

Update on Prescription and Over-the-Counter Histamine Inverse Agonists in Rhinitis Therapy

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Allergic rhinitis (AR) is associated with histamine-mediated physiologic events. The currently used histamine antagonists are all inverse agonists that bind and inactivate histamine H1 receptors. Second-generation antihistamines are much more H1-receptor selective with less central nervous system penetration than first-generation agents. Antihistamines typically are more effective in seasonal than perennial AR and do not demonstrate significant relief of nasal congestion. The recent availability of some second-generation antihistamines as over-the-counter products clearly places them as the preferred first-line treatment for mild to moderate AR based on safety when compared with first-generation over-the-counter antihistamines. The remaining prescription-only second-generation antihistamines, fexofenadine, desloratadine, and levocetirizine, all have unique attributes. Antihistamines in oral, intranasal, or intraocular formulations will likely remain among the mainstays of allergy therapeutics.

Introduction

Allergic rhinitis (AR) affects approximately 10% to 30% of adults and up to 40% of children each year. Each year in the United States, AR is associated with direct total costs of about \$4.5 billion and indirect costs related to approximately 4 million days of lost productivity at work and school [1]. Although AR is not a life-threatening disease, it is a major cause of suffering and impaired quality of life (QoL). Affected individuals report problems with social and daily activities, often experience difficulty sleeping at night, suffer from daytime somnolence, and have poorer mental health and well-being than patients

without rhinitis or asthma [2–5]. Moreover, AR often is associated with comorbid asthma and, if not managed properly, exacerbates other conditions, including acute/chronic sinusitis, recurrent nasal polyposis, otitis media, sleep apnea, respiratory infections, and asthma [6]. Traditionally, AR has been classified as seasonal (SAR) or perennial (PAR), depending on the time of occurrence during the year and the nature of the major allergens triggering the symptoms. A classification of intermittent or persistent AR, based on symptom duration, was recently proposed by the Allergic Rhinitis and Its Impact on Asthma (ARIA) group in collaboration with the World Health Organization [7].

The symptoms of SAR and PAR, which influence the nose and can influence the eye, are associated primarily with histamine released from mast cells and acting in conjunction with other mediators.

Histamine and Its Receptors

Histamine is a 112-D biologic amine that is synthesized in mast cells and basophils by decarboxylation of L-histidine in a reaction catalyzed by the enzyme L-histidine decarboxylase. When it is released from cells, histamine is rapidly metabolized via methylation or oxidation [8]. The former reaction is catalyzed by histamine N-methyltransferase and the latter by diamine oxidase (histaminase). Histamine was first described more than 100 years ago. Since then, its crucial role in allergic reactions has been documented in many studies.

Histamine exerts biologic effects acting on four distinct receptors referred to as H1 through H4 [8,9], all of which are G-protein-coupled receptors (GPCRs). They are encoded by four separate genes located on different chromosomes. The H1 receptor is involved in wheal and flare skin reactions upon injection of histamine into the skin—the reaction being dependent on dilation of microvessels and increased permeability of microvascular endothelium. Moreover, in the airways, activation of the H1 receptor leads to contraction of smooth muscles and increased mucus secretion. In the nose, histamine stimulates sensory nerve endings, resulting in itching and sneezing; increases vascular permeability, leading to nasal

obstruction; and enhances glandular secretion, causing rhinorrhea. The H₂ receptors are predominantly distributed in the stomach; H₃ in the nervous system; and H₄ on hematopoietic cells, including inflammatory cells (eg, eosinophils and T cells).

