Although it is generally considered that many antihistamines have little or no efficacy in managing asthma, they are worth another look, because histamine is a major mediator that can cause airway smooth muscle constriction and because it is a major product of mast cells and basophils, the primary cells responsible for allergic reactions. In addition, bronchial hyperresponsiveness to histamine is a key feature in the diagnosis of asthma. The role of histamine, through its H1 receptors, in activating various immune system cells, such as macrophages, dendritic cells, or even lymphocytes, and contributing to airway inflammation should not be underestimated.

The failure of antihistamines to produce meaningful clinical effects in asthma can be attributed to drug potency, dose-limiting anticholinergic effects and central nervous system side effects, particularly with first-generation agents, and redundancy in the immune system where other mediators, such as leukotrienes and prostanoids, are also potent causes of lower airway obstruction.

**Antihistamines Have Anti-Inflammatory Effects**

Studies have shown that antihistamines have a dose-response effect on the release of various mediators in human and animal allergic reaction models. Other anti-inflammatory properties have also been recognized. For example, one study using ovalbumin (OVA) stimulated T-cells from mice treated with desloratadine and challenged with OVA found that desloratadine reduced proinflammatory Th2 cytokines but had no significant effect on anti-inflammatory Th1 cytokines.

Several studies evaluating the role of antihistamines in blood-cell trafficking in asthma and seasonal allergic rhinitis suggest that antihistamines reduce the movement of inflammatory cells from the circulation into the tissues. In one study, antihistamines produced a significant dose-related reduction in soluble intracellular adhesion molecule-1 from nasal epithelial cells cultured in the presence of eosinophils treated with latex beads, and this was associated with a dose-related attenuation of eosinophil adherence to endothelial cells.

Similarly, a study of 20 children with seasonal allergic rhinitis in which nasal lavage was performed before and after seasonal treatment with cetirizine found that the antihistamine reduced the number of eosinophils in the nasal lavage, suggesting decreased trafficking into the nasal mucosa. A similar finding was noted in a study of 12 asthmatic patients who were treated with cetirizine 15 mg twice daily or placebo for 4 weeks in the beginning of the pollen season and then challenged with allergen. Bronchial alveolar lavage 24 hours after allergen challenge revealed significantly fewer eosinophils in the cetirizine group compared with the placebo group.

**Seasonal Allergic Rhinitis with Asthma**

Several studies evaluating the effects of antihistamines on asthma in the context of seasonal allergic rhinitis have found that these agents exert beneficial effects on asthma symptoms. In a 6-week parallel-group study comparing cetirizine with placebo in 90 patients with asthma and seasonal allergic rhinitis during pollen season, cetirizine significantly reduced asthma symptoms, such as chest tightness, wheezing, breathlessness, and cough. Patients taking cetirizine also reported improvement in quality of life measures and...
were more likely to continue with the study compared with those taking placebo. These results are a far cry from a recommendation made in 1983 that antihistamines be contraindicated in asthma. A more recent 4-week study of desloratadine 5 mg once daily versus montelukast 10 mg once daily versus placebo, which included patients with severe asthma, found that both active treatments improved symptom severity scores and reduced bronchodilator requirements. It is not known whether these beneficial effects result from the reduction in the magnitude of the nasal airway disease or whether they reflect direct effects of antihistamines on the lower airways.

**BRONCHIAL HYPERRESPONSIVENESS**

Antihistamines have been shown in several studies to exert beneficial effects on bronchial hyperresponsiveness. In one study, 16 patients who were shown to have a dual response to allergen challenge were treated with twice-daily cetirizine 15 mg or placebo. Although there was no change in early allergic response, there was a significant reduction in the late allergic response in the cetirizine-treated group versus placebo, as measured by maximum fall in forced expiratory volume in 1 second (FEV1) and area under the curve at 3 and 8 hours.

Exercise-challenge testing in 11 children taking loratadine or placebo demonstrated improved airway function during exercise with loratadine versus placebo. Mannitol-challenge testing in 20 subjects with mild asthma who had received either fexofenadine 180 mg or montelukast 10 mg 2 days prior to challenge revealed that fexofenadine significantly increased the provocation dose (PD 15) compared with placebo and delayed recovery from baseline, whereas the leukotriene antagonist montelukast showed no change in PD 15 compared with placebo but significantly improved return to baseline.

