an additive inhibitory effect on the HPA axis in patients receiving concomitant ICS and INS therapy [80].

**Leukotriene Modifying Agents**

Leukotrienes appear to be important mediators of nasal allergic reactions, and their presence in the nose induces nasal obstruction [11]. Leukotrienes have significant proinflammatory effects as well as causing vasodilatation, increased vascular permeability, airway smooth muscle contraction, mucus secretion and chemoattraction towards eosinophils [62]. Therefore, they are involved in both the early and late phase allergic response. A meta-analysis demonstrated that montelukast, compared to placebo, demonstrated a moderate but significant reduction in relieving nasal symptoms in patients with AR, whereas INS induced a significant and substantial reduction in symptoms [97, 98]. A randomized, double-blind, placebo controlled trial comparing montelukast, loratadine and placebo in patients with SAR demonstrated that montelukast was more effective than placebo in improving scores for the primary endpoint of daytime nasal symptoms and the secondary endpoints of night-time, composite, and daytime eye symptoms, patient’s and physician’s global evaluations of AR, rhinoconjunctivitis and quality-of-life [99]. Loratadine also improved scores for the primary endpoint and the majority of the secondary endpoints. When analyzed by week, the treatment effect of montelukast was more persistent than loratadine over all 4 weeks of treatment. A combined analysis of three multicenter, randomized, double-blind, parallel-group studies was performed involving 1,862 patients with SAR, comparing montelukast to placebo over a two week treatment period. Montelukast significantly improved daytime nasal symptoms score and individual scores of congestion, rhinorrhea, itching, and sneezing compared with placebo [100].

A meta-analysis of seventeen randomized controlled trials involving 6,231 adults with SAR was performed to evaluate the effect of oral leukotriene receptor antagonists as monotherapy or combined with other drugs in the treatment of SAR [101]. Oral leukotriene antagonists significantly reduced daytime nasal symptoms, nighttime nasal symptoms, eye symptoms, and significantly improved quality of life compared with placebo. There were no significant differences between oral leukotriene antagonists and oral histamine H\textsubscript{1} antagonists on nasal and eye symptoms, and quality-of-life. However, the authors found that leukotriene receptor antagonists were inferior to INS for decreasing daytime and nighttime nasal symptoms. The combination of leukotriene receptor antagonists plus histamine H\textsubscript{1} antagonists produced greater relief of eye symptoms compared with histamine H\textsubscript{1} antagonists alone. Finally, INS significantly reduced nasal congestion compared with leukotriene receptor antagonists plus histamine H\textsubscript{1} antagonists. Therefore, the authors concluded...
that leukotriene receptor antagonists were better than placebo, equivalent to oral histamine $H_1$ antagonists, and inferior to INS for treating SAR. Alternatively, leukotriene receptor antagonists plus histamine $H_1$ antagonists were more effective than histamine $H_1$ antagonists alone but inferior to INS.

In a multicenter, double-blind, randomized, parallel-group, placebo-controlled 2-week trial, 460 men and women, aged 15–75 years, with SAR were randomly allocated to receive one of the following five treatments: montelukast 10 or 20 mg, loratadine 10 mg, montelukast, 10 mg with loratadine 10 mg, or placebo, once daily in the evening [102]. Concomitant montelukast with loratadine significantly improved daytime nasal symptoms score compared to placebo. Compared with placebo, montelukast with loratadine also significantly improved eye symptoms, nighttime symptoms, individual daytime nasal symptoms, global evaluations, and quality of life.

**Local Chromones**

Mast cell stabilizers inhibit mast cell degranulation and thus inhibit the release of histamine and other mediators of the early phase of allergic inflammation. Cromolyn sodium, which is available over-the-counter, is generally not as effective as antihistamines or INS but has been shown to be superior to placebo in reducing symptoms of the early phase [62]. Cromolyn is likely to be more effective when administered just prior to contact with an allergen [11]. Although the safety profile of cromolyn is very good, the dosing interval of four times a day make this a less attractive option.

**Local Anticholinergics**

Double-blind, placebo-controlled studies have shown that ipratropium bromide is effective in controlling watery nasal discharge, but that it does not affect sneezing or nasal obstruction in perennial allergic and nonallergic (vasomotor) rhinitis [103, 104]. Anticholinergic side effects are uncommon and usually dose-dependent [11].

**Decongestants**

Decongestants reduce nasal congestion by activating $\alpha$-adrenergic receptors on the nasal vasculature leading to vasoconstriction [62]. Decongestants do not improve nasal itching, sneezing or rhinorrhea associated with AR. Oral decongestants such as ephedrine, phenylephrine, phenylpropanolamine and pseudoephedrine are the
most commonly used oral decongestants. Systemic side effects include irritability, dizziness, headache, tremor, insomnia as well as tachycardia and hypertension [11]. Patients with glaucoma or hyperthyroidism and elderly men with prostate enlargement are also at risk when using oral sympathomimetic decongestants. Pseudoephedrine was recently banned for Olympic athletes [105].

A recent study showed that the combination of pseudoephedrine and an antihistamine was significantly more effective in reducing total nasal symptoms than either agent alone [106]. There are very few randomized/controlled clinical studies on the effects of pseudoephedrine alone in AR.

Topical decongestants, oxymetazoline and phenylephrine are also available over-the-counter. These medications can be effective with nasal congestion associated with AR. However, prolonged use (>10 days) of intranasal decongestants may lead to tachyphylaxis, a rebound swelling of the nasal mucosa and “drug-induced rhinitis” termed rhinitis medicamentosa [107].

Summary

AR is a common chronic disorder that can significantly interfere with a patient’s QOL. The goals of treatment are to provide the patient with symptom relief and improvement in QOL with minimal number of side effects. Prescribing physicians must take into account patient preferences, symptoms and side effect profile. Lack of treatment or treatment with suboptimal therapy may result in reduced quality of life and compromise productivity at work or school. Many different classes of medications are now available, and they have been shown to be effective and safe in a large number of well-designed clinical trials. Table 3 provides a stepwise approach to the treatment of AR [11].

| Table 3 | Management of allergic rhinitis |
|--------------------------------|
| **Intermittent symptoms** | **Persistent symptoms** |
| Mild<sup>a</sup> | Moderate/severe<sup>a</sup> | Mild<sup>b</sup> | Moderate/severe<sup>b</sup> |
| • Oral or intranasal H<sub>1</sub> antihistamine and/or | • Oral or intranasal H<sub>1</sub> antihistamine and/or | • Oral or intranasal H<sub>1</sub> antihistamine and/or | • INS and Oral or intranasal H<sub>1</sub> antihistamine or LTRA |
| • Oral/intranasal decongestant or LTRA | • Oral/intranasal decongestant or | • Oral/intranasal decongestant or | • Add decongestant for blockage |
| LTRA | INS or LTRA or Intranasal chromone | INS or LTRA or Intranasal chromone | Add intranasal anticholinergic for rhinorrhea |

<sup>LTRA</sup> leukotriene receptor antagonist; <sup>ICS</sup> intranasal corticosteroid

<sup>a</sup>Not in preferred order

<sup>b</sup>In preferred order
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http://www.springer.com/978-4-431-99361-2

Allergy Frontiers: Therapy and Prevention
Pawankar, R.; Holgate, S.T.; Rosenwasser, L.J. (Eds.)
2010, 800 p., Hardcover
ISBN: 978-4-431-99361-2