Antihistamines: Inverse Agonists of Histamine Receptor

Most allergic symptoms are elicited by action of histamine through the H₁ receptor; therefore, H₁ antihistamines have been used for years to treat allergic diseases, including SAR and PAR. It was originally assumed that H₁ antihistamines acted as antagonists of the H₁ receptor. However, recent functional studies have demonstrated that they act as inverse agonists rather than neutral antagonists [9]. The H₁ receptor exists on the cell surface in both active and inactive states, and both forms of the receptor exist in equilibrium. Therefore, even without any extracellular activation, some residual signals are transduced into the cell by the active form of the histamine receptor, leading to activation of appropriate second messenger-signaling pathways. Agonists such as histamine bind to the active form of the receptor and shift the already established equilibrium toward the more active form. Neutral antagonists would inhibit binding of the agonist to the receptor; however, they would not inhibit the residual cell activation by the naturally existing active form of the histamine receptor. On the contrary, inverse agonists act by switching the equilibrium toward the dominance of the inactive conformation. Thus, inverse agonists not only prevent histamine from binding to its receptors but also decrease agonist-independent, constitutive activity of the receptors. Binding affinity of antihistamines is a critical aspect of their function, as high receptor-binding affinity favors inactivation of the histamine receptors. In addition, high antihistamine concentration in the vicinity of the histamine receptor is critical and is achieved by having either a long elimination half-life or smaller volume of distribution. All these properties influence the extracellular concentrations of a given antihistamine and are vital in determining the agent's ultimate efficacy.

All H₁ antihistamines used to treat allergic diseases are inverse H₁-receptor agonists [9]. Theoretically, inverse agonists have at least two advantages over neutral antagonists in inhibiting histamine receptors. First, spontaneous mutations frequently lead to increased constitutive activity of GPCRs. In contrast to neutral antagonists, inverse agonists decrease the constitutive activity of the GPCRs and therefore exert beneficial effects in situations in which increased signaling depends not only on increased agonist concentration but also on intrinsic defects of the GPCRs. Second, if the receptor can be activated by a process that bypasses agonist binding, then only an inverse agonist can inhibit its activation.

Largely depending on their effects on the central nervous system (CNS), H₁ antihistamines have been classified as first or second generation. First-generation H₁ antihista-

mines—such as chlorpheniramine, doxepin, hydroxyzine, and diphenhydramine—suppress CNS function that is clinically reflected as sedation, somnolence, and impairment of psychomotor performances. Second-generation H₁ antihistamines—such as acrivastine, cetirizine, ebastine, loratadine, mizolastine, fexofenadine, desloratadine, and levocetirizine—are characterized by their having little or no effect on CNS function at therapeutic doses. Several H₁ antihistamines, including azelastine, levocabastine, olopatadine, and epinastine, are used topically in AR patients to treat nasal and ocular symptoms. Although second-generation H₁ antihistamines penetrate the blood–brain barrier to some degree, they achieve much less binding to CNS histamine receptors and bind at a much slower rate than first-generation antihistamines, which rapidly saturate histamine receptors in the brain. Second-generation antihistamines are highly selective H₁-receptor inverse agonists whose affinities to other receptors—such as cholinergic, adrenergic, or serotonergic receptors—are much lower than those to the H₁ receptor. First-generation antihistamines tend to be much more readily bound to nonhistamine receptors, such as muscarinic, serotonergic, and dopaminergic receptors, with receptor-binding affinities for many antihistamines showing little difference when assessing binding to histamine versus nonhistamine biogenic amine GPCRs. Moreover, in contrast to first-generation H₁ antihistamines, second-generation H₁ antihistamines are slowly metabolized; therefore, most may be administered once daily.

H₁ antihistamines can be divided into systemically administered (ie, including orally or parenterally) and topically administered (ie, as intranasal or intraocular) medications.

Although H₁ antihistamines have the same mechanisms of action, they differ in terms of their chemical structure, pharmacokinetics, clinical efficacy, and potential side effects.

Pharmacokinetics and Pharmacodynamics of H₁ Antihistamines

First-generation H₁ antihistamines are rapidly absorbed and in most cases rapidly metabolized to inactive metabolites. Therefore, they should be administered three or four times daily. However, hydroxyzine is metabolized to an active metabolite (cetirizine), which significantly prolongs its antihistamine activity. All first-generation antihistamines are lipophilic (ie, they easily penetrate the blood–brain barrier and occupy receptors in the CNS), which leads to impairment of psychomotor performances and sedation.

