

Minimal persistent inflammation, an emerging concept in the nature and treatment of allergic rhinitis: the possible role of leukotrienes

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Objective: To review the emerging concept of minimal persistent inflammation in allergic rhinitis and its implications for therapy.

Data Sources: Relevant clinical studies in the English language were reviewed.

Study Selection: Material was taken from academic/scholarly journals.

Results: Accumulating evidence suggests that allergic rhinitis is a chronic inflammatory disease instead of a disease of acute symptoms. An approach to the therapy for allergic rhinitis should consider that even when symptoms are absent, a minimal level of persistent inflammation may persist. To prevent unexpected exacerbations, the treatment strategy may need to include managing subclinical persistent inflammation. Therapeutic options addressing the major inflammatory elements in allergic rhinitis, including eosinophils, the cysteinyl leukotrienes, and histamine, must be evaluated as management strategies that can achieve effective control. Traditional medications include intranasal corticosteroids, antihistamines, and immunotherapy. Recently, a leukotriene receptor antagonist has been approved for major rhinitis symptoms (congestion, rhinorrhea, sneezing, and pruritus), suggesting a new option for the treatment of allergic rhinitis.

Conclusions: Because of the possible presence of a minimal persistent inflammation during rhinitis patients' asymptomatic periods, it is important to consider a prophylactic approach to treating allergic rhinitis to prevent or reduce exacerbations during an acute increase in allergen. In light of the advances in the understanding of the pathogenesis of allergic rhinitis, agents must be considered based on their safety, efficacy, and ability to deal with underlying inflammation as well as symptom relief.

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INTRODUCTION

During the past 10 to 20 years, significant progress has been made in understanding the mechanisms of allergic rhinitis (AR). Considerable advances have been made in its pharmacotherapy as well. Unfortunately, the growth of knowledge about AR has not halted its sharp rise in prevalence during the same period.^{1,2} In the United States alone, AR affects 9% to 24% adults,³⁻⁵ and its prevalence in children, which has doubled in the last decades, ranges from 9% to 42%.⁵⁻⁷ Because nearly one-third of individuals with AR never visit a physician,⁸ these reported numbers are, very likely, underestimations.

This rapid growth of AR prevalence comes with a rapidly escalating financial burden. Cost estimates for AR totaled US\$1.8 billion in 1990.⁸ In 1996, prescriptions for AR alone totaled \$593.2 million.⁹ The two most commonly used agents for relief of AR symptoms are intranasal glucocorticosteroids (INs) and antihistamines. Sales revenue for the most popular INs (fluticasone, budesonide, triamcinolone, and mometa-

sone) totaled nearly \$1.5 billion in 2001,¹⁰⁻¹² and the most popular second-generation antihistamines garnered \$5 billion in US sales in that same year (although both of these are not used for AR only).^{10,11,13} In addition to these medication costs, 3.4 million lost workdays have been attributed to AR.⁸

Instead of considering AR as a disease of acute symptoms, it needs to be understood as a chronic inflammatory disease that involves a level of persistent inflammation even in the absence of symptoms. AR should be considered a systemic inflammatory disease that manifests itself as specific, observable symptoms in the upper airway. In this light, therapeutic agents that address the major inflammatory elements in AR, which include activated eosinophils, cysteinyl leukotrienes (CysLTs), and histamine, should be re-evaluated as part of new management strategies for achieving effective, persistent control.

AR IS AN INFLAMMATORY DISEASE

It has become clear in the last decade that AR is an inflammatory disease of the nasal mucosa that initiates the release of mediators from antigen-sensitized immune cells.¹⁴ In the nasal lavage of patients with AR, the baseline eosinophil levels significantly correlated with congestion ($P < 0.05$) and rhinorrhea ($P < 0.01$) that occurred 15 minutes after nasal

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allergen challenge, indicative of an underlying persistent sub-clinical inflammation. As early as 2 hours after allergen exposure, eosinophil levels significantly ($P < 0.05$) increased in nasal lavage fluids (cells present on the epithelial surface). Similarly, eosinophil levels were significantly ($P < 0.05$) elevated 4 hours after nasal allergen challenge in samples recovered using the brush technique (cells present within the epithelium). In addition to the rapid increase of eosinophil levels in the nasal mucosa, the number of activated eosinophils increased from 20% at baseline to 72% 8 hours after challenge ($P < 0.05$). Clearly, eosinophil activation and their levels are essential to the allergic inflammation.¹⁵

Immediately after allergen exposure, mast cells of sensitized subjects release granules that contain preformed mediators, including histamine, chymase, and tryptase. Within minutes to hours, the activated mast cells synthesize and release new mediators: the CysLTs, prostaglandins (PGs), platelet-activating factor, bradykinin, interleukin (IL)-4, IL-5, IL-13, tumor necrosis factor α , and granulocyte-macrophage colony-stimulating factor (Fig 1).¹⁶

The CysLTs act through the CysLT₁ receptor^{17,18} and are important to the chemotaxis of eosinophils.¹⁹ The additional influx of eosinophils leads to the synthesis of more CysLTs, which are capable of modulating the production of other cytokines, such as tumor necrosis factor α and IL-6, endothelin, adhesion molecules, nitric oxide (NO), proteases, and reactive oxygen intermediates.^{20–26} Finally, the activated eosinophils release granules containing toxic basic proteins, the major part of which is represented by the eosinophil cationic protein (ECP), which is measured in high levels in the nasal fluid of patients with different upper airway diseases.²⁷ The CysLTs have been reported to increase the expression of histamine receptors on macrophages and smooth muscle cells, providing a mechanism for amplifying responses to histamine.²⁸ Most of the studies cited here have been performed in animals or in *in vitro* tissue cultures; these results may or may not reflect what occurs in humans.

