

AAOA asthma primer: improvement and prevention of asthma with concomitant treatment of allergic rhinitis and allergen-specific therapy

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Background: Asthma and allergic rhinitis are 2 of the most prevalent chronic medical diseases. Asthma is estimated to affect 8% of adults and 9% of children, with nearly 300 million people affected worldwide. Poorly controlled allergic rhinitis may be associated with worsening asthma symptoms over time. Various treatments have been proposed in the improvement and prevention of asthma in children and adults with allergic symptoms, which have included pharmacotherapy with antihistamines and topical intranasal corticosteroids, as well as allergen-specific immunotherapy.

Methods: Articles were selected through PubMed and personal knowledge of the authors based on a comprehensive literature review examining whether treatment of allergic rhinitis improves and/or prevents concomitant symptoms of asthma. The largest and highest-quality studies were included in the literature review. The search selection was not standardized. Articles written in a language other than English were excluded.

Results: Clinical trials have showed improvement in asthma symptoms with concomitant treatment of allergic rhinitis with antihistamines and topical intranasal corticosteroids, though improvement in objective pulmonary function pa-

rameters has not been uniformly demonstrated with antihistamine use alone. There is very strong evidence to suggest that subcutaneous and sublingual immunotherapy may in addition prevent the progression of asthma in high-risk atopic patients by inducing immunological tolerance.

Conclusion: Traditional pharmacotherapy with antihistamines and topical intranasal steroids has been shown to improve allergic rhinitis symptoms with concomitant allergic asthma; however, only allergen-specific immunotherapy offers long-term control in improving asthma symptoms, exacerbations, and likely ultimate prevention in developing asthma. © 2015 ARS-AAOA, LLC.

Key Words:

allergic rhinitis; asthma; allergen-specific immunotherapy; sublingual immunotherapy; subcutaneous immunotherapy; intranasal corticosteroids; antihistamines

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Asthma and allergic rhinitis (AR) are 2 of the most prevalent chronic medical diseases, with asthma affecting nearly 8% of adults, 9% of children,¹ and encompassing nearly 300 million persons worldwide.² The prevalence of AR has nearly doubled since 1970³ and is estimated to cost more than 2 billion dollars annually in the United States.⁴ Nearly 80% of patients with typical asthma symptoms also report general nasal symptoms, with 40% of rhinitis patients reporting coexisting asthma.⁵

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AR encompasses symptoms consistent with an allergic cause such as clear rhinorrhea, nasal congestion, pale nasal mucosa, red and watery eyes in response to inhaled allergens.⁶ Asthma is a condition that encompasses chronic inflammation of the lower airway resulting in expiratory obstruction, with recurrent attacks consisting of cough, wheezing, and chest tightness. Bronchial hyperreactivity may represent an intermediate phase along the disease spectrum leading from nasal AR to asthma.⁷ Asthma and AR both affect the mucosa of the respiratory tract and may share a common TH2 immunologic-mediated imbalance.⁸ In addition, AR has been shown to be a 2-fold to 7-fold risk factor for development of asthma,^{9,10} with more than 20% of all patients with asthma suffering from rhinitis¹¹ and 40% of infants with atopic dermatitis¹² developing asthma ultimately.^{11,12} Both conditions may be exacerbated by re-exposure of airborne allergens. This may lead

to subsequent mast cell sensitization, release of inflammatory mediators, cytokines (interleukin [IL]-4, IL-5, and IL-6), and cysteinyl leukotrienes, which may cause chronic mucosal inflammation,^{8,13} vascular permeability, vasodilation, and rhinorrhea.¹⁴ This subsequently results in ongoing inflammation by antigen-mediated activation of mast cells, basophils, and eosinophils.¹⁵ In a more prolonged late-phase response occurring 4 to 8 hours after the initial immunoglobulin E (IgE)-mediated reaction to the allergen exposure, nasal congestion and lower airway obstruction ensue, with increased bronchial hyperresponsiveness to airborne allergens and irritants.¹⁶ Thus, poorly controlled AR may be associated with worsening asthma symptoms over time.¹⁷

Repeated exposure to inhaled antigens (such as seasonal pollens, mold, and perennial indoor allergens) in patients with allergic predisposition may be the underlying etiology leading to advancement of the allergic march.¹⁸ The link between AR and asthma has been explained by various mechanisms, which include elicitation of the nasal-bronchial reflex, preferential increase in oral vs nasal inhalation due to nasal obstruction, reduction in filtration/humidification of the nose, and postnasal drainage of inflammatory material into the lower airways;¹⁹ however, the latter has not been well supported.²⁰ Primary mouth breathing is hypothesized to bypass the nasal mucociliary filtration system that naturally entraps particles (ie, potential allergens) and irritants, thereby reducing exposure to the lower airways.¹⁶ Prevention of nasal congestion and rhinorrhea resulting from the early allergic response may reduce bronchial hyperresponsiveness. Current treatment for AR consists of pharmacotherapy with antihistamines, topical intranasal steroids, and immunotherapy.

Concomitant improvement and prevention of asthma with treatment of AR with allergen-specific therapy has been observed to be an additional beneficial consequence.²¹ This may be because of reduced nasal inflammation, suppression of histamine-driven immunologic changes, and immunomodulation leading to a more TH1-dominated vs TH2-dominated response.²² Interestingly, as ambient grass pollen increases above 19 grains/m³, the risk of children presenting to the emergency department for asthma exacerbations increases; this association appears to be dose-responsive.²³ Various treatment strategies have been proposed in the prevention and development of asthma in children and adults with allergic symptoms, which have included allergen avoidance, pharmacotherapy (namely antihistamines and topical intranasal steroids), and allergen-specific immunotherapy (ASI).¹⁵

Antihistamines in the improvement and prevention of asthma

Histamine has been shown to increase vascular permeability, facilitate plasma proteins and leukocytes extravascularly, produce cough by direct stimulation of H1 receptors,

lead to mucous production by direct stimulation of H2 receptors, and cause bronchoconstriction through direct muscle stimulation; this cascade ultimately leads to lower and upper airway mucosal edema and inflammation.^{17,24} Elevated histamine levels after allergen-specific challenge have been noted in early and late bronchoconstriction responses during spontaneous acute asthma episodes.¹⁷ The clinical practice guidelines for AR make a strong recommendation that clinicians recommend oral second-generation antihistamines for patients with AR and primary complaints of sneezing and itching.⁶

Cetirizine and loratadine are the 2 most highly studied second-generation antihistamines in regard to concomitant use in AR and asthma. Cetirizine is a highly specific H1 receptor antagonist that infrequently crosses the blood-brain barrier.²⁵ Cetirizine also may inhibit the infiltration of tissues by eosinophils after allergen challenge,²⁶ as well as reduce neutrophil and monocyte chemotaxis in the nose, lungs, and skin,²⁴ which may help with concomitant asthma.²⁶ Unlike older conventional antihistamines that may cause severe sedation and cognitive impairment, cetirizine is only reported to have modest sedation and anticholinergic effects at doses necessary to improve bronchodilation;²⁷ terfenadine, an older antihistamine that has since been removed from the market due to safety concerns, was only effective at ameliorating asthma symptoms at high doses.²⁸

Cetirizine (10 mg daily) given to patients with pollen-induced asthma has been shown to eliminate asthma symptoms of dyspnea and wheezing in 32% percent of patients within 3 months and reduce pharmacotherapy use, with no patients noted to have incapacitating acute asthma attacks.²⁹ Furthermore, cetirizine appears to have an additive bronchodilatory effect when combined with albuterol³⁰ and improve bronchial hyperresponsiveness within 6 hours after nasal allergen challenge.¹³ Moderate doses (20 mg daily) and standard doses (10 mg daily) of cetirizine have been shown to significantly reduce asthma symptoms of chest tightness, wheezing, shortness of breath,^{25,31} and nocturnal asthma in patients with mild to moderate asthma²⁵ in as early as 6 weeks.³¹ Not surprisingly, a dose-responsive relationship has been noted with cetirizine, with higher doses (20 mg daily) generally more effective in improving forced expiratory volume in 1 second (FEV1), peak expiratory flow rate, forced expiratory flow rate, and vital capacity than lower doses (10 mg and 5 mg daily).³⁰ A large randomized prospective clinical trial (Early Treatment of the Atopic Child [ETAC] trial) in infants with a history of atopic disease treated with cetirizine (0.25 mg/kg twice daily) for 18 months interestingly reduced the incidence of asthma in 50% of infants sensitized to grass pollen and 40% of infants sensitized to dust mites.³²

Low-dose loratadine (5 mg daily), another highly potent and specific H1-histamine antagonist, given for 2 to 6 weeks has been shown in patients with AR to decrease asthma symptom severity scores, cough, shortness of breath, chest tightness, need for pharmacotherapy, peak expiratory flow

rates, and FEV1.^{33–35} Improvement in asthma scores has been noted as early as day 1 of treatment.³⁴ Desloratadine, the active metabolite of loratadine, has been shown in patients with grass-pollen AR to decrease circulating eosinophils and bronchial symptom scores in as early as 1 week.³⁶

The effectiveness of antihistamines improving subjective and objective asthma parameters in patients with AR has not been consistently demonstrated. Improvement in pulmonary function with objective clinical parameters such as methacholine challenge and pulmonary function tests with antihistamine use has not been demonstrated universally with loratadine or cetirizine.^{13,25,36,37} Although improvement in cough and sputum production, reduced pharmacotherapy, increased mean expiratory flow and FEV1³⁴ have been noted with cetirizine,²⁹ these results were not statistically significant.^{25,31} Furthermore, although desloratadine has been shown to reduce systemic eosinophilia in patients treated for 7 days, there was no reduction in eosinophilia in the nasal or bronchial mucosa.³⁶ Last, some physicians have been reluctant in practice to use antihistamines in patients with AR and asthma because of concerns about mucous inspissation from anticholinergic effects.³⁸

When evaluating the addition of a variety of antihistamines to existing asthma therapy with leukotriene receptor antagonists, several studies have reported that patients receiving antihistamines reported no significant changes in overall asthma symptoms,^{37,39} dyspnea, or satisfaction with treatment,³⁹ with only a clinically small (4.5%) but statistically significant improvement in forced end vital capacity.⁴⁰ A large multicenter clinical trial among children with atopic dermatitis was unable to demonstrate a reduction in the development of asthma with cetirizine treatment.³² It has been postulated that antihistamines, even at higher doses, may only be effective in mild or moderate persistent asthma rather than in severe persistent asthma.¹⁷

Nasal steroids in the improvement and prevention of asthma

Potent topical nasal steroids are considered first-line therapy for AR,³⁸ are strongly recommended by the current clinical practice guidelines⁶ for long-lasting chronic nasal cavity inflammation, and may be more effective than antihistamines in controlling symptoms.⁴¹ Topical nasal steroids may improve lower airway inflammation in patients with established AR and asthma as follows: reduction in nasal inflammation, improvement in nasal airflow, reduction in the nasopulmonary reflex,^{42,43} decrease in IL-4 and IL-5 expression, promotion of transforming growth factor (TGF)- β expression, decreased influx of eosinophils into the nose,⁴² and promotion of epithelial reconstitution.⁴⁴ Improvement in bronchial responsiveness from intranasal steroids has been theorized to occur because of reduction

of postnasal rhinorrhea, mild systemic absorption, and inhalation into the bronchial lower airway.⁴² Remarkably, a Mayo Clinic study demonstrated that topical nasal steroid treatment with beclomethasone in patients with ragweed AR and coexisting asthma unexpectedly improved both AR and asthma symptoms.⁴⁵

Initial treatment of children with chronic nasal obstruction attributed to AR with intranasal budesonide resulted in decreased asthma scores and reduced exercise induced bronchoconstriction; however, the study was unable to exclude the possibility of intranasal intrapulmonary deposition of steroids.⁴⁶ More recently though, intranasal corticosteroids have been shown to likely improve asthma symptoms by improving nasal function rather than a direct effect on the lungs because less than 2% is delivered to the lung, and only a small amount is swallowed and absorbed through the gastrointestinal tract.⁴⁷

Recent clinical trials have shown that topical nasal steroids reduce inflammation, polypsis, and may improve concomitant asthma symptoms.⁴⁸ Treatment with intranasal aqueous beclomethasone in patients with AR and concomitant asthma for as few as 4 weeks improved bronchial hyperreactivity and evening/morning asthma symptom scores.⁴⁷ This is further supported by evidence that patients with asthma and AR were observed to improve bronchial hyperresponsiveness with nasal beclomethasone after exposure to ragweed pollen⁴⁸ within 6 weeks of therapy; compared to patients treated with intranasal beclomethasone, patients in the placebo group had significantly worse bronchial responsiveness to inhaled methacholine.⁴⁸ Intranasal and oral inhaled budesonide, when combined, have been shown to improve peak expiratory flow, rescue inhaler requirement, asthma score, and daily activity score.⁴⁹ Improvement in lower airway disease symptoms, need for pharmacotherapy, bronchial hyperresponsiveness, and FEV1 has been duplicated with intranasal mometasone,⁵⁰ fluticasone,⁴² and triamcinolone.⁵¹ Improvement has been observed in patients as early as the first day of treatment.⁵⁰

Extraordinarily, patients with pollen-induced AR who received mometasone intranasal therapy, training on the proper use of nasal sprays, and a lesson on the relationship of AR and asthma had significantly fewer asthma symptoms and required less pharmacotherapy than patients without detailed training.⁵² Furthermore, improvement in asthma symptoms may be extrapolated to reduce utilization of health care services. A retrospective cohort of children and adult patients aged 12 to 60 years treated with intranasal corticosteroids for AR resulted in one-half the risk of asthma-related events such as hospitalizations compared to untreated patients.⁵³ Last, analysis of health insurance claims in a large cohort of patients showed the greatest reduction in emergency department visits for patients with asthma occurred in those who received the greatest number of prescriptions for topical nasal steroids.⁵⁴

Most studies examined have shown clinical improvement in asthma with concomitant use of intranasal steroids

for AR. However, the Preventive Allergy Treatment (PAT) study demonstrated in a multicenter open clinical trial that the use of nasal steroids was lowest in children who ultimately did not develop asthma.⁵⁵ Although intranasal corticosteroids are generally considered to be safe and well-tolerated, a recent meta-analysis demonstrated concerns regarding decreased knemometry growth in children with as short as 4 weeks of treatment,⁵⁶ potentially limiting long-term use for children with concomitant AR and asthma.

ASI in the improvement and prevention of asthma

ASI should be strongly considered in patients with allergic diseases, those who prefer to potentially avoid long-term pharmacotherapy, and those who desire to alter immunological tolerance to improve asthma symptoms, bronchial hyperresponsiveness, and pulmonary function. With ASI, small, controlled doses of allergens are given to patients over a period of time and titrated to doses necessary to promote immune tolerance.⁵⁷ The mechanism of action of ASI is likely the result of a switch from TH2-mediated to TH1-mediated immunity with a subsequent reduction in the production of IL-4, IL-5, and IL-13 cytokines, resulting in reduced upper and lower airway inflammation.⁵⁸ ASI may prevent progression from AR to asthma.⁵⁹ Clinicians should refer patients with AR for immunotherapy who have had an inadequate reduction in symptoms with standard pharmacotherapy according to current practice guidelines.⁶

Subcutaneous immunotherapy (SCIT) has been shown to improve asthma symptoms, pulmonary function, and reduce pharmacotherapy intake in a large meta-analysis consisting of prospective, randomized controlled trials involving 962 patients suffering from asthma.⁶⁰ A Cochrane review studying SCIT specific to dust mite, pollen/grass, animal dander, and mold evaluated 88 studies consisting of 3459 subjects with asthma, and found that SCIT improved asthma symptoms, reduced pharmacotherapy use, and decreased bronchial hyperresponsiveness⁶¹ against dust mite and pollen allergens. The overall conclusion was that treatment of 3 asthma patients with allergen SCIT would prevent an asthma exacerbation in 1 person, and treatment of 4 asthma patients would decrease pharmacotherapy use and bronchial hyperresponsiveness in 1 person; however, there was no consistent effect of immunotherapy on lung function or reduction of asthma symptoms when using animal dander extracts.⁶¹ Long-term prevention of asthma in allergy sensitized children with immunotherapy has also been shown. Over an observation period of 14 years, 72% of children with asthma treated with ASI compared with 22% of children treated with placebo were free of asthma.⁶² Long-term prevention of asthma has been shown at follow-up at 5 years⁶³ and 10 years¹⁵ despite 2-year termination of immunotherapy.

The development of sublingual immunotherapy (SLIT) in the 1980s was an important advancement, with reduc-

tion in systemic side effects from SCIT and improved tolerance in pediatric patients.⁸ SLIT has also been studied extensively; 2 large meta-analyses consisting of 256 children and 1000 adults and children showed significant improvement in asthma symptom and medication requirement scores.^{21,64} Similarly, the Efficacia nella rinite allergica di SlitOne (EFESO) trial in Italy demonstrated that adults with AR who later developed asthma were significantly less likely to have been treated with 2 years of SLIT compared to individuals taking traditional pharmacotherapy.⁶⁵ A comprehensive systematic review found modest evidence to support that SLIT improves asthma symptoms.⁶⁶ The cumulative strength of evidence has been suggested to be class 1a for SCIT and class 1b for SLIT in preventing the subsequent development of asthma^{67,68} by inducing immunological tolerance with continued clinical improvement despite cessation of treatment. Despite the overwhelming evidence, there are no sublingual aqueous forms of immunotherapy approved for use by the U.S. Food and Drug Administration (FDA), but tablet forms were approved in 2014 for ragweed and grass pollen.⁶⁶

Dust mites

Two large meta-analyses consisting of 441 children and 452 children with asthma showed that treatment with dust mite SLIT resulted in decrease in symptom and medication scores compared to placebo.^{69,70} Nearly one-half of patients allergic to house dust mites that were treated with *Dermatophagoides pteronyssinus* extract encapsulated in liposomes showed decreased symptom and medication scores after only 1 year of therapy.⁷¹ In addition, children and adults with asthma exacerbations attributed to house dust mite allergies have demonstrated significant reductions in asthma exacerbations, decrease need for pharmacotherapy, and decreased bronchial hyperreactivity after treatment with allergen-specific SCIT for 3 years.^{22,72,73}

In children aged 6 to 17 years with asthma and allergies to house dust mites, SCIT resulted in mean daily fluticasone propionate reductions from 330.3 μ g to 151.5 μ g compared to no reduction in the control group. Surprisingly, patients treated with SCIT to *D. pteronyssinus* in a 6-week cluster accelerated regimen were observed to have faster decreases in asthma symptoms compared to patients in the conventional 12-week schedule.⁷⁴ A small randomized controlled trial consisting of children with mild persistent asthma and rhinitis treated with 12 months of SLIT, SCIT, or standard pharmacotherapy, showed significant decreases in total asthma scores in children treated with immunotherapy.⁷⁵ Children receiving 12 months of sublingual immunotherapy to standardized *D. pteronyssinus* and *Dermatophagoides farinae* also showed improvement in forced expiratory flow, bronchial hyperactivity, reduction in the number of acute asthma exacerbations, and significant reduction in the need for pharmacotherapy; clinical improvement was even noted as early as 6 months.⁷⁶ However, a recent Cochrane review found only a

borderline reduction in asthma symptoms among studies treating patients with dust mite immunotherapy.⁶¹

Pollen

Overall, a recent Cochrane review demonstrated superior reduction in asthma symptoms with immunotherapy extracts of pollen compared to dust mites.⁶¹ Grass pollen SCIT given to asthma patients aged 3 to 16 years over 2 seasons have showed decreased asthma symptoms scores, decreased need for pharmacotherapy, and improvement in bronchial reactivity to allergens.⁷⁷ A large multicenter clinical trial (the PAT study), the first prospective long-term follow-up study testing the hypothesis of whether ASI may reduce the development of asthma, showed that ASI in children with grass and/or birch allergy for 3 years resulted in significantly fewer asthma symptoms after 5 years⁵⁵ and 10 years¹⁵ despite treatment termination after 2 years. However, bronchial responsiveness to methacholine showed no significant improvement, attributed to possibly the natural history of improvement in control patients from infancy to adulthood.

Tree pollen SLIT for over 2 years has likewise been shown to decrease asthma symptoms, decrease pharmacotherapy use, increase force expiratory volumes, and decrease rescue medication usage.^{78,79} In Italy, SCIT to *Parietaria judaica* pollen reduced development of new asthma symptoms from 47% to 14%, reduced prevalence of asthma by 12%, and the need for rescue medications; however, bronchial hypersensitivity and sputum eosinophilia were unchanged.⁵⁹ It is estimated that 6.6 patients with AR need to undergo immunotherapy with *Parietaria* to prevent 1 patient from subsequently developing asthma.⁵⁹ Long-term asthma prevention was shown at follow-up 6 years after termination of immunotherapy, with none of the patients initially presenting with rhinitis developing asthma.⁷⁹ Similar findings have been demonstrated in children with seasonal allergic rhinoconjunctivitis caused by allergy to birch and grass pollen; children treated with specific immunotherapy with grass⁸¹ and birch allergens⁵⁵ were over 3 times less likely to develop asthma after 3 years.⁸⁰ It has been estimated that atopic children not undergoing immunotherapy

are 3.8 times more likely to develop asthma than similar children undertaking ASI.⁸⁰ A large meta-analysis of 441 children with asthma showed that treatment with pollen SLIT reduced symptom and medication scores compared to placebo.⁶⁹ Patients undergoing SLIT with birch and *Parietaria* showed improvement in methacholine sensitivity/bronchial hyperresponsiveness,⁸¹ pulmonary function, and nasal eosinophil counts as early as 12 months, likely due to the estimated 12-fold increase in cumulative dose compared to SCIT.⁷⁸

Conclusion

There is a very strong anatomic, functional, and immunologic relationship between the nasal upper airway and bronchial lower airway. Nasal stimulation by airborne allergens induces nasal obstruction and edema, thereby reducing nasal breathing and filtration, leading to bronchial inflammation and lower airway obstruction. A common mechanism proposed includes local irritation of the nasal mucosa leading to upregulation of inflammatory mediators within the respiratory tract.⁸² Asthma may be the most significant potential morbidity in patients suffering from AR. Understanding the critical environmental risk factors influencing AR to later manifest as bronchial asthma is crucial to implementing effective pharmacotherapy. Traditional pharmacotherapy with antihistamines and topical intranasal steroids has overall been shown to improve the symptoms of AR with concomitant allergic asthma; however, only ASI offers long-term control and outcomes in improving asthma symptoms, reduces exacerbations, and likely prevents development of asthma. The mechanism of action of ASI is likely the result of a switch from TH2-mediated to TH1-mediated immunity with a subsequent decrease in IL-4, IL-5, and IL-13 cytokines, resulting in reduced upper and lower airway inflammation. Treatment of AR proactively has been shown to reduce asthma symptoms, bronchial hyperreactivity, and reduce the need for pharmacotherapy. Additional studies are necessary to examine whether early treatment of AR may ultimately prevent the progression to asthma, though clinical studies to date seem to support this hypothesis as well. 

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