In contrast to first-generation H₁ antihistamines, which are more slowly metabolized or eliminated and whose clinical effect is seen for at least 24 hours, orally administered second-generation H₁ antihistamines—cetirizine, loratadine, fexofenadine, desloratadine, and levocetirizine—are rapidly absorbed and achieve peak plasma concentration within 1 to 3 hours [10]. However, in children, metabolism or elimination of some second-generation H₁ antihistamines, such as cetirizine,

levocetirizine, and fexofenadine, is increased; therefore, the daily dose may be split into two doses administered every 12 hours. The duration of action of a single dose of H1 antihistamines, assessed from suppression of histamine- or allergen-induced wheals and flares in the skin or objectively by suppression of nasal symptoms after natural allergen exposure or allergen challenge, is more prolonged than might be expected from plasma H1-antihistamine concentrations and $t_{1/2}$ values. This persistent effect is associated with high tissue-to-plasma concentration ratios such as with cetirizine, levocetirizine, and fexofenadine or with the presence of active metabolites, such as desloratadine, ebastine, and loratadine. Individual second-generation H1 antihistamines differ in their volumes of distribution (Vds), with levocetirizine having the lowest Vd (0.4 L/kg), followed by cetirizine. Loratadine and desloratadine have very large Vds and have longer elimination $t_{1/2}$ (> 24 hours) compared with fexofenadine and levocetirizine (< 8 hours) and differ in their mechanism of clearance. Cetirizine and levocetirizine are predominantly excreted in urine and stool as unchanged compounds and depend heavily on renal elimination, whereas loratadine and desloratadine are metabolized in the liver, and fexofenadine is predominantly excreted in the stool. Topically administered H1 antihistamines such as azelastine or levocabastine have to be given every 12 hours despite long $t_{1/2}$. This is due to continuous washing of the conjunctivae or nasal mucosa by tears and nasal secretions, respectively.

Clinical Efficacy and Safety of H1 Antihistamines in AR

First- and second-generation H1 antihistamines have been proven effective in the treatment of AR, as they both alleviate both nasal and associated ocular symptoms. Frequent undesired side effects such as sedation or impairment of psychomotor performances made the first-generation medications difficult to use for treatment of SAR and PAR. Therefore, most clinical guidelines, including ARIA, recommend using second- but not first-generation H1 antihistamines in treatment of AR [7].

Desloratadine

Desloratadine, 5 mg once daily, has been shown to be an effective therapy for SAR [11] and PAR [12,13]. During pollen season, 2 weeks of therapy with desloratadine in patients suffering from SAR symptoms was superior to placebo in reducing symptom scores and improving nasal airflow [11]. In a large Canadian, multicenter, open-label trial, 6829 symptomatic SAR patients were enrolled to receive desloratadine, 5 mg once daily, over a period of 7 days [14]. Nasal, ocular, respiratory, and overall symptoms were rated 0 to 3 on a scale. After 7 days of treatment with desloratadine, significant reductions in individual and overall symptom scores were demonstrated in comparison with baseline values. Interestingly, 88% of

patients reported improvement in nasal stuffiness/congestion. The effect was observed in patients on desloratadine monotherapy and in those already receiving intranasal corticosteroids [14]. In a 2-week, multicenter, randomized, double-blind, parallel-group study of 483 patients with SAR, treatment with desloratadine, 5 mg once daily, was compared with placebo [15]. At day 14, desloratadine was associated with a significantly larger improvement from baseline in the mean total Rhinoconjunctivitis Quality of Life Questionnaire score compared with placebo. In an open-label study, clinical efficacy of desloratadine syrup, 2.5 mg/d for 4 weeks, was demonstrated in children 6 to 12 years old with at least a 2-year history of SAR [16]. Symptoms of rhinorrhea, sneezing, nasal congestion, and nasal itch were reduced in a considerable proportion of the children. Cough was effectively treated in all patients [16]. Although it was not a randomized, controlled trial, this study provides evidence of the efficacy and safety of desloratadine in children [16].

The efficacy of desloratadine, 5 mg once daily over 4 weeks, in PAR patients was demonstrated in a large ($n = 1179$), multicenter, international, randomized, double-blind, placebo-controlled study [12]. At the end of the study, patients treated with desloratadine showed significantly greater improvement in total symptom scores, total nasal and nonnasal symptom scores, and morning peak nasal inspiratory flow rates [12].