As CysLTs amplify Th₂ cytokine production and other mediators important to inflammation, other mediators similarly enhance CysLT generation. It has been observed for mediators including IL-4, IL-5, granulocyte-macrophage colony-stimulating factor, eotaxin, endothelin, and transforming growth factor β in mast cells, eosinophils, and macrophages.^{27,29–33} Therefore, CysLTs are an important element of the inflammatory process and not just a mediator that is released to produce upper airway symptoms. They perpetuate the inflammatory process, and their production is perpetuated by other elements of inflammation. Their actions self-perpetuate the inflammation until the inflammatory cycle is broken by inhibiting their production, blocking their receptor, or another anti-inflammatory intervention.³⁴

MEDIATORS OF AR SYMPTOMS

This inflammatory disease is characterized by a dual response separated by 3 to 12 hours. The early-phase response occurs within minutes of allergen exposure and is characterized by sneezing, rhinorrhea, pruritus, and congestion. The late-phase response is characterized primarily by congestion and, to a lesser extent, by sneezing and rhinorrhea. During the late-phase response, symptoms can persist for an extended period, far beyond the time expected from a brief allergen exposure. This would seem to be the manifestation of the self-perpetuating inflammation. The mediators released from inflammatory cells that produce the symptoms of AR are summarized in Figure 2, with the predominant symptom listed first for each mediator.

Histamine

Histamine is the major mediator of the early allergic reaction, leading to sneezing, pruritus, rhinorrhea, and, to some extent, nasal congestion.³⁵ In AR patients, histamine-induced rhinorrhea peaks within 5 minutes and returns to baseline within 10

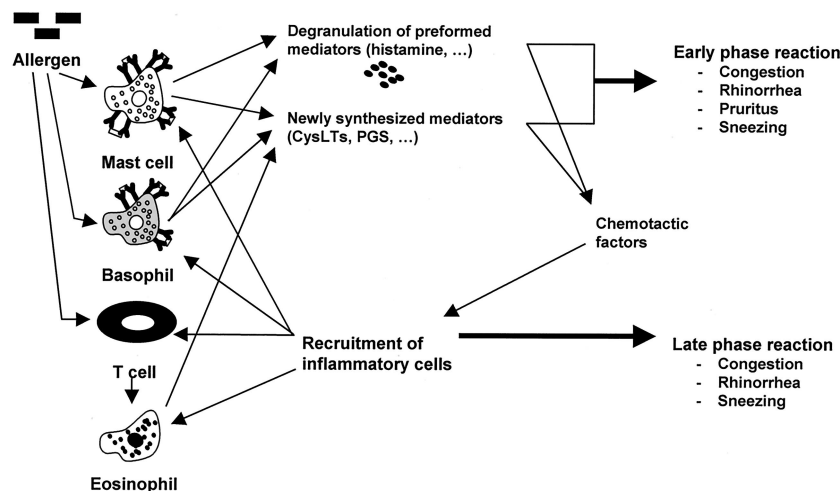


Figure 1. With its multiple cells and mediators, allergic rhinitis is a complex inflammatory disease. Within minutes of allergen exposure, mast cells synthesize and release mediators, leading to the symptoms of the early-phase reaction. Some 3 to 12 hours after exposure, the infiltration of inflammatory cells (basophils, T cells, and the eosinophils) and the release of mediators into the nasal mucosa produce the symptoms of the late-phase reaction, namely, congestion, rhinorrhea, and sneezing. Released mediators such as the cysteinyl leukotrienes (CysLTs) promote the recruitment of additional inflammatory cells. PG, prostaglandin.

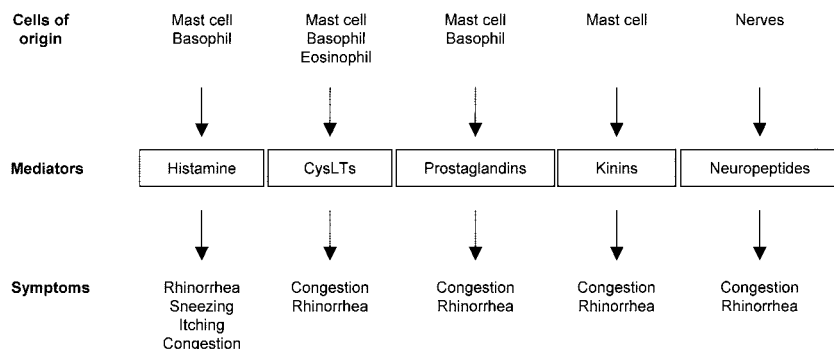


Figure 2. Specific cells release specific mediators, which, in turn, generate specific allergic rhinitis symptoms. In this diagram, the predominant symptom has been listed first. Histamine, for example, is primarily responsible for rhinorrhea, with some sneezing, itching, and congestion. The cysteinyl leukotrienes (CysLTs), prostaglandins, kinins, and neuropeptides are largely responsible for congestion.

