

Pharmacotherapeutic strategies for allergic rhinitis: Matching treatment to symptoms, disease progression, and associated conditions

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ABSTRACT

The selection of specific pharmacotherapy for patients with allergic rhinitis (AR) depends on several factors, including age, most prominent symptoms, symptom severity, patient preference, cost, and comorbid conditions. Guidelines focus on immediate symptoms and monotherapy. However, given the often variable course of disease, understanding symptom patterns, and recommending intervention transitions among agents and classes (and from alternative single and combination medications) can aid in optimization of treatment. This review focuses on considerations for combination therapy for AR, particularly in the context of step-up and step-down treatment, and individual symptoms and comorbidities that may benefit from such treatment (e.g., asthma). Relevant clinical studies for treatment of AR and of AR with comorbid asthma and information on treatment guidelines were identified through MEDLINE searches from inception through 2012. Search terms and phrases included "allergic rhinitis," "asthma," "treatment guidelines," and "stepwise treatment." Stepped methodology is individualized according to patient-specific factors and severity of disease. A possible step-up/step-down approach might move through five stages: step 1, for mild intermittent symptoms, intranasal or oral antihistamine, as needed; step 2, daily intranasal antihistamine (an oral antihistamine or leukotriene antagonist may be considered as an alternative); step 3, daily intranasal corticosteroids (INS); step 4, combination INS and intranasal antihistamines; step 5, further add-on therapy options in severe cases. A step-up/step-down approach to AR pharmacotherapy based on patient response may hold the potential for optimal control of AR symptoms while minimizing side effects and cost of treatment.

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Allergic rhinitis (AR) affects ~10–30% of American adults and as many as 40% of children.¹ It is a significant cause of morbidity because of symptoms, reduced quality of life (QOL), lost work and school days, compromised work and school productivity, and increased medical treatment costs.^{1,2}

The traditional classification of AR as either seasonal or perennial, depending on the individual's sensitization to seasonal/cyclic pollens or year-round allergens (e.g., dust mites and animal dander), is often inaccurate, because sensitization to multiple seasonal allergens may result in continual disease, whereas sensitization to "perennial" allergens may result in sporadic symptoms due to episodic exposure (e.g., animal dan-

der).^{1,3} International guidelines for classification and treatment of AR, such as Allergic Rhinitis and Its Impact on Asthma (ARIA), categorize AR as either intermittent or persistent and mild or moderate-severe to guide initial therapy.⁴ To further refine the analysis of symptom severity, the US Joint Task Force on Practice Parameters for Allergy and Immunology developed a modified seven-point visual analog scale for grading severity of nasal and nonnasal symptoms of AR and their effects on QOL.¹ This scale (not yet validated) scores nasal symptoms such as sneezing, congestion, itchy nose, and runny nose in a range from none to unbearably severe.

Ongoing monitoring of rhinitis control to guide optimization of therapy is important after the initial therapeutic intervention, particularly given the often variable course of the disease. Toward that end, a recently developed, validated, patient-completed instrument, the Rhinitis Control Assessment Test, may help identify patients whose nasal and ocular symptoms are not adequately controlled, thus signaling the need for a change in management or referral to a respiratory specialist.⁵ The reliability, validity, and responsiveness of the six-question form of the Rhinitis Control Assessment Test (RCAT; Fig. 1) were recently shown in a study of 402 subjects recruited from allergist or otolaryngologist offices, after content validity was es-

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1. **During the past week, how often did you have nasal congestion?**

Never	Rarely	Sometimes	Often	Extremely often
☐ ⁵	☐ ⁴	☐ ³	☐ ²	☐ ¹

2. **During the past week, how often did you sneeze?**

Never	Rarely	Sometimes	Often	Extremely often
☐ ⁵	☐ ⁴	☐ ³	☐ ²	☐ ¹

3. **During the past week, how often did you have watery eyes?**

Never	Rarely	Sometimes	Often	Extremely often
☐ ⁵	☐ ⁴	☐ ³	☐ ²	☐ ¹

4. **During the past week, to what extent did your nasal or other allergy symptoms interfere with your sleep?**