A recent meta-analysis of randomized, double-blind, controlled trials concerning efficacy of desloratadine in the treatment of AR demonstrated significant reduction of total symptom scores and nasal symptom scores in patients treated with desloratadine compared with placebo [17]. The efficacy of desloratadine was demonstrated in real life treatment of AR and in preventing symptoms elicited by allergen challenge [17]. Desloratadine was superior to placebo in improving nasal airflow, an effect possibly related to this medication's anti-inflammatory effects.

In a study evaluating regular versus on-demand use of desloratadine for treatment of SAR in children, on-demand use of desloratadine during the pollen season was as effective as regular treatment [18]. No difference was observed between the groups in symptom or medication scores except for salbutamol, which was used more frequently in the on-demand group. More children receiving on-demand desloratadine also had increased bronchial reactivity to methacholine during pollen season (provocative concentration causing a 20% drop in forced expiratory volume in 1 second < 8 mg/mL) [18]. Therefore, it seems that regular treatment may provide better control of lower airway symptoms and airway reactivity.

No clinical trials have compared the overall efficacy of desloratadine versus that of loratadine. Loratadine obtained US Food and Drug Administration approval for treatment of SAR but not PAR, whereas desloratadine achieved both indications. Several studies have demonstrated a benefit for nasal congestion when using desloratadine, whereas little evidence was generated from

loratadine trials related to improvement in nasal congestion. Desloratadine has more predictable absorption than loratadine, with the latter having increased absorption when administered with food, whereas the former showed no dietary impact on absorption. Loratadine is metabolized to at least eight metabolites of varying activity. By administering the most active metabolite, desloratadine, it was hypothesized (although not proven) that interference in histamine-receptor binding, which could occur due to the presence of loratadine metabolites of varying binding affinities, could be avoided and thereby enhance the therapeutic potential of desloratadine. In general, treating SAR and PAR with loratadine reduced symptoms by about 25% to 40% from baseline in clinical trials during the daytime and 24 hours after dosing, which is consistent with a true 24-hour duration of action.

Fexofenadine

Fexofenadine, 180 mg once daily or 60 mg twice daily in adults or 30 mg twice daily in children, effectively treats SAR, alleviating all nasal and ocular symptoms, including nasal obstruction, although like loratadine and desloratadine, it has no specific product labeling in the United States for relief of nasal congestion [19,20]. In addition, it did not achieve an indication for PAR in the United States.

Fexofenadine, 60 mg twice daily, has been shown to not only improve overall QoL but also to improve work productivity in patients with SAR [21]. Performance impairment due to allergy symptoms was assessed using the Work Productivity and Activity Impairment-Allergy Specific instrument, which had been validated to measure generic and allergy-specific performance impairment in work and classroom productivity and regular activity. Scores were expressed as impairment percentages, ranging from 0% to 100%, with higher scores reflecting greater impairment and greater loss of productivity. Overall work impairment decreased by 5.5% in the fexofenadine group and increased by 3.4% in the placebo group ($P = 0.016$).

Two multicenter, randomized, placebo-controlled studies evaluated safety and tolerability of fexofenadine in children 6 months to 2 years old and 2 to 5 years old, respectively [22,23]. In the first study, children 6 months to 2 years old with AR symptoms received fexofenadine, 15 or 30 mg twice daily, or placebo for 8 days. The incidence of treatment-emergent adverse events was comparable in all three groups, with the most common event being vomiting. In young children, the study demonstrated a good safety profile for fexofenadine, 15 or 30 mg twice daily. Similarly, a good safety profile for fexofenadine, 30 mg twice daily, was demonstrated in children 2 to 5 years old who suffered from AR [23]. In that population, digestive system involvement was the most frequent adverse event. No clinically relevant differences in laboratory parameters, vital signs, and physical examination were observed between fexofenadine and placebo groups. In children 2 to 5 years old with AR, oral suspension of fexofenadine was shown to be effective and safe in a multicenter, open-

label, single-dose study [24]. The safety of fexofenadine has been demonstrated in many studies that have shown it to be free from psychomotor adverse effects and free from sedation, even at greater-than-recommended doses. Fexofenadine was comparable to placebo in its effect on cognitive skills [25•] in a study that was performed in healthy naval flight personnel using the Aeromedical Vigilance Test at both ambient atmospheric conditions and normobaric hypoxic conditions.