minutes,³⁶ whereas sneezing appears 2 to 6 minutes after histamine challenge.³⁷

Histamine's participation in congestion and in AR's late phase is limited.^{38,39} Nasal congestion is likely to be the result of other mediators, a fact that is supported by the incomplete therapeutic efficacy of antihistamines in relieving nasal congestion.³⁸ Thus, although antihistamines have proven to be effective in the early phase of an allergic response, their effectiveness diminishes during the late phase.

Cysteinyl Leukotrienes

Because the CysLTs are important mediators of nasal symptoms, a nasal challenge with leukotriene (LT)₄ or LTD₄ induces nasal congestion by an increase in nasal airway resistance and nasal vascular permeability with less of an effect on nasal itching or sneezing.^{36,40–42} In sensitized symptom-free patients, an allergen challenge with grass pollen induced a significant ($P < 0.05$) dose-dependent increase in LTC₄ levels that persisted for 30 minutes and correlated with a composite symptom score for congestion, rhinorrhea, itching, and sneezing.⁴² Similarly, CysLT levels increased in the nasal fluid of ragweed-sensitive patients with increased levels of nasal ragweed pollen challenge (Fig 3).⁴³ The clinical sneezing response correlated with the appearance of CysLTs ($P < 0.001$).

During pollen season, in patients with seasonal AR (SAR), LTC₄ and ECP occurred in high concentrations, and a significant correlation was found between the concentrations of LTC₄ and ECP.⁴⁴ Because the CysLTs are involved in eosinophil chemotaxis, they help to maintain a continuous influx of eosinophils to the tissue.^{45,46}

Other Mediators

Kinins. The kinins may be important mediators of inflammatory reactions in the upper airways. Bradykinin, which has been found in increased amounts in nasal lavage fluid after allergen challenge *in vivo*, has proven more potent than histamine in inducing both nasal obstruction and plasma protein exudation.^{38,47}

Prostaglandins. Within minutes of exposure to allergen along with histamine, PGs are released by mast cells.³⁵ Nasal challenge with PGD₂ has been shown to increase rhinorrhea and congestion.⁴⁸ The PGs may also contribute to pruritus.³⁵

Neuropeptides. Neuropeptides may induce vasodilation and contribute to congestion.^{35,49} On a molar basis, substance P is 375- to 500-fold more potent than methacholine in increasing nasal airway resistance.⁴⁹

MINIMAL PERSISTENT INFLAMMATION

Recently, a new hypothesis proposed that the presence of AR symptoms alone is not the only parameter to suggest rhinitic inflammation. In fact, it has been shown that even when exposure to allergen is too low to provoke symptoms, there is still inflammatory infiltration in the nasal mucosa.⁵⁰ Obviously, this concept has profound implications for AR management. Minimal persistent inflammation has become an important hypothesis, and it has now been confirmed in

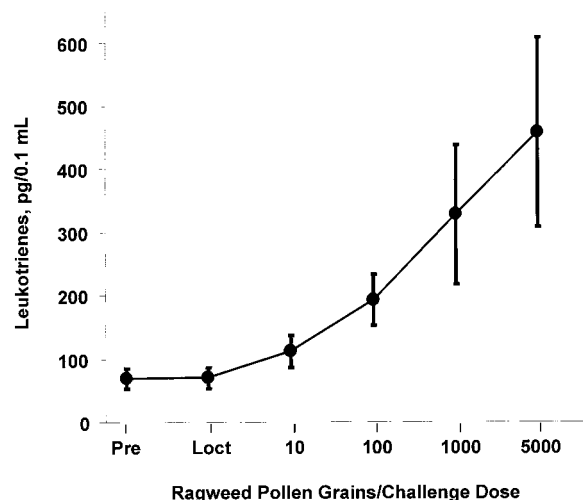


Figure 3. Production of cysteinyl leukotrienes (CysLTs) in 17 allergic subjects challenged with various doses of ragweed pollen. After nasal allergen challenge with ragweed pollen in sensitive patients, CysLT levels increased in nasal fluid. Values are shown as means $\pm$ SEM. "Pre" denotes CysLTs present in nasal washes at baseline; "Loct" denotes CysLTs present in nasal washes after lactose (diluent) challenge. Each pollen challenge resulted in a statistically significant increase in CysLT production, as compared with levels after the preceding dose and with baseline levels (at 10 grains, $P = 0.03$; at 100 grains, $P = 0.004$; at 1,000 grains, $P = 0.02$; and at 5,000 grains, $P = 0.01$). Data are from Creticos et al.⁴³