Not at all	A little	Somewhat	A lot	All the time
☐ ⁵	☐ ⁴	☐ ³	☐ ²	☐ ¹

5. **During the past week, how often did you avoid any activities (for example, visiting a house with a dog or cat, gardening) because of your nasal or other allergy symptoms?**

Never	Rarely	Sometimes	Often	Extremely often
☐ ⁵	☐ ⁴	☐ ³	☐ ²	☐ ¹

6. **During the past week, how well were your nasal or other allergy symptoms controlled?**

Completely	Very	Somewhat	A little	Not at all
☐ ⁵	☐ ⁴	☐ ³	☐ ²	☐ ¹

Figure 1. The Rhinitis Control Assessment Test (RCAT). (Reprinted with permission Ref. 6.)

established in a separate group of 58 patients.⁶ Use of such an instrument is similar to the approach used in asthma management, in which national treatment guidelines endorse the use of patient-rated screening tools (e.g., the Asthma Control Test) that gauge the level of disease control to help physicians provide the most effective treatment plan.^{7,8}

This review focuses on considerations of combination therapy for AR in the context of transitioning among symptomatic medication classes in a step-up and step-down approach that can be adjusted to symptom severity, individual symptom patterns, and comorbidities (e.g., asthma) that may benefit from such treatment.

METHODS

Relevant clinical studies of treatment of AR with and without comorbid asthma and information on treatment guidelines were identified through searches of the English language literature indexed on MEDLINE from inception to present. Search terms and phrases included "allergic rhinitis," "asthma," "treatment guidelines," and "stepwise treatment."

OVERVIEW OF PHARMACOLOGIC TREATMENT

Optimal treatment of AR requires (1) patient education on the disease, goals of therapy, proper medication