Recently, interaction of fexofenadine with other medications has also been studied extensively [26–30]. Evidence indicates that a high-fat diet may inhibit absorption of fexofenadine, as will a diet very high in fruit juices, including grapefruit juice, orange juice, or apple juice, and a diet very high in salt content. All effects on uptake of fexofenadine were dependent on the quantity of the fat, fruit juice, or salt ingested and showed dose-dependent reduction in the amount of bioavailable fexofenadine.

Efficacy of fexofenadine was greater than that of loratadine when it was administered to patients with SAR in one large European study authored by Van Cauwenberge and Juniper [31]. Similar efficacy was seen in a smaller American study authored by Prenner et al. [32]. Fexofenadine has been shown to reduce typical symptoms of SAR, including nasal itch, rhinorrhea, sneezing, and ocular itch. The duration of maximal effect is somewhat less than 24 hours when assessed in pollen chamber studies, which have demonstrated superiority in symptom relief of SAR for cetirizine and levocetirizine compared with fexofenadine at time points from 22 to 24 hours after dosing. As fexofenadine is not metabolized by the liver, it is likely the safest antihistamine for patients with hepatic impairment.

Levocetirizine

Levocetirizine, 5 mg once daily, is effective in treating SAR and PAR in adults and children older than 6 years of age [33–36]. One study evaluated the effect of treatment with 2.5-, 5-, or 10-mg levocetirizine tablets or placebo once daily for 2 weeks on severity of nasal and ocular symptoms in 470 adults with SAR to grass and/or weed pollen [33]. The study showed that all doses of levocetirizine were well tolerated and significantly superior to placebo in reducing the severity of sneezing, rhinorrhea, nasal pruritus, and ocular pruritus, which was recorded as the reflective Total Four-Symptom Score (T4SS) in a dose-dependent manner. The 5-mg dose showed an optimal therapeutic index [33]. Similarly, the efficacy of levocetirizine was demonstrated in children 6 to 12 years old with SAR over 6 weeks [34]. For this age group, 5 mg once daily is the dose approved in Europe, whereas the dose approved in the United States is 2.5 mg, because the systemic exposure with the 5-mg dose is approximately twice that for adults. Levocetirizine, 5 mg once daily, was significantly more effective than placebo at reducing the severity of mean T4SS from baseline over the entire study period [34]. Levocetirizine was nearly

twice as effective as placebo over the first 2 weeks of treatment, and the effect was maintained over the entire study period (6 weeks).

The efficacy and safety of levocetirizine in adults and children 6 to 12 years of age with PAR were evaluated in two double-blind, placebo-controlled, parallel-group multicenter trials designed similarly to those in patients with SAR [35,36]. In adolescents and adults, the study investigated the effect of 6 weeks of treatment with levocetirizine, 5 mg/d, or placebo on nasal and ocular symptoms recorded as T4SS in 294 house dust mite-sensitized PAR patients [35]. Levocetirizine showed an 86% improvement in T4SS from baseline over the first week of treatment and a 47% improvement over the entire treatment period compared with placebo. Interestingly, therapy with levocetirizine, in comparison with placebo, was associated with significantly reduced nasal congestion [35]. Efficacy and safety of a 4-week treatment with levocetirizine, 5 mg once daily, were also evaluated in a study conducted in 306 house dust mite-sensitive children (6–12 years old) with PAR [36]. Levocetirizine was superior to placebo in improving the T4SS at 2 and 4 weeks of treatment [36]. Another study evaluated whether long-term treatment with levocetirizine, 5 mg once daily, improves health-related QoL and health status in adult patients with persistent AR over a period of 6 months [37]. Significant improvement with levocetirizine in comparison with placebo was seen as early as 1 week after therapy initiation, and levocetirizine was more effective than placebo over the entire 6-month study period [37].