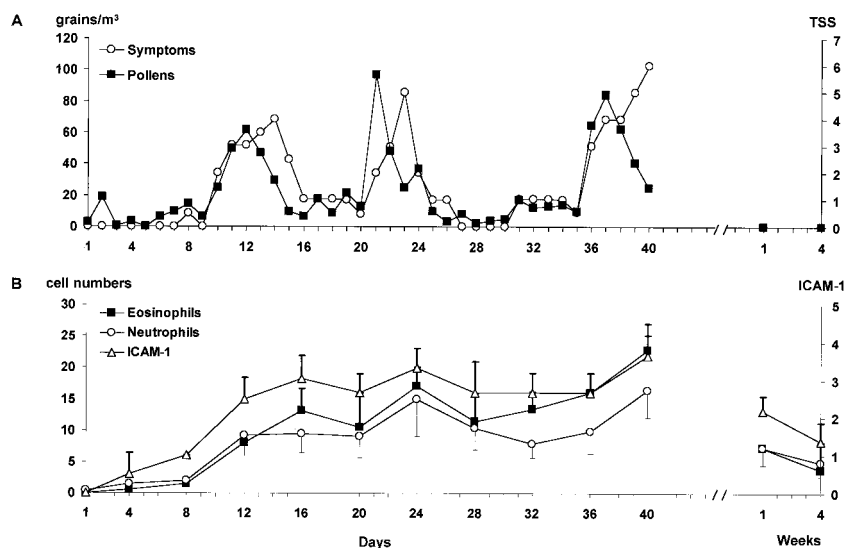


Figure 4. A, Daily total symptom scores (TSSs) and pollen counts. In patients with seasonal allergic rhinitis, the total symptom score for allergic rhinitis followed the pollen level. When the pollen count was low, patients' symptoms were low or nonexistent. B, Eosinophil and neutrophil counts in nasal scrapings and intercellular adhesion molecule 1 (ICAM-1) positivity on nasal epithelial cells ($\pm$ SD) show that the inflammatory parameters were elevated persistently. Data are from Ricca et al.⁵²

studies of patients with seasonal and perennial allergy.^{51–53} Although there is not a wealth of data on perennial AR, and most data are on SAR, it is generally thought that the inflammatory process is similar in both. The new data that suggest minimal persistent inflammation would be applicable to SAR or perennial AR (and possibly to subjects with both).

As shown in Figure 4A, in patients with SAR the total symptom score for AR followed the pollen level closely. When the pollen count was low, the symptoms were low or nonexistent. In contrast, the inflammatory parameters (eosinophils, neutrophils, and intracellular adhesion molecule 1 [ICAM-1]) were elevated throughout the entire pollen season (Fig 4B), even with low pollen count and low or absent symptoms. Furthermore, the inflammation persisted up to 4 weeks after the end of the pollen season.⁵² Similarly, patients with perennial AR (sensitive to dust mite) showed an inflammatory infiltration in the conjunctival and nasal epithelia and a weak expression of ICAM-1/CD54 even when they were totally symptom-free. The patients' relatives and healthy volunteers had few inflammatory cells and no ICAM-1/CD54 expression. A detectable level of house-dust mite was found in all participants' houses, and although no correlation was found between dust mite exposure level and inflammatory parameters, the data suggested that even a low exposure level was sufficient to induce a subclinical inflammation in sensitive patients.⁵³

If both inflammation and hyperresponsiveness can persist without symptoms, then symptoms can no longer be considered the unique markers of allergic disease.⁵³ The underlying goal of treatment guidelines for AR is the effective treatment of symptoms, but this concept of minimal persistent inflammation suggests a different approach to therapy in which symptoms can be considered the "tip of the iceberg" of the allergic reaction, with inflammation and hyperresponsiveness representing the submerged iceberg (Fig 5).⁵²

This new approach to therapy is admittedly subtle. When patients with SAR are asked if they experience sneezing, cough, or fatigue outside pollen season, they generally claim not to have any symptoms. Indeed, any symptoms they experience will be mild, and patients will have long adapted to them. Outside pollen season, when winter's cold, dry air may be irritating, patients who begin to sneeze or cough more than usual will probably assume they have a cold when they may actually be experiencing symptoms from persistent allergic inflammation instead. One might speculate that the SAR patient could be constantly exposed to some level of indoor pollen outside the pollen season. During the peak season, the pollen in the air settles into the household's carpets, upholstered furniture, mattress, pillows, and drapes. With this pollen in the house it might be possible that the patient would be exposed when sleeping from the pillow or mattress or when lying on the floor or an upholstered couch. This might lead to a minimal inflammatory process in the nose.

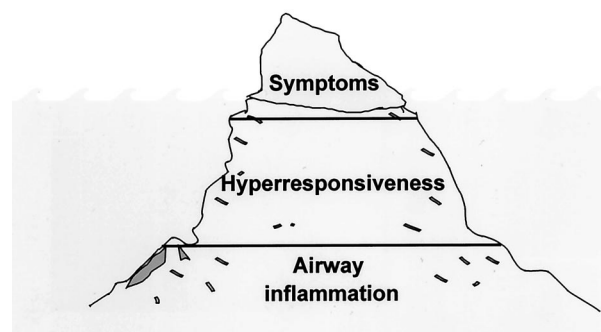


Figure 5. The concept of minimal persistent inflammation suggests a different approach to therapy in which symptoms can be considered the "tip of the iceberg" of the allergic reaction, with inflammation and hyperresponsiveness representing the submerged part of the iceberg.