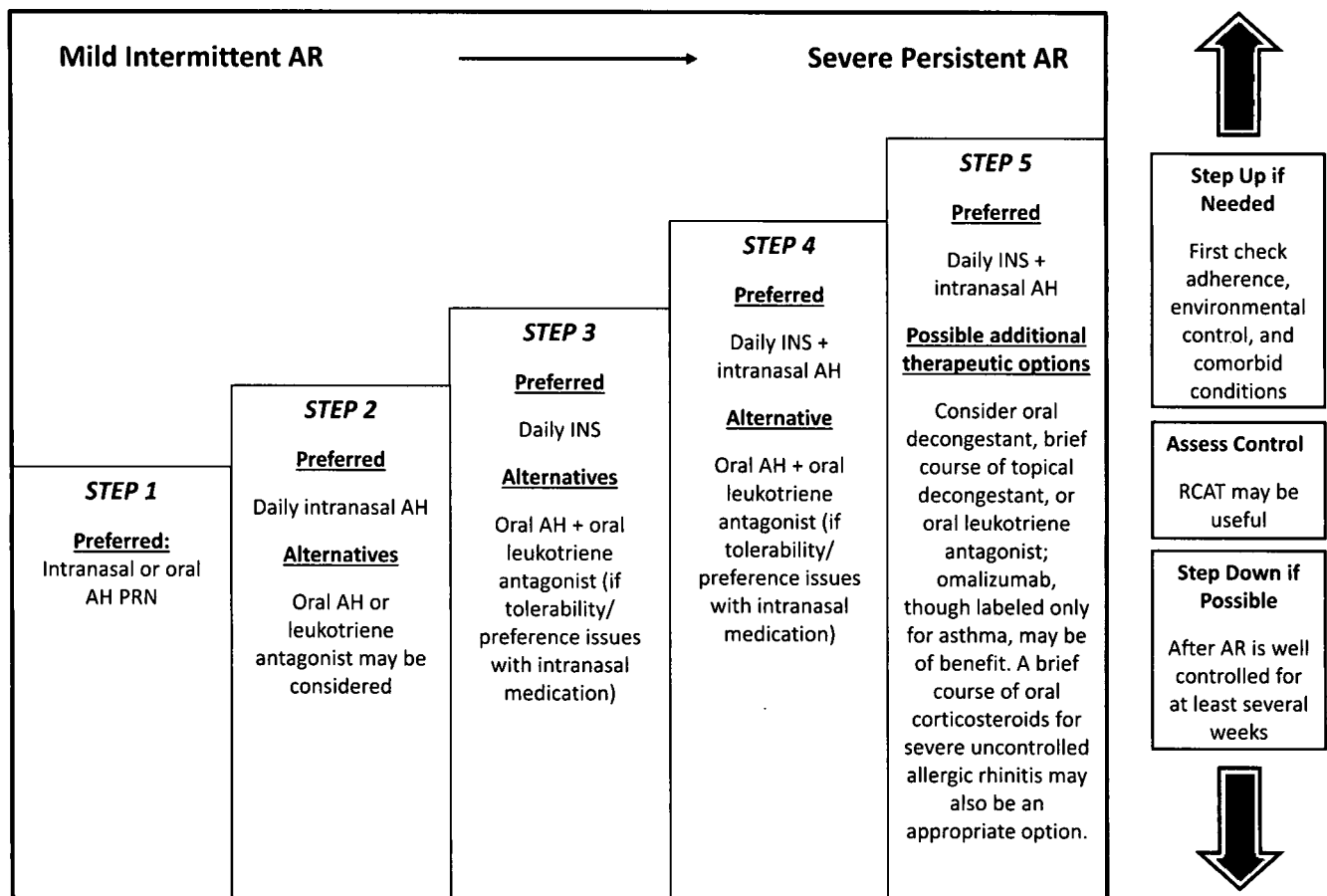


Figure 2. Step therapy algorithm for pharmacologic treatment of allergic rhinitis. Each step should include patient education, environmental control, and management of comorbidities. ADR, adverse drug reaction; AH, antihistamine; AR, allergic rhinitis; INS, intranasal corticosteroid; PRN, as needed. (Based on information from Refs. 1, 4, and 9.)

administration, trigger avoidance, use of appropriate environmental controls, and adherence; (2) pharmacotherapy; and (3) in certain patients, immunotherapy (not addressed in this review), during which pharmacotherapy may still be required.^{3,9} A proposed pharmacologic treatment algorithm for AR derived from evidence-based treatment guidelines and consensus panel findings is presented in Fig. 2.^{1,4,9} Patient monitoring ~2–4 weeks after a treatment regimen is initiated will help assess symptom control and enable the clinician to adjust therapy to be more or less intensive (step up/step down), as needed.

STEPPED PHARMACOTHERAPY

Optimal management of AR is individualized, based on the severity and duration of each patient's specific symptoms and the presence of any comorbidities. Initial treatment with a single agent may progress to combination treatment with multiple classes of pharmacotherapy, and a step-up/step-down approach is recommended using these agents in a manner indicated by continuing monitoring of the degree of rhinitis control.^{9,10} For example, step 1 would be initiated for

the patient with mild intermittent symptoms, with treatment progressing through each succeeding step if symptoms remain uncontrolled. A simplified progression concordant with evidence-based treatment guidelines and consensus panel recommendations might be as follows:

Step 1. Intranasal or oral antihistamine, as needed

Step 2. Daily intranasal antihistamine (an oral antihistamine or leukotriene antagonist may be considered as an alternative)

Step 3. Daily intranasal corticosteroid (INS)

Step 4. Daily combination INS and intranasal antihistamine

Step 5. If symptoms remain uncontrolled, consider adding oral decongestant, brief course of topical decongestant, or oral leukotriene antagonist; although omalizumab is indicated only for asthma, evidence suggests that it may be beneficial in AR as well. A brief course of oral corticosteroids for severe uncontrolled AR may also be an appropriate option.

At each stage, if the patient responds to treatment, the physician may consider reverting to a lower step, taking into consideration for that individual patient the

magnitude of current symptoms, exposure factors (including sensitization to allergens known to be only seasonably present), compliance issues, potential adverse effects, and costs. Similar to recommendations in the National Asthma Education and Prevention Program guidelines for asthma management,¹¹ once AR control is achieved and maintained for at least several weeks, it is reasonable for the clinician to consider decreasing treatment to a less intensive step of pharmacologic therapy. Monitoring is necessary regardless of the direction in which therapy is moving. For instance, although many patients may be apparently sensitized to a purely seasonal allergy, symptoms can persist after pollen season is over¹ and should be monitored for continuing treatment.