Levocetirizine was also clinically effective in patients suffering from persistent AR and asthma, resulting in improvement of rhinitis-asthma-related QoL [38]. In that small study, 50 adult patients suffering from persistent AR with and without asthma were randomly selected to receive levocetirizine or placebo. Upper respiratory symptoms (rhinorrhea, itching, sneezing, nasal congestion, ocular itching) and lower respiratory symptoms (cough, wheezing, dyspnea, chest tightness, night awakenings) were evaluated. Significant improvement in upper respiratory symptom score and total symptom score were demonstrated after the first week of therapy with levocetirizine. The clinical effects of levocetirizine were associated with decrease in nasal scraping eosinophilia [38].

Recent studies demonstrated that levocetirizine is safe in young, atopic children [39,40]. In the first study of 12- to 24-month-old children, the pharmacokinetic and pharmacodynamic profiles of levocetirizine, 0.125 mg/kg twice a day, were adequate, and the safety profile was good [39]. The second study was designed to evaluate the safety profile of levocetirizine, 0.125 mg/kg twice daily over a period of 18 months, in 12- to 24-month-old children [40]. No significant differences were noted between the levocetirizine and placebo groups in height, mass, attainment of developmental milestones, and hematology and biochemistry tests, indicating a very good safety profile for levocetirizine in young children [40].

Effects of H1 antihistamines on nasal symptoms induced by histamine inhalation have been investigated objectively using facial thermography in adult SAR patients [41]. Compared with placebo, levocetirizine significantly reduced the rise in nasal cavity temperature induced by histamine inhalation in the nose 2 and 24 hours after the challenge [41].

It has been suggested recently that on-demand use of levocetirizine may be an effective approach in the treatment of persistent AR [42]. In this small pilot study, 33 adult patients with persistent AR were randomly assigned to levocetirizine, 5 mg, administered continuously once daily in the morning or on demand over a 6-month period [42]. Both treatment regimens considerably decreased the total and individual symptom scores and substantially improved QoL and sleep quality. However, continuous therapy was generally better than on-demand therapy from week 15 onward, and the on-demand group reported more adverse events [42].

Finally, levocetirizine is cost-effective in treating persistent AR [43,44]. Direct and indirect costs of persistent rhinitis are substantial. Treatment with levocetirizine, 5 mg once daily over a period of 6 months, reduces the cost of persistent AR and its comorbidities while improving symptoms and health-related QoL [43,44]. Levocetirizine has not been compared with cetirizine in any large, controlled studies as treatment for AR. In the United States, both levocetirizine and cetirizine are US Food and Drug Administration approved for SAR and PAR. Both show symptom reduction from baseline for SAR and PAR of 20% to 50%, prolonged duration of action of greater than 24 hours, and rapid onset of action of 1 to 2 hours. Neither cetirizine nor levocetirizine is impacted by food or drug interactions. Both must have their dosages reduced for patients with chronic renal impairment but not those with hepatic function decline. As cetirizine is a 50/50 mix of levocetirizine with high histamine-receptor-binding potential and dextrocetirizine with much lower histamine-receptor-binding potential, there is a theoretical advantage to using levocetirizine rather than cetirizine. In skin wheal and flare experiments, levocetirizine has been shown to surpass cetirizine in suppression of wheal and flare responses, suggesting that the presence of dextrocetirizine may negatively impact the efficacy of levocetirizine when administered as racemic cetirizine. Levocetirizine also produces less sedation than cetirizine due to elimination of the dextrocetirizine, which has greater potential to cross the blood-brain barrier than levocetirizine. These aspects suggest that levocetirizine may provide enhanced safety and efficacy when compared with cetirizine, although no head-to-head clinical trial results are available.

Comparative studies of the efficacy and safety of the newest H1 antihistamines

The efficacy and safety of the newest H1 antihistamines in the treatment of AR were compared in several recent clinical trials. Passalacqua and Canonica [45] carried out a com-

parative analysis of recently published studies concerning levocetirizine and desloratadine in the treatment of AR.