**ATOPIC MARCH**

Asthma often coexists with allergic conditions, such as eczema, dermatitis, and rhinitis. In a study of children at high risk for developing asthma because of allergy, high immunoglobulin E levels, and a strong positive family history of allergy, only 3 of 45 children taking ketotifen for 3 years developed asthma, compared with 14 of 40 children taking placebo, a statistically significant difference. Another important study, the Early Treatment of the Atopic Child (ETAC) study evaluated the development of asthma in children aged 1 to 2 years with atopic dermatitis and a positive family history of atopy but no history of wheezing after 6 months of age after 18 months of treatment with cetirizine 0.25 mg/kg twice daily or placebo. Although there was no significant effect with cetirizine therapy, when the entire subject population was considered, cetirizine showed significant protective effects against developing asthma in children with high IgE levels to grass pollen and house dust mites. These effects were maintained after discontinuation of treatment.

**ADDITIVE THERAPY**

Histamine and the leukotrienes are released in concert during the early phase of allergic reactions. Similarly, increased levels of histamine and leukotrienes are found in the airways during the late phase. A study by Roquet and colleagues showed that the combination of loratadine (antihistamine) and zafirlukast (leukotriene receptor antagonist) had impressive, additive inhibitory effects on both the early and the late bronchoconstrictive reaction induced by allergen inhalation challenge in subjects with asthma. In a placebo-controlled study evaluating combined therapy with montelukast (also a leukotriene receptor antagonist) and loratadine in 117 patients with moderate persistent asthma and high rates of allergic rhinitis (95%), the investigators found that the addition of the antihistamine to the leukotriene antagonist had a statistically significant beneficial effect on FEV1, morning and evening peak expiratory flow, and beta-agonist use.

In a single-blind, double-dummy, randomized crossover study comparing cetirizine plus montelukast with inhaled and intranasal corticosteroids in 14 patients with moderately severe asthma and seasonal allergic rhinitis during grass pollen season, Wilson and his colleagues found that the combination of cetirizine and montelukast had a significantly greater effect on adenosine monophosphate challenge compared with inhaled and intranasal budesonide, but the corticosteroids were significantly better in terms of exhaled nitric oxide measurements. There was no significant difference between the cetirizine/montelukast combination and the corticosteroids in terms of symptom scores and bronchodilator use.
CONCLUSION

Antihistamines protect the lower airways from the bronchoconstrictive effects of allergic reactions, have anti-inflammatory effects, and seem to influence bronchial hyperresponsiveness and the atopic march. There is evidence that antihistamines are beneficial in asthma, especially when it coexists with seasonal allergic rhinitis or when antihistamines are combined with leukotriene antagonists. More studies are required to examine whether—and most importantly, in what instances—antihistamines should be used alone or in combination with other agents for the treatment of asthma.

REFERENCES

Inhaled corticosteroids are first-line therapy for asthma in the United States and many other countries; however, particularly at high doses, they can produce unwanted local and systemic side effects. Physicians should therefore consider the potential side effects of these agents in every patient receiving them and at every visit.

Corticosteroids exert their beneficial effects on asthma symptoms and lung function by interacting with a corticosteroid receptor. Because the corticosteroid receptor in the lung is the same as the corticosteroid receptors elsewhere in the body, the amount of inhaled drug that actually gets into the systemic circulation is the major determinant of systemic risk. The lower the percentage of drug that gets into the lung, the higher the percentage of drug that is lost to deposition in the oropharynx, where it is swallowed and ultimately becomes available to circulate throughout the body. Absorption of corticosteroids by the lung and subsequent distribution into the systemic circulation is another source of systemic exposure. The quest for the “ideal” inhaled corticosteroid thus begins with the requirement that the agent be highly potent in the lung and inactive elsewhere. The pharmacologic properties needed for an agent to produce such effects clinically are summarized in the Sidebar.