Another possible explanation for this proposed theory of minimal persistent inflammation is the observation that many SAR patients also have evidence of perennial AR, although they may not express symptoms. If this is the case, then patients who only complain of their seasonal allergies may be exposed to perennial allergens, which could cause minimal persistent inflammation and a constant underlying allergic response. At this time this is speculative, as studies have not been performed to prove this. If there is a minimal persistent inflammation in the nose of these SAR patients, then they might have a priming effect, which could lead to symptoms when they are re-exposed to allergens, even at a low dose.

Clinical observations in the last decade have provided compelling evidence for an interrelationship between asthma and AR. More detailed consideration of the mechanism of inflammation suggests a strong relationship between the nose and the bronchi, and minimal persistent inflammation suggests that this important link can be present without symptoms.⁵⁰

In asthma, the airway epithelium is affected along its entire length. In asthmatic patients who had no signs or symptoms of AR, eosinophil infiltration has been shown in the nasal mucosa. Nasal mucosal biopsy specimens were taken from 27 nonatopic subjects (9 patients with asthma and AR, 8 with asthma but no AR, and 10 healthy control subjects), and bronchial biopsy specimens were also taken from 10 patients. Eosinophil counts were higher in the nasal mucosa ($P < 0.01$) in both asthma groups compared with healthy controls, and there was a significant ($P < 0.001$) correlation between these eosinophil cell counts in the nose and those in the bronchial mucosa (Fig 6).⁵⁴

Although a nasal allergic response does not induce airflow limitation in the lower airways, it can alter bronchial responsiveness. The relationship between AR and lower airway hyperresponsiveness has been studied using double-blind, randomized nasal challenges with allergen or placebo in subjects (15 to 39 years of age) after the onset of seasonal symptoms. All patients had histories of rhinitis and asthma symptoms during May and June, with or without mild nasal or chest symptoms outside the pollen season.⁵⁵ Nasal challenge with allergen or placebo caused no changes in lung function (forced expiratory volume in 1 second, specific airway conductance, or lung volumes) after 30 minutes or 4.5 hours. Nasal allergen provocation, however, did cause a significant increase in bronchial responsiveness to methacholine compared with that of placebo ($P = 0.011$ and $P = 0.0009$ at 30 minutes and 4.5 hours after challenge, respectively).⁵⁵ Although neural effects could have caused the changes that persisted 4.5 hours after challenge, these changes were more likely attributable to the action of inflammatory products that reached the lower airway either through postnasal drainage or by way of the systemic circulation. This example could suggest how the presence of minimal inflammation could be initiated in the lower airway of these patients.⁵⁵

Similarly, in the lower airways of nonasthmatic patients with AR, the inflammatory response after nasal allergen challenge was similar to that of asthma. In both the nasal and bronchial mucosa, there was an increased expression of en-

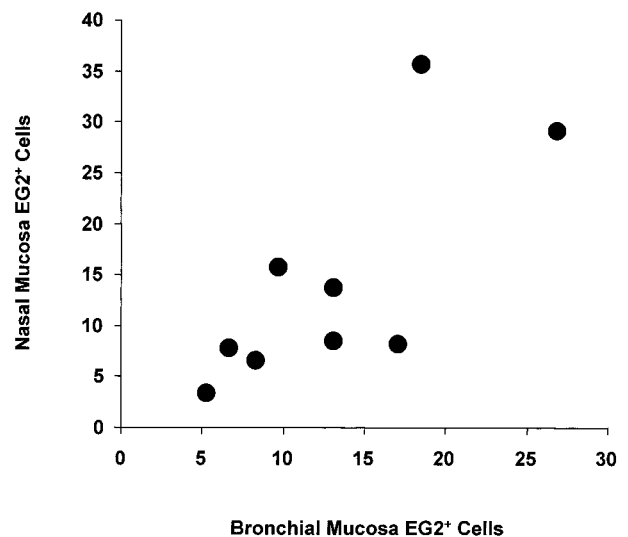


Figure 6. Correlation ($r = 0.851$, $P < 0.001$) between eosinophils in the bronchial and the nasal mucosa. Data are from Gaga et al.⁵⁴

dothelial adhesion molecules and eosinophilic inflammation.⁵⁶ Conversely, segmental bronchial provocation in non-asthmatic, grass pollen-sensitive AR patients resulted in peripheral blood eosinophilia and an increased inflammatory cell number in the nasal mucosa.⁵⁷ These data support a connection between the upper and lower airways in which inflammation present in the lower airway affects the level of inflammation of the upper airway and vice versa. The data also suggest how the persistence of a minimal inflammation in one part of the airway may be initiated by inflammation elsewhere in the airway.

Therefore, any optimal therapeutic strategy for AR should focus on minimizing inflammatory phenomena rather than only on alleviating acute symptoms.⁵² This could be achieved by using persistent treatment with anti-inflammatory agents throughout the entire period of allergen exposure and after suspected contact subsequently with the allergen. With this in mind, a review of current and potential AR therapies would evaluate their place in the strategy to minimize persistent minimal inflammation.