Levocetirizine is absorbed rapidly and reaches a steady-state plasma concentration more quickly than desloratadine. It is metabolized to a lesser extent than desloratadine, has a lower V_d , and has higher specificity for H1 receptors. It also has faster onset of action and longer duration of clinical effect in patients with AR. In PAR patients, the efficacy of levocetirizine, 5 mg once daily, was compared with desloratadine, 5 mg once daily, and placebo in a randomized, double-blind, placebo-controlled, parallel-group study [46]. Levocetirizine and desloratadine were more effective in relieving rhinitis symptoms than placebo, but levocetirizine had a stronger effect than desloratadine that was particularly evident in their respective effects on nasal airflow. After treatment, a significant increase in nasal airflow was seen with levocetirizine but not with desloratadine or placebo. Levocetirizine also seemed to be more effective than desloratadine in relieving sneezing, itching, rhinorrhea, and nasal obstruction.

The Environmental Exposure Unit has been used to compare single doses of cetirizine with fexofenadine in SAR patients [47]. Cetirizine produced greater relief of SAR symptoms than fexofenadine at 12 hours post-dose and over the 5- to 12-hour postdose period in the Environmental Exposure Unit studies. Levocetirizine's duration of effect over the 24-hour period in Environmental Exposure Unit studies has been shown to be greater than that of fexofenadine.

Because H1 antihistamines are often prescribed for a prolonged period of time, the possibility of their interaction with other medications and food should be taken into consideration while prescribing individual H1 antihistamines. Administration of H1 antihistamines, which are metabolized by cytochrome P450 with other medications that inhibit that cytochrome (eg, antibacterial macrolides or antifungal imidazoles), increases plasma concentration of H1 antihistamines and increases the risk of adverse effects. This situation was especially dangerous with the initial second-generation antihistamines terfenadine and astemizole, which were shown to induce cardiac arrhythmias such as torsades des pointes based on QT-interval prolongation in susceptible individuals. There can be an increase in bioavailable loratadine and desloratadine based on similar interaction of these drugs with metabolism and with fexofenadine based on interference with drug elimination by P-glycoprotein. However, no QT prolongation is seen, and no significant increase in sedation occurs.

Topical H1 antihistamines

In patients with AR, topical H1 antihistamines are approved for relieving nasal and ocular symptoms as nasal sprays and ocular drops, respectively. These include azelastine, levocabastine, and olopatadine. An increasing body of evidence indicates that topical H1 antihistamines demonstrate a more rapid onset of action and stronger antiallergic efficacy [48–51].

Azelastine as a nasal spray taken at two sprays per nostril twice daily was better tolerated and produced greater improvement in symptom scores and QoL score than 10-mg cetirizine tablets taken once daily [48,49]. The onset of action for azelastine occurs as rapidly as 15 minutes, making it significantly faster than cetirizine or desloratadine [51]. Azelastine is also effective as treatment for vasomotor nonallergic rhinitis, including relief of nasal congestion in this condition. However, azelastine does demonstrate a dose-dependent sedation and taste disturbance that can be limited by reducing the dose and using techniques of administration that limit swallowing. Olopatadine in nasal spray format was also recently approved by the US Food and Drug Administration as a treatment for SAR. Although no head-to-head studies have compared it with azelastine, intranasal olopatadine has a lower incidence of sedation and taste disturbance in placebo-controlled studies.

Combination therapy

Several recent studies evaluated the efficacy and safety of second-generation H1 antihistamines in combination with other antiallergic medications in the treatment of AR.