SINGLE-AGENT PHARMACOTHERAPY

Potential monotherapy considerations for patients with AR include INSs, oral antihistamines, intranasal antihistamines, leukotriene modifiers, intranasal mast cell stabilizers, oral decongestants, intranasal decongestants, intranasal saline, and intranasal anticholinergic agents.

Intranasal Steroids

INSs have been identified by U.S. and international guideline committees as the most effective medication class for controlling the four major AR symptoms: sneezing, nasal itching, rhinorrhea, and nasal congestion.^{1,4} Their superior efficacy has been shown in numerous clinical trials, meta-analyses, and systematic reviews.^{12–15} At their recommended dosages, all INSs have indicated an excellent safety profile.^{16–20} Of note, the newer INSs (ciclesonide, fluticasone furoate, fluticasone propionate, and mometasone furoate) have favorable pharmacokinetic characteristics that minimize their systemic bioavailability (<1%) versus older INSs. Based on their well-established efficacy and safety, INS agents are recommended as first-line therapy by both national and international task forces for moderate-to-severe intermittent rhinitis and persistent rhinitis of any severity.^{1,4} INSs are available as aqueous nasal sprays and, with the 2011 discontinuation of chlorofluorocarbon nasal aerosols because of environmental concerns, in newer aerosol hydrofluoroalkane formulations (e.g., beclomethasone dipropionate and ciclesonide).^{21,22} Some patients may prefer the aqueous formulations, whereas many others may choose treatment with the aerosols. Preference matters, because satisfaction with a drug product increases the likelihood of adherence to a therapeutic regimen.^{23,24}

Oral Antihistamines

Oral H₁-antagonist (inverse agonist) antihistamines reduce sneezing; itching of the nose, throat, and palate;

and rhinorrhea, but have only a mild effect on nasal congestion.^{1,3} Oral antihistamines may also reduce allergic conjunctivitis symptoms, which are often associated with AR.¹ Second-generation oral antihistamines (e.g., loratadine, desloratadine, fexofenadine, cetirizine, and levocetirizine) are preferred, because they are associated with little or no risk of the sedation, performance impairment, and/or anticholinergic effects including dry/blurry eyes associated with older agents. Thus, second-generation oral antihistamines may be considered for first-line treatment, particularly for those who can not tolerate nasally administered agents or who have minimal congestion but are particularly bothered by cutaneous itching and/or itchy, watery eyes.^{3,9,25}

Intranasal Antihistamines

In addition to their H₁-antagonist effects, intranasal antihistamines (e.g., azelastine and olopatadine) exhibit anti-inflammatory effects *in vitro* on mast cell stabilization, interleukins, cytokine expressions, neural mechanisms, and cellular migration.^{9,26} Given the role of inflammatory mediators in AR, this dual activity may represent an advantage of intranasal antihistamines over their oral counterparts.²⁶

Unlike oral antihistamines, intranasal antihistamines have been associated with markedly reduced nasal congestion in several clinical trials.²⁷ A total of 554 patients with moderate-to-severe SAR received twice-daily intranasal azelastine for 2 weeks in two placebo-controlled U.S. trials.²⁸ Similarly, the efficacy of olopatadine was assessed in two 2-week multicenter studies totalling 1240 patients with SAR.^{29,30} In all four studies, mean reduction from baseline in total nasal symptom score (TNSS) was significantly greater with intranasal antihistamines versus placebo. Reductions in individual nasal symptom scores were also statistically significant, including reduction in nasal congestion in one azelastine study and one olopatadine study. In the other studies, nasal congestion improved numerically but not significantly versus placebo.^{27–30}