CURRENT RECOMMENDATIONS FOR MANAGING AR

The 2001 ARIA Guidelines ("Allergic Rhinitis and Its Impact on Asthma: the ARIA Workshop Report in collaboration with the World Health Organization")⁵¹ outline the current recommended therapy for AR. These guidelines recommend a course that includes allergen avoidance, pharmacologic treatment, immunotherapy, and patient education.

The INs are the most potent medication available for AR, and they are now considered to be first-line therapy for moderate to severe cases of seasonal and perennial AR. Regular persistent use of INs has been effective in reducing nasal congestion, rhinorrhea, sneezing, and nasal itching in

both adults and children. The INS can suppress multiple mediators of and several stages of the allergic inflammatory process and may explain their potent effect on allergic symptomatology.⁵¹ Although INSs are effective, their onset of action is not immediate and show some efficacy within 8 hours. For optimal control of nasal symptoms induced by repeated maximal allergen challenges, it takes days for their maximal efficacy to develop.⁵⁸

Figure 7 schematically summarizes AR management as recommended by the ARIA guidelines with a slight addition: patients with persistent AR with nasal congestion should be managed with INSs, and mild or intermittent AR should be managed with H₁ antihistamines. Immunotherapy should be used if these first options do not prove effective.⁵¹ The leukotriene receptor antagonists (LTRAs), which are mentioned in the ARIA guidelines as a therapeutic option, have been shown in the time since these guidelines were written to be effective in the relief of all four primary symptoms of AR.^{59–64} The approval of montelukast for the treatment of SAR in the United States allows health care providers another option for treatment.

POTENTIAL ROLE FOR LTRAs IN TREATING AR

As monotherapy the LTRAs would be useful in reducing the inflammation and relieving the symptoms of AR.⁵¹ For example, the LTRA pranlukast, which is approved in Japan, has reduced nasal mucosal swelling in AR patients.⁶⁵ The therapeutic effects of a single dose of the LTRA zafirlukast were evaluated on symptoms of acute SAR. One hundred sixty-four patients, sensitive enough to ragweed pollen to require treatment, were exposed for 8 hours daily for 2 consecutive days in a park during the peak of ragweed season. Compared with placebo, zafirlukast improved the principal symptoms of AR (congestion, rhinorrhea, and sneezing). Patients' nasal congestion improved ($P < 0.01$) most consistently from the evening of the first day through the second day, whereas their sneezing and rhinorrhea ($P < 0.05$) improved more on the second day.⁵⁹ The secondary symptoms (itchy nose, throat, and palate) also improved significantly compared with placebo ($P < 0.01$). Onset of action of zafirlukast was rapid, with symptom relief occurring within 2 hours of dosing. These data showed that zafirlukast was able to rapidly and effectively alleviate symptoms of acute AR.

The LTRA montelukast improved primary and secondary symptoms, inflammation, and quality of life (QOL) in patients with SAR. Treatment produced consistent and significant improvement in nasal congestion, rhinorrhea, itching, and sneezing (Fig 8).⁶⁰ Significant ($P < 0.05$) relief also occurred for the secondary symptoms at night related to sleep (Fig 9). Disease-specific QOL improved significantly ($P = 0.003$) across all seven domains of QOL (activity, sleep, non-nose/eye symptoms, practical problems, nasal symptoms, eye symptoms, and emotional symptoms).^{60,61} Finally, montelukast treatment reduced peripheral blood eosinophilia