Combination formulations of second-generation H1 antihistamines with oral decongestants have been proven useful in treating AR, as the addition of pseudoephedrine to H1 antihistamines potentiates their clinical effects, especially on nasal stuffiness/congestion. Moreover, combination formulations seem to exert the effects faster than an H1 antihistamine alone. The onset of action and efficacy of fexofenadine, 60 mg/pseudoephedrine, 120 mg, in patients 12 years of age and older with moderate to severe AR have been evaluated in a pooled analysis of two single-dose, double-blind, placebo-controlled allergen exposure unit studies [52]. The study demonstrated rapid onset of action for the combination formulation and significant clinical improvement of the major symptoms complex in comparison with placebo 45 minutes after administration of a single dose of fexofenadine/pseudoephedrine. Since then, the beneficial clinical effect in comparison with placebo was observed for at least 6 hours (the period of observation). All studied symptoms—watery eyes, itchy nose, runny nose, stuffy nose, itchy eyes, itchy ears/throat, headache, sniffles, post-nasal drip, sneezing, nose blowing, and cough—improved significantly compared with placebo. The fastest onset of response was demonstrated for watery eyes (30 minutes) and the latest for cough (240 minutes).

A 24-hour extended-release formulation of fexofenadine hydrochloride, 180 mg/pseudoephedrine hydrochloride, 240 mg, has been approved by the US Food and Drug Administration for relief of SAR symptoms, including nasal congestion. All combination products with a second-generation antihistamine and 240 mg of pseudoephedrine typically provide 30% to 35% symptom reduction from baseline for nasal congestion.

Combined therapy of montelukast, 10 mg once daily, with levocetirizine, 5 mg once daily, or desloratadine, 5

mg once daily, was superior to monotherapy with either medication in reducing symptoms in persistent AR patients [53]. Nasal congestion appears to be better relieved with this combination of montelukast plus second-generation antihistamine. Synergism was also evident when evaluating QoL improvement [54•].

Combination therapy with azelastine nasal spray and fluticasone propionate nasal spray is more effective in treatment of SAR patients than treatment with either agent alone [55•]. Topical H1 antihistamines nasal spray has much more rapid onset of action than inhaled corticosteroids [56].

Conclusions

Antihistamines remain the main pharmacotherapy for SAR and PAR. Their efficacy in SAR is greater than in PAR, with only desloratadine, cetirizine, and levocetirizine having proven efficacy in PAR. Typically, antihistamines provide marginal benefit—if any—for nasal congestion, with the addition of pseudoephedrine being required to relieve this symptom. Second-generation antihistamines are clearly preferred based on enhanced safety compared with first-generation agents. Studies comparing intranasal corticosteroids to oral antihistamines have conclusively shown that intranasal corticosteroids provide superior symptom relief and impact PAR and congestion more effectively. The future is likely to bring more combination products using antihistamines and other mediator antagonists in oral and intranasal formulations. The over-the-counter second-generation antihistamines, such as loratadine and cetirizine, are effective in treating SAR, with cetirizine also being effective in PAR. Although loratadine has an advantage related to less sedation, many studies have demonstrated that cetirizine is among the most rapid-acting and longest-acting second-generation agents. On balance of safety plus efficacy, loratadine and cetirizine would be first choices compared with agents such as diphenhydramine or chlorpheniramine, which produce considerably more sedation and impairment in addition to anticholinergic effects. The antihistamine comparative literature would suggest that first-line treatment of SAR should include either loratadine, based on safety, or cetirizine, based on efficacy for both SAR and PAR, which frequently coexist. The other more recently developed second-generation antihistamines appear to be effective when these agents have failed as initial treatment. Topical intranasal antihistamines are also effective and may be effective in situations in which oral antihistamines have failed. There is no evidence of synergism between oral and intranasal antihistamines.

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Disclosures

Dr. DuBuske has served as an investigator for Sanofi-Aventis, Schering-Plough, Alcon, Novartis, Genentech, UCB, and Allergy Therapeutics; on the speakers' bureau for Sanofi-Aventis, Schering-Plough, Alcon, Novartis, Genentech, UCB, Merck & Co., GlaxoSmithKline, and AstraZeneca Pharmaceuticals; and as a consultant for Sanofi-Aventis, UCB, Schering-Plough, and Allergy Therapeutics. No other potential conflicts of interest relevant to this article were reported.

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This study demonstrated the value of combination antihistamine and antileukotriene therapy for QoL improvement in patients with AR.

This was an important article showing the efficacy of combined intranasal antihistamines and intranasal corticosteroids.