Is there such an agent? Recent and accumulating data show that ciclesonide, a novel inhaled corticosteroid that is currently under investigation, possesses some of these properties, is the safest inhaled corticosteroid studied to date, and may be the “ideal” corticosteroid for the treatment of asthma. The efficacy and safety of ciclesonide were evaluated in a double-blind, randomized, placebo-controlled clinical trial including 360 asthma patients with a forced expiratory volume in 1 second of 60% to 90% and evidence of reversibility. Patients were pretreated with beclomethasone dipropionate and, after 2 weeks, were randomized to inhaled ciclesonide (80 µg and 320 µg) or placebo once daily in the morning for 12 weeks. The efficacy of the study regimens was estimated as follows: 62% for ciclesonide 80 µg, 77% for ciclesonide 320 µg, and 45% for placebo. Compared with baseline, morning peak expiratory flow increased by 129 mL and 192 mL in patients taking the 80 µg and 320-µg doses of ciclesonide, respectively, and decreased by 28 mL in patients taking placebo. No significant differences between treatments were found in the incidence of adverse events.

**The Ideal Inhaled Corticosteroid**

*NEGligible Local Side Effects*
- Inactive parent compound
- Low oropharyngeal deposition
- Limited exposure of oropharynx to active molecule

*HIGH Potency*
- High affinity for glucocorticoid receptor
- Prolonged residence time in lung
- Lipid conjugation in airways

*NEGligible Systemic Side Effects*
- Low oral bioavailability/first-pass metabolism
- Rapid systemic clearance
- Complete plasma protein binding


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*Based on a presentation given by Michael A. Kaliner, MD, at a dinner symposium held in conjunction with the 2003 World Allergy Congress.
†Medical Director, Institute for Asthma and Allergy, and Clinical Professor of Medicine, George Washington University School of Medicine, Washington, DC.
SELECTED PRESENTATION

Table. Pharmacologic Properties of Ciclesonide and Fluticasone Propionate

<table>
<thead>
<tr>
<th></th>
<th>Ciclesonide/Desciclesonide</th>
<th>Fluticasone Propionate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Formulation</strong></td>
<td>Solution</td>
<td>Suspension</td>
</tr>
<tr>
<td><strong>Inhaled form</strong></td>
<td>Inactive parent compound</td>
<td>Active compound</td>
</tr>
<tr>
<td><strong>Particle size</strong></td>
<td>1.1 µm to 2.1 µm</td>
<td>65% &gt;5 µm</td>
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<tr>
<td><strong>Oropharyngeal</strong></td>
<td>≤38% (total)</td>
<td>72% to 78% deposition</td>
</tr>
<tr>
<td><strong>Oral bioavailability</strong></td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td><strong>Pulmonary deposition</strong></td>
<td>52%</td>
<td>12% to 13%</td>
</tr>
<tr>
<td><strong>Residence time in lung</strong></td>
<td>Prolonged (lipid conjugation)</td>
<td>Prolonged (low solubility)</td>
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<tr>
<td><strong>Receptor binding affinity</strong></td>
<td>12/1200</td>
<td>1800</td>
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<tr>
<td><strong>Protein binding</strong></td>
<td>98% to 99%</td>
<td>90%</td>
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<tr>
<td><strong>Clearance</strong></td>
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<td>69 L/hr</td>
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<tr>
<td><strong>Volume of distribution</strong></td>
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<td>318 L</td>
</tr>
<tr>
<td><strong>Elimination half-life</strong></td>
<td>3.5 hr</td>
<td>7.8 hr</td>
</tr>
</tbody>
</table>

Similar efficacy was observed in a group of 283 patients with persistent asthma who had received ciclesonide (160 µg and 640 µg once daily) or placebo for 12 weeks. These patients were included in an open-label extension study to determine the long-term safety of ciclesonide. Patients first received a dose of 640 µg of ciclesonide once daily or twice daily for 4 weeks, followed by an individualized dose ranging from 160 µg to 1280 µg daily for another 36 weeks. The incidence of oropharyngeal adverse events during the extension study was low and consisted mainly of pharyngitis (4%), voice alteration (2%) and oral candidiasis (1%). No relevant systemic or oral adverse events were reported, and most respiratory adverse events were considered unlikely or unrelated to ciclesonide. Long-term administration of ciclesonide was associated with a 28% increase in 24-hour urine cortisol excretion.