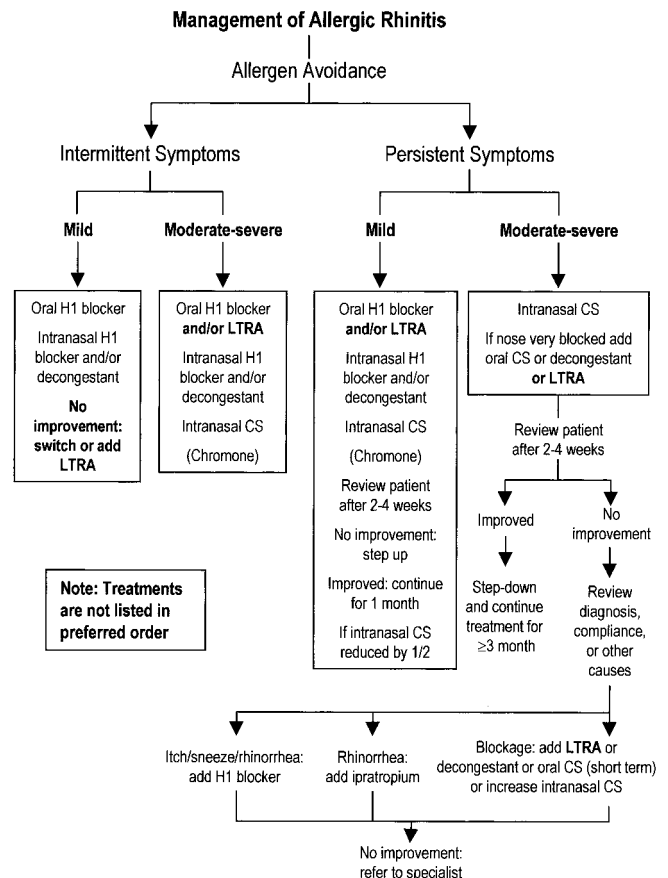


Figure 7. Management of allergic rhinitis (AR) adapted from the Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines. This diagram represents a stepwise approach to treating AR. The treatments are not listed in preferred order except for the management of moderate-to-severe persistent symptoms where the intranasal glucocorticosteroids are the first line of therapy. Although few data were available for the leukotriene receptor antagonists (LTRAs) at the time these guidelines were prepared, recent evidence suggests that these drugs may be helpful in treating AR. To reflect the more recent therapeutic developments, LTRAs were included in this scheme. From: Storms WW. Rethinking our approach to allergic rhinitis management. *Ann Allergy Asthma Immunol.* 2002;88(Suppl):30–35, and adapted from Bousquet et al.⁵¹ CS, corticosteroid.

(Fig 10).⁶⁰ These same benefits were also observed in a fall rhinitis study.⁶³

THERAPEUTIC IMPLICATIONS OF MINIMAL PERSISTENT INFLAMMATION

A therapeutic approach that includes minimal persistent inflammation shifts from alleviating symptoms to a strategy of treating subclinical persistent inflammation. Such an approach would require a re-evaluation of all available therapies. A prophylactic approach using continuous therapy to prevent or reduce exacerbations requires a careful balance between effectiveness and safety.

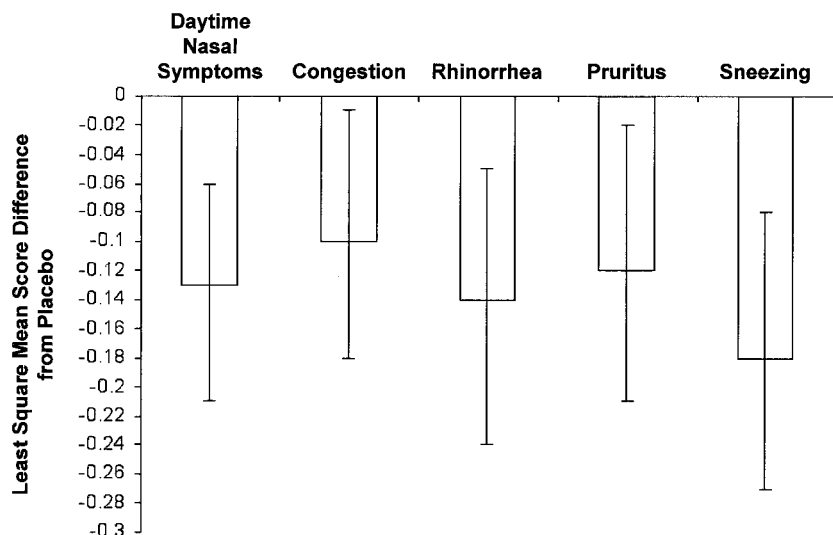


Figure 8. Daytime symptom scores for each of the four cardinal symptoms of allergic rhinitis were significantly reduced by montelukast as well as the total daytime symptom score, compared with placebo. Each bar represents the least square mean difference from placebo (95% confidence interval). All differences were different from zero. Data are from Philip et al.⁶⁰

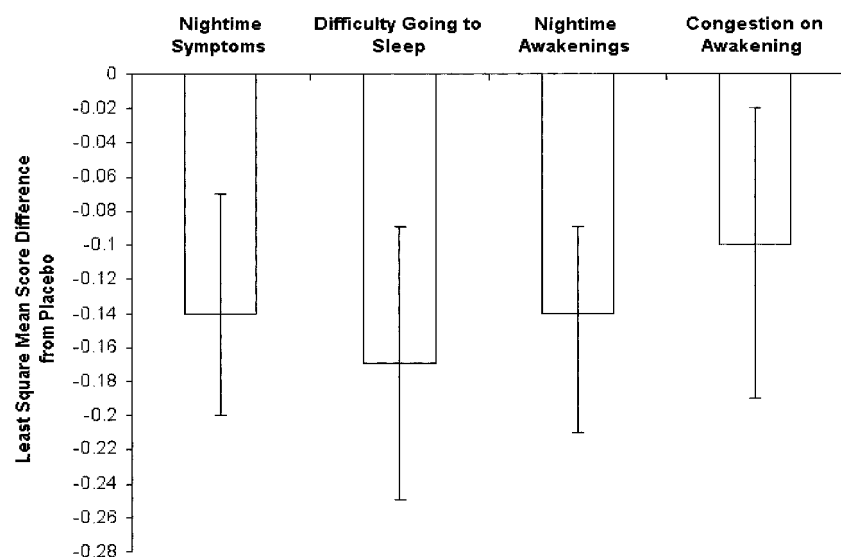


Figure 9. Nighttime symptom scores for each of the three symptoms occurring with allergic rhinitis were significantly reduced by montelukast as well as the total nighttime symptom score, compared with placebo. Each bar represents the least square mean difference from placebo (95% confidence interval). All differences were different from zero. Data are from Philip et al.⁶⁰

The effectiveness and the mechanism of action by which specific agents act on inflammation become important for continuous therapy. The INSs, for example, are the current first-line therapy for moderate to severe cases of seasonal and perennial AR, and they reduce all symptoms. They also suppress several stages of the inflammatory process. Although actual adverse effects may be minimal, many patients have a concern with the long-term use and dosage requirements of these agents, especially in children and patients with concomitant asthma in whom an INS would add its potential adverse effects to those of an inhaled corticosteroid. If, for effective control of AR, continuous therapy is needed to reduce persistent inflammation, studies will be required to evaluate the effects of continuous INS therapy vs "on-demand" INS treatment for their benefits and potential adverse effects.

Second-generation oral H₁ antihistamines reduce effectively the early-phase symptoms, but they are less effective for nasal congestion and minimally address the problem of inflammation. For example, continuous treatment with topical azelastine proved more effective than on-demand use to reduce symptoms and inflammation.⁶⁶ The on-demand therapy provided acceptable clinical control, but it did not reduce allergic inflammation. Similar results were obtained with continuous oral cetirizine treatment in AR patients with pollen allergy (reduced symptoms, inflammatory cells, and even costs) compared with symptomatic use.⁶⁷ Topical H₁ antihistamines have a rapid onset of action and are best used for mild disease, but they usually require twice-daily administration to maintain satisfactory clinical effect. Further evaluation of their anti-inflammatory actions is needed.

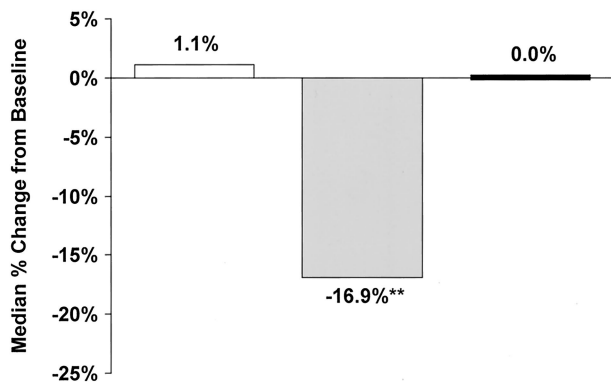


Figure 10. Median percent change from baseline in peripheral blood eosinophil counts. ** $P \leq 0.001$ compared with placebo. White bar, placebo; shaded bar, montelukast; black bar, loratadine. Data are from Philip et al.⁶⁰

Immunotherapy, which must be administered in a physician's office, should be considered when allergen avoidance and drug treatment do not work. This is an option that has been available since 1900, and it is extremely efficacious. Fewer patients receive this mode of therapy, however, than those who are taking medications. The LTRAs have shown benefit in randomized clinical trials,^{60,63} significantly reducing the primary and secondary symptoms of AR by effectively targeting inflammatory mediators of AR. Montelukast and zafirlukast, for example, are safe, with no reported adverse effects, and one could speculate that they might be appropriate to treat minimal persistent inflammation, assuming that patients would be compliant with the respective daily dosing regimen. There is no direct biopsy evidence that LTRAs reduce inflammation in the nose; studies are needed to investigate this.

The argument for treatment of the persistent inflammation in asthma has been developed because of the hypothesis that this chronic inflammation may lead to irreversible changes if it is not treated. AR is associated with inflammation in the nose, but there has not been evidence of any chronic irreversible changes in the nose, which would reflect what is happening in the lungs with asthma. In asthma we assume that inflammation is present in the asymptomatic patient if the forced expiratory volume in 1 second is reduced; this is an indication for therapy. We do not have standard techniques to evaluate subclinical inflammation in the nose that have been correlated with clinical findings; future research studies may help us in finding such a test.

Not all patients with minimal persistent inflammation would be adherent to therapy when the allergen load is minimal or absent and their symptoms were minimal. However, there would be patients for whom minimal persistent inflammation is easily or frequently raised above the threshold for an exacerbation of symptoms, and they would likely adhere to a once-daily regimen to avoid or minimize preventable exacerbations. For example, the only data to date on adherence to montelukast are in patients with asthma, and in a study⁶⁸ evaluating more than 48,000 patients, adherence to montelukast was twice that of adherence

to an inhaled corticosteroid. Future studies will be required to determine whether the known action of montelukast to effectively reduce the activation of eosinophils and thereby reduce inflammatory mediators is beneficial for treating minimal persistent inflammation.

CONCLUSION

According to recent evidence, AR is an inflammatory disease and not only a disease of symptomatic response to allergen. Indeed, inflammation may persist at a minimal level, even in the absence of symptoms. Among the many cellular and molecular inflammatory mediators involved in AR, eosinophils and CysLTs play a substantial role. Studies have shown that the LTRAs are a potentially important new option for the treatment of AR. Because of the possibility of minimal persistent inflammation during the patient's asymptomatic periods, it may be important to consider a prophylactic approach to AR treatment to prevent or reduce exacerbations during an acute increase in allergen. In light of the recent advances in the understanding of the pathogenesis of AR, agents must be considered based on their safety, efficacy, and ability to deal with underlying inflammation as well as symptoms.

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