Findings from several clinical studies suggest that intranasal antihistamines are superior to oral antihistamines in reducing TNSS.^{26,31–34} In three such studies, intranasal antihistamines also reduced nasal congestion significantly more compared with oral antihistamines.^{26,31,32} In two meta-analyses, intranasal antihistamines yielded lower number-needed-to-treat values than their oral counterparts.^{25,35,36} Furthermore, the intranasal antihistamines have a decidedly more rapid onset of action versus the oral agents. Studies have shown that both azelastine and olopatadine produce significant reduction in symptoms versus placebo within 15–30 minutes.^{31,37–39} Oral antihistamines generally require 2–3 hours before symptom reduction is significantly different from placebo.^{40–43}

The few published comparisons between INSs and intranasal antihistamines show comparable or superior efficacy for INSs.^{13,27,44–47} A 2002 meta-analysis of nine studies comparing INS with azelastine in 648 subjects reported significantly greater reductions in nasal symptoms with INS but no differences in ocular symptom improvement.¹³ In contrast, a recently published double-blind, randomized noninferiority comparison of olopatadine nasal spray and fluticasone propionate in 130 patients with seasonal AR (SAR) showed comparable reductions from baseline in 2-week reflective and instantaneous TNSS with both agents (45.4% for olopatadine and 47.4% for fluticasone).²⁷ Similarly, two separate 2-week double-blind trials in patients with SAR reported comparable reductions from baseline in TNSS for azelastine and fluticasone nasal sprays administered as monotherapy (24.8% versus 27.1% for azelastine versus fluticasone in one study [$n = 151$]; and 16.4% versus 20.4% for azelastine versus fluticasone in the other [$n = 610$]).^{46,47}

Based on the available evidence, intranasal antihistamines are a first-line consideration for intermittent symptoms of any severity and for mild persistent symptoms. They are an option for moderate-to-severe persistent symptoms and may certainly be considered as a rescue medication to relieve breakthrough symptoms, based on their quick onset of action.²⁵ Intranasal antihistamines may be considered for add-on or combination therapy with an INS for patients who are inadequately controlled on monotherapy (see Combination Pharmacotherapy section later in text).⁴⁷

Leukotriene Modifiers

Leukotriene receptor antagonists (LTRAs) have shown efficacy comparable with that of oral antihistamines (with loratadine as the usual comparator) in producing statistically significant improvement in nasal symptoms in patients with SAR or perennial AR.^{1,15,48–50} As monotherapy, LTRAs are less effective than INSs for AR.^{51,52} The combination of an LTRA and an oral antihistamine is superior to either agent alone but comparable or inferior to INSs in reducing AR symptoms.^{1,51,52} These observations are supported by a meta-analysis of 11 studies of LTRAs in 4004 patients with AR, in which INSs reduced mean daily rhinitis symptom scores (in absolute terms) 12% more than LTRAs; LTRAs improved nasal symptom scores 5% more than placebo, and oral antihistamines improved nasal symptom scores 2% more than LTRAs.¹⁵ Although LTRAs can not be considered a preferred treatment option because of their efficacy profile, they are not uncommonly used in patients with both upper and lower airway disease and should be considered part of the pharmacotherapy armamentarium.

Mast Cell Stabilizers

The mast cell stabilizers cromolyn sodium and nedocromil can be considered for first-line pharmacologic treatment for mild intermittent AR, particularly in children, because of their safety profile.⁵³ They are effective in episodic AR, before anticipated allergen exposure, *e.g.*, in which case they protect against allergic response for 4–8 hours.¹ However, mast cell stabilizers are less effective than either INSs or antihistamines.⁵³ Therefore, in moderate-to-severe AR in children, INSs are the treatment of choice,⁵³ the safety profile of mometasone furoate and fluticasone furoate have led to their Food and Drug Administration approval for use in children as young as 2 years of age.

Decongestants

Oral and intranasal decongestants exert a vasoconstrictive effect *via* the α 1- and α 2-adrenoreceptors on the nasal capacitance vessels responsible for mucosal swelling and associated nasal congestion.³ Increased nasal patency occurs within 5–10 minutes after intranasal administration and within 30 minutes after oral administration.³ Monotherapy with oral vasoconstrictors in AR is typically limited to cases in which congestion is the sole or most bothersome symptom,³ as associated, dose-related side effects include insomnia, anxiety, tremors, palpitations, and increased blood pressure. The daily use of topical decongestants for longer than a week may result in tolerance and rebound congestion.

Anticholinergic Agents

Intranasal ipratropium bromide controls nasal secretory output *via* inhibition of parasympathetic function within the nasal mucosa. Therefore, it is primarily effective in controlling watery anterior nasal discharge, with little impact on postnasal drip or other nasal symptoms and a very limited role as monotherapy in AR.³

COMBINATION PHARMACOTHERAPY

Results of clinical studies of combination treatments for AR have shed light on their potential place in therapy.

INSs and Oral Antihistamines

Results of most studies combining INSs with oral antihistamines indicate that the combined treatment provides no significant advantage versus INS monotherapy at improving TNSS and total symptom scores (TSS).^{54,55} For example, in a multicenter, randomized, double-blind, placebo-controlled clinical trial of 702 patients for 15 days, adding loratadine to mometasone furoate nasal spray (MFNS) provided no significant benefit over MFNS monotherapy for symptoms of

SAR.⁵⁶ However, in a study in 95 patients with AR, MFNS plus desloratadine or montelukast showed significantly greater improvement in TNSS scores versus MFNS monotherapy.⁵⁷ A recent investigation found that when eosinophil survival was induced by nasal mucosa human epithelial conditioned media, combined MFNS and desloratadine inhibited survival significantly more than either single drug ($p < 0.01$).⁵⁸ The potential clinical application of these *in vitro* findings requires further study.

INSs and Intranasal Antihistamines

Results of several clinical trials suggest that combination therapy with INSs and intranasal antihistamines may be more effective than either agent alone. In a 14-day, randomized, double-blind study, 610 patients with moderate-to-severe nasal SAR symptoms received either monotherapy with azelastine or fluticasone nasal spray, both sprays, or placebo.⁴⁷ The change from baseline in TNSS was significantly greater in all active treatment groups versus placebo, and combination therapy was statistically superior ($p \leq 0.003$) to either active agent alone. TNSS improved by 28.4, 20.4, and 16.4% with combination therapy, INS monotherapy, and azelastine monotherapy, respectively.⁴⁷

Similar results were seen in a randomized, double-blind, multicenter, 2-week trial in which 151 patients with moderate-to-severe nasal SAR symptoms received monotherapy with azelastine, fluticasone nasal spray, or both.⁴⁶ Combined therapy provided significantly greater improvement from baseline in TNSS compared with monotherapy with either agent (37.9%, combination therapy; 27.1%, fluticasone monotherapy; 24.8%, azelastine monotherapy). A study of 779 subjects with SAR treated with azelastine, fluticasone propionate, combined azelastine/fluticasone, or placebo found significantly greater improvement in TNSS with combined therapy versus either component alone or placebo.⁵⁹ LaForce and colleagues showed comparable efficacy between combination treatment with either olopatadine plus fluticasone or azelastine plus fluticasone in a 2-week, randomized, double-blind, parallel-group study.⁶⁰ In research including >3000 patients, a meta-analysis of three trials of a combined fluticasone propionate/azelastine formulation showed the combination to reduce total nasal symptoms significantly more than placebo or either active agent alone.⁶¹ Based on these results, combination therapy with an INS and a nasal antihistamine is a reasonable consideration for patients whose symptoms do not respond adequately to monotherapy with either agent.³

INS and LTRAs

Studies have yielded variable results regarding the efficacy of adding the LTRA montelukast to INS therapy. In

the study of MFNS plus desloratadine or montelukast mentioned earlier, patients receiving combination treatment showed significantly greater improvement in TNSS scores compared with MFNS monotherapy.⁵⁶ In contrast, Esteitie and colleagues reported that the addition of montelukast had no beneficial impact on either QOL assessments or on nasal symptom scores in individuals with perennial AR with residual symptoms despite 2 weeks of treatment with fluticasone.⁶² Results of a randomized study in 90 patients with AR who received either fluticasone monotherapy, fluticasone plus cetirizine, or fluticasone plus montelukast indicated no statistically significant benefit from the addition of montelukast or cetirizine to fluticasone monotherapy.⁶³

INS and Intranasal Decongestants

Combined administration of INS with intranasal decongestants would offer the theoretical potential for both rapid onset from the decongestant and anti-inflammatory activity plus protection from receptor tachyphylaxis by the INS, yielding better efficacy than either alone. Evidence from two recent trials suggests that combined administration may provide stronger early treatment effect than INS monotherapy while providing a beneficial effect against tachyphylaxis or rebound congestion from prolonged decongestant use.^{64,65}

Oral Antihistamines and LTRA

Several studies have indicated that combining an oral antihistamine and oral montelukast may be more effective than oral antihistamine monotherapy but is generally less effective than INS monotherapy. Cingi and colleagues conducted a 21-day randomized study in 275 patients with SAR who received fexofenadine alone, fexofenadine and montelukast, or fexofenadine and placebo.⁶⁶ Active combination therapy yielded better congestion relief, as measured by patient diary and visual analog scale evaluations as well as rhinomanometry and physical examination.⁶⁶ In the meta-analysis of LTRA studies discussed earlier, 3 of the 11 studies evaluated a combination of LTRA plus antihistamines. The combination was significantly more effective than either agent alone but not more effective than INS.¹⁵ A systematic review of 17 studies of LTRA in 6231 adults with SAR yielded similar findings in terms of the relative efficacy of monotherapy and combination therapy with LTRA.⁶⁷ Specifically, combination therapy with LTRA and oral antihistamines produced greater relief of eye symptoms compared with oral antihistamines alone, but INS was superior in reducing nasal congestion compared with the same combination.⁶⁷ Rhinitis guidelines issued by the U.S. Joint Task Force suggest that combined oral antihistamines and montelukast may provide an alternative for patients with AR

who are unresponsive to or not compliant with INS treatment.¹

Omalizumab

Omalizumab is a monoclonal anti-IgE antibody that modulates allergic inflammation by reducing free IgE and decreasing IgE receptors. Its primary use is in the management of poorly controlled atopic asthma, although it has been shown to be effective for AR in allergen challenge studies and clinical trials.⁶⁸⁻⁷⁰ Given its high cost, reports of anaphylaxis, and lack of oral or topical routes of administration, its role in the treatment of AR will likely remain limited to those with asthma as a comorbid condition.^{3,71}

MATCHING TREATMENT TO SYMPTOMS

Optimal management of AR is based on each patient's specific symptom profile. For example, for rhinorrhea that is not fully controlled by other pharmacologic agents, the addition of the topical anticholinergic agent ipratropium could be indicated.^{3,72} In patients with congestion not adequately controlled by INS and/or nasal antihistamines, addition of a decongestant may be considered. Oral decongestants may be added to an oral antihistamine to target congestion, the primary AR symptom not effectively treated by oral antihistamines and the one that is considered the most bothersome by many patients.⁷³⁻⁷⁶ Topical decongestants may be considered for short-term and possibly intermittent or episodic therapy of nasal congestion. Long-term use is believed to carry potential for rhinitis medicamentosa¹; as noted previously, INS coadministration may attenuate the risk of tachyphylaxis/rebound congestion.^{64,65}

For patients with ocular symptoms accompanying SAR (itching, watering/tearing, and redness), evidence-based guidelines recommend INS as first-line therapy for moderate-to-severe AR, with the addition of intranasal antihistamines or cromone eye drops only when ocular symptoms persist despite the use of INSs or oral antihistamines.^{4,77} Meta-analysis and review of data from randomized placebo-controlled clinical trial data indicates the efficacy of the INS drug class against ocular AR symptoms,⁷⁸⁻⁸¹ and two agents in the class have Food and Drug Administration indication for treatment of ocular symptoms.^{80,82} Intranasal antihistamines have shown efficacy comparable with that of intranasal steroids in several studies of ocular allergy symptoms and to that of oral antihistamines in at least one study.^{14,83,84} Ocular antihistamine drops (whether "pure" antihistamines such as antazoline or pheniramine or antihistamines with mast cell stabilizing activity such as olopatadine and bepotastine) are also an appropriate add-on treatment option when ocular symptoms are uncontrolled by an INS or intranasal or oral antihistamines.^{1,4,77,85-89} In cases of severe ocular

symptoms the topical corticosteroid loteprednol, which has a greatly reduced risk of increased intraocular pressure compared with other topical steroids, may be considered.^{1,90}

COMORBIDITY CONSIDERATIONS

Rhinitis and asthma are linked by common epidemiological and pathophysiological mechanisms, leading to the concept of "one airway, one disease."¹ A conservative estimate by the ARIA work group proposed that AR occurs in ~500 million people worldwide and that ~200 million people also have comorbid asthma.⁴ Symptomatic rhinitis can be associated with poor asthma control and increased risk of exacerbations.⁷² Optimal management of upper airway inflammation may lead to better asthma control for patients in whom asthma is poorly controlled.^{4,91}

Trials of INS in patients with AR and comorbid asthma have found benefits of these agents versus placebo in lower airway hyperresponsiveness.^{92,93} INS use may contribute to improved asthma control, which could be expected to be associated with fewer exacerbations.^{94,95} Indeed, investigations of asthma-related emergency department visits or inpatient hospitalizations have found a lower rate of such events among patients using INSs or, to a lesser degree, oral antihistamines.⁹⁵⁻⁹⁷ It must be noted that despite some clinical trial and retrospective evidence of their efficacy in patients with AR and asthma, INSs are not considered recommended asthma therapy.⁹⁸

Results of several studies of desloratadine in patients with comorbid asthma and AR have shown improvements in asthma and AR symptoms. In a 4-week, multicenter, parallel-group, double-blind trial in 331 subjects with SAR and mild seasonal allergic asthma,⁹⁹ desloratadine compared with placebo significantly reduced mean morning/evening (A.M./P.M.) reflective TSS for SAR (−4.90 versus −2.98; $p < 0.001$) and A.M./P.M. reflective total asthma symptom scores ($p = 0.023$) through days 1–15; the difference in A.M./P.M. reflective TSS for SAR remained significant for days 1–29. Results of a 4-week, double-blind, placebo-controlled trial of 924 patients with SAR and asthma showed significantly improved asthma symptoms and reduced β_2 -agonist use with either desloratadine or montelukast.¹⁰⁰ Both treatments also significantly improved forced expiratory volume in 1 second in a subset of patients with a forced expiratory volume in 1 second of <80% of predicted normal at entry.

The efficacy of montelukast for comorbid AR and asthma is also suggested by the results of an 8-week, multicenter, open-label, observational study in patients with AR and asthma who remained uncontrolled while receiving inhaled corticosteroids with or without long-acting β_2 -agonists. Eight weeks after montelukast was

added to therapy, 76.1% achieved asthma control, with a statistically significant reduction in overall Mini Rhinitis QOL questionnaire scores, representing clinically significant improvement.¹⁰¹

Two studies of cetirizine in SAR patients with asthma showed no consistent differences between cetirizine and placebo in nasal congestion scores, albuterol use, or spirometric lung function parameters.^{102,103} In one of the studies, however, in which treatment was started just before the onset of the fall pollen season, cetirizine maintained significantly better symptom relief than placebo at weeks 1–4, based on mean total rhinitis symptom scores.¹⁰² In addition, there was significant improvement in the total asthma treatment score at weeks 1–5.¹⁰²

World Health Organization and U.S. Approaches to Pharmacotherapy

Both the ARIA guidelines (World Health Organization) and the Practice Parameters on Rhinitis (United States) are referenced in this article and serve as the basis for many of the recommendations discussed here.^{1,4} There are differences, however, between the two, and several Practice Parameter recommendations are more consistent with current practice in the United States. For example, the Practice Parameters look more favorably than ARIA on the use of intranasal antihistamines and oral LTRA in the management of AR.¹⁰⁴

CONCLUSIONS

Defining the optimal pharmacotherapy for AR should be personalized for each patient and depends on multiple factors, including age, most prominent symptoms, symptom severity, patient preference, patient adherence, and comorbid conditions. Ongoing monitoring of the patient's level of disease control is critical to guide adjustments to therapy. A step-up/step-down approach is warranted for continued control of the variable AR symptoms while minimizing the adverse effects and cost of medications.

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