Fluticasone propionate, the most frequently prescribed inhaled corticosteroid for asthma in the United States, possesses several of the properties listed in the Sidebar. Both fluticasone and ciclesonide are potent; have high receptor-binding affinities; have prolonged residence time in the lung, albeit by different mechanisms; and are rapidly cleared from the systemic circulation by the liver. However, considerably more oropharyngeal deposition and considerably less pulmonary deposition occur with fluticasone than with ciclesonide (Table). The high percentage of oropharyngeal deposition with fluticasone is associated with several local side effects, including dysphonia, pharyngitis, and oral candidiasis. By comparison, ciclesonide is inhaled as an inactive parent compound that converts to desciclesonide, or activated ciclesonide, in the lung, leaving very little activated compound to be deposited in the oropharynx.

With fluticasone and several other inhaled corticosteroids, the dose response in terms of improvement in lung function is rather flat. A higher dose will not necessarily produce additional clinical improvement but will increase suppression of cortisol and will produce other unwanted effects. Increased cortisol suppression with fluticasone is most commonly seen in patients taking a daily dose of 880 µg or more. The daily dose should therefore be lowered to 660 µg or less. In contrast, studies have shown that ciclesonide has no effect on the adrenals and very little cortisol suppression.

REFERENCES

THE CASE FOR

Immunotherapy is a viable treatment option for asthma, particularly allergic and established asthma. Current therapies for asthma, such as inhaled corticosteroids, improve lung function but do not cure the disease; however, they may also mask symptoms of allergy, an important cause of asthma that warrants treatment itself. Immunotherapy is an important alternative because it treats allergy rather than masking it.

As demonstrated in a meta-analysis of clinical studies evaluating the efficacy of immunotherapy against a wide range of allergens, immunotherapy was associated with reductions in symptom scores, exacerbations, and both specific and nonspecific airway responses, the most important endpoints in clinical trials.1

The scale of improvement can be substantial. For example, a 1-year, randomized, placebo-controlled, double-blind trial in 31 adults with asthma and allergy to house dust mites found that specific immunotherapy significantly reduced inhaled steroid use by 38%, beta-agonist use by 46%, and symptom score by 57% and significantly increased forced expiratory volume in 1 second (FEV$_1$) from 85% to 89% of predicted values.2

Another important observation comes from a 3-year prospective nonrandomized study in 22 children younger than 6 years of age with asthma and allergy to house dust mites and with or without rhinitis. The study included 22 age-matched controls and demonstrated that specific immunotherapy prevents the onset of new sensitizations.3

With regard to disease prevention, a randomized, but not double-blind, study of pollen immunotherapy in 205 children between 6 and 14 years of age with moderate-to-severe hay fever symptoms and with and without mild asthma symptoms demonstrated that immunotherapy reduced the risk of developing asthma.4 Although no children in the study had asthma requiring daily treatment at study entry, 20% were found to have mild asthma, as evaluated clinically and by peak flow, during the pollen season. In the study population as a whole, 26% developed asthma after 3 years of pollen immunotherapy, compared with 44% in the control group.

Immunotherapy also has beneficial effects on disease progression. In a 4-year study of hyposensitization therapy for mild and moderate bronchial asthma in children, 70% of the subjects who received therapy outgrew their asthma by 16 years of age, compared with only 21% of those in the untreated control group. Any symptoms in the treated group were classified mostly as mild, whereas asthma in 70% of the untreated group (at age 16 years) was graded as moderate or severe.5

Although immunotherapy takes time to exert its beneficial effects, which may prompt physicians to avoid using it or discontinue it too soon, these effects are more sustained than those of inhaled steroids. This was demonstrated in a head-to-head comparison of immunotherapy and inhaled budesonide in 51 young patients with bronchial asthma who were given one treatment or the other for 1 year and assessed for global symptom scores and FEV$_1$ values.6 When both treatments were discontinued abruptly at 1 year and the effects of cessation were analyzed, it was clear that budesonide produced faster and more striking improvement during the first few months of treatment than immunotherapy, but its benefits declined rapidly.
once therapy was discontinued. Immunotherapy, by comparison, produced slow but steady improvement during the treatment period and a more gradual decline in beneficial effect after therapy was stopped. The effects of combining immunotherapy with inhaled steroids have not been formally studied.

Another reason to consider immunotherapy in asthma management is cost. Asthma is an expensive disease, with drugs accounting for most of the costs associated with mild asthma and a considerable portion of costs associated with moderate and more severe disease.

A 2-year study comparing immunotherapy with placebo in adults with asthma exacerbated by seasonal ragweed exposure found that the reduced medication costs in patients receiving immunotherapy were counterbalanced by the costs of immunotherapy.\textsuperscript{7} The important point, however, is that specific immunotherapy may be cost effective if it reduces the need for medication in future years or stops progression of disease.

Several surveys assessing the safety of immunotherapy have found that a high proportion of deaths attributed to this treatment occurred in patients with asthma. Most of these deaths, however, were from precipitation of asthma rather than anaphylaxis, suggesting that safety can be considerably improved with careful patient selection and appropriate management of treatment-induced asthma. Other strategies to improve safety include adequate staff training and the use of antihistamine premedication.

**The Case Against**

The use of immunotherapy for asthma does not hinge on whether it is effective but on whether it is clinically indicated. Although immunotherapy may be effective in treating asthma, it is not clinically indicated if better therapies can accomplish the same clinical endpoints—therapies that are more efficacious, produce less morbidity and mortality, and are more cost effective. In addition, immunotherapy is not clinically indicated if its unique benefits (ie, an additive effect, the ability to promote earlier or more frequent remissions, or the ability to alter long-term outcome) are not significant.

The proposal to consider, then, is that allergen immunotherapy is not clinically indicated for most cases of allergic asthma, especially those involving moderate or severe persistent asthma, because immunotherapy is no better than currently available therapies and because there is little or no evidence that its unique benefits are significant. For example, in a 2-year study comparing immunotherapy with placebo in adults with asthma exacerbated by ragweed allergy, the positive clinical effects of immunotherapy on objective measures of asthma and allergy were limited, and many were not sustained over the course of the study.\textsuperscript{7}

A meta-analysis of 24 studies of prophylactic inhaled corticosteroid use in children with asthma found that the average relative improvement in morning peak flow with inhaled steroids was 11%, twice that of immunotherapy.\textsuperscript{8}

In the only study comparing inhaled corticosteroids with immunotherapy in patients with asthma, there was no significant difference between the early response to budesonide in moderate doses and the delayed response to immunotherapy.\textsuperscript{6} Although a valiant study, it excluded patients with rhinitis and did not evaluate higher doses of immunotherapy. A randomized, controlled, parallel-group study is needed.

In contrast, a randomized, double-blind, controlled study done at Johns Hopkins University assessed the effects of immunotherapy in 121 children with asthma and 4 to 7 major allergic sensitivities who were already practicing allergy avoidance.\textsuperscript{9} The study found no discernible effect of immunotherapy on medication requirements, days of oral steroid use, use of medical care for asthma, reported asthma symptoms, methacholine sensitivity, or the rate of partial or complete remission from asthma.

Historical data indicate that there are 3 to 5 deaths per year in the United States due to immunotherapy, with 75% of the deaths occurring in patients with asthma. A French team has defined risk for systemic reactions to immunotherapy as a function of the depression in FEV\textsubscript{1} measurements taken at the time of injection, indicating very clearly that uncontrolled asthma is a major risk factor for all types of systemic reactions.\textsuperscript{10}

As a result, practice standards now include guidelines that underscore the need to observe patients and monitor pulmonary function. These guidelines, however, do not appear to have altered fatal outcomes of immunotherapy in the United States. This reflects the fact that immunotherapy is often administered by general practitioners and specialists in areas other than allergy and that treatment errors and patient factors are not completely understood. In contrast, inhaled steroids are not yet known to produce iatrogenic mortality.
Several potential unique benefits of immunotherapy have been touted. One is immunologic specificity, which differs from anti-inflammatory agents and anti-immunoglobulin E therapy. Specificity, however, is a double-edged sword and may not be an advantage. Another potential unique benefit is compliance, which may be an advantage in patients with mild asthma and in populations with limited access to medical care but not in patients with moderate or severe asthma.

Cost is purported to be an advantage, but because the costs of immunotherapy and inhaled corticosteroids vary so widely, it is difficult to determine cost effectiveness. In the United States, however, estimates suggest that the cost of 1 year of immunotherapy is the same as or slightly higher than the cost of 1 year of inhaled corticosteroids.

With regard to nonspecific bronchial hyperreactivity as assessed by methacholine challenge, most studies show no consistent change, and all multiallergen immunotherapy studies have been negative. Responses seen with immunotherapy are comparable to those seen with moderate doses of inhaled corticosteroids. The effects of both therapies on bronchial hyperreactivity are very small relative to the gap between asthmatic and normal subjects. Furthermore, no evidence has demonstrated that immunotherapy produces permanent changes in airway hyperreactivity. The potential unique benefit of immunotherapy regarding remission rates requires further study.

Groups that appear to derive the most benefit from immunotherapy include children, patients with mild asthma, and individuals with restricted sensitivities (ie, monosensitized). The most positive immunotherapy studies reported over the past decade were conducted in monosensitized subjects. Most immunotherapy in the United States, however, is administered to patients who are polysensitized.

Although immunotherapy is not appropriate for patients with moderate or severe persistent asthma who are already taking inhaled corticosteroids, it appears to hold promise in preventing disease progression in patients with early and mild asthma. Efforts to reduce the risk of systemic reactions, including death, are still needed.

REFERENCES
The role of cats and other fur-bearing pets on allergies and asthma is now a controversial topic. As such, it has engendered numerous discussions, articles, and debates, as well as a host of questions that go beyond a recommendation to “kill the cat or buy one.”

For example, do pets exacerbate allergies and/or increase the risk for asthma? Is the prevalence of pet ownership in a community related to the prevalence of allergy and asthma in that community? Does having a pet in childhood promote or protect against the development of asthma in adulthood? Is there a dose-response relationship between cat allergen exposure and sensitization rates? Are avoidance measures effective?

**“Kill the Cat”**

There is considerable evidence in support of eliminating cat exposure, in particular as a part of the management of cat-allergic patients. Studies have shown that sensitization to cat allergen is an important risk factor for asthma, and that commonly used avoidance measures, such as high-efficiency particulate arrest air cleaners, high-filtration vacuum cleaners, and washing the cat, are ineffective in reducing the amount of inhaled cat allergen (vacuum cleaners may actually increase it). Thus, for cat-allergic cat owners who experience symptoms upon exposure, the only solution is to remove the cat from the home.

The relationship between cat ownership and the development of allergy and asthma is much more complex. However, a number of studies have shown that owning a cat is a significant risk for sensitization to cat, and that there is a significant correlation between community prevalence of cat ownership and community prevalence of respiratory symptoms and asthma. It has also been shown that the chances of being sensitized in adulthood increase with the duration of exposure to cats in the home during childhood.

Other studies have shown that cat ownership in childhood is associated with more asthma in sensitized adults who grew up in communities with a low frequency of cat ownership, but not in communities with a high proportion of cat ownership. The relationship between cat ownership and the development of allergic disease differs between different areas and age groups, and is additionally influenced by the family history of allergy.

**Buy a Cat**

There is now evidence that increasing exposure to cat allergens, ie, a cat in the home, does not increase either the prevalence of sensitization or the risk of asthma.¹ The reason(s) for these observations are not understood. Do cats in the environment promote exposure to bacteria or to bacterial products that alter the immune system towards a “low allergy” phenotype (hygiene hypothesis), or do cat antigens promote a specific form of immune tolerance? In most recent studies, the presence of cats is not associated with increased airborne endotoxin in a house; therefore, the second possibility appears more plausible.

It is quite possible that some allergens are created “more equal than others” and this may have extensive biological and clinical implications. The early forms of the hygiene hypothesis predicted that nonallergic individuals would have a Th₁ immune response to allergens. However, both serological and T-cell results suggest that the tolerant response to cat allergens has the features of a “modified” Th₂ response.²³ This may
not be the case with other allergens. The problem with these data is that they do not provide any information on what will happen to a particular individual. Even if buying 2 cats would be good advice for the average allergic person, it could still be very bad advice for a sizeable minority.

**Recommendations**

Before making a recommendation to “kill the cat” or buy one, physicians should carefully assess all causes of all allergic/asthmatic symptoms, the level of allergen exposure, the presence of other allergic conditions such as allergic dermatitis and the propensity for allergy (family history). At this point, allergen avoidance (including cat) may still need to be recommended in highly atopic individuals. More data will be hopefully available in the near future to clarify this matter.

**REFERENCES**


**Benefit of Montelukast for Asthma in Patients with Both Asthma and Allergic Rhinitis: A Post-Hoc Analysis from the COMPACT Trial**

Based on an oral presentation by Price DB,* Swern AS,† Toczi CA,‡ Phillip G,‡ Polos P,‡ Yu Q†

*General Practice and Primary Care, University of Aberdeen, Aberdeen, Scotland; †Merck & Co, Inc, Rahway, New Jersey

A post-hoc analysis of the multicenter Clinical Observation of Montelukast as a Partner Agent for Complementary Therapy (COMPACT) trial has found that adding montelukast to budesonide is superior to doubling the budesonide dose in improving morning peak flow in the subgroup of asthma patients with concomitant allergic rhinitis. The initial COMPACT study demonstrated that adding montelukast to budesonide was at least as effective as doubling the budesonide dose in improving morning peak flow in patients with asthma.1

The COMPACT trial included 889 patients between 15 and 70 years of age with chronic asthma for 1 year or longer who were not optimally controlled (as judged by an investigator) despite the use of inhaled corticosteroids (ie, 600 µg to 1200 µg daily of budesonide or equivalent) for at least 12 weeks. All had a minimal level of daytime symptoms and beta-agonist use prior to randomization. After a 4-week, single-blind, run-in phase during which all patients received budesonide 400 µg twice daily, patients were randomized in double-blind fashion to receive montelukast 10 mg once daily plus budesonide 400 µg twice daily (n = 448) or budesonide 800 µg twice daily (n = 441) for 12 weeks.

In this post-hoc analysis, the effect of montelukast plus budesonide versus double-dose budesonide was compared in the subgroup of patients with concomitant allergic rhinitis, defined by both a positive patient history and a confirmed physician diagnosis. Reasons for pursuing this line of investigation include the following: rhinitis occurs in more than 75% of patients with allergic asthma; the same triggers (ie, allergens) can cause rhinitis and asthma; rhinitis can be a risk factor for asthma exacerbations; and upper and lower airways share a common and probably interconnected inflammatory process, as evidenced by common inflammatory cells and mediators and the fact that nasal challenge leads to bronchial inflammation and vice versa.2 Moreover, optimal management of rhinitis may be beneficial in managing coexistent asthma, and montelukast, which is approved for the treatment of asthma, has recently been approved for the treatment of allergic rhinitis in several countries, including the United States.

Overall, 410 patients in the COMPACT trial with asthma had concomitant allergic rhinitis (defined by having both a positive patient history of rhinitis and a confirmed physician diagnosis), whereas 479 had asthma without both a patient history and physician-confirmed allergic rhinitis. Of the 448 patients randomized to montelukast plus budesonide, 216 had asthma and concomitant allergic rhinitis; 33 were using rhinitis medications, such as intranasal steroids, antihistamines, or other rhinitis treatments, prior to randomization. Of the 441 patients randomized to double-dose budesonide, 184 had asthma with concomitant allergic rhinitis; 23 were using rhinitis medications prior to randomization.

At the end of the 12-week, double-blind treatment phase, there were increases in morning peak flow...
values in patients randomized to montelukast plus budesonide of 8.6% in the total group and 9.2% in those with asthma and allergic rhinitis; these values were noted versus increases in patients randomized to double-dose budesonide of 7.7% in the total group and 6.0% in those with asthma and allergic rhinitis.

The addition of montelukast to budesonide significantly improved morning peak flow in patients with concomitant asthma and allergic rhinitis (\(P < .03\) vs double-dose budesonide). Furthermore, this additional treatment effect of montelukast was greatest in patients taking rhinitis medication prior to randomization (\(n = 33\)). The treatment effect of doubling the dose of budesonide among patients taking rhinitis medication prior to randomization (\(n = 23\)) was less than adding montelukast (increases in peak flow values of 12.1% for patients taking montelukast plus budesonide vs 1.9% for those taking double-dose budesonide; \(P < .02\)).

Results of this post hoc analysis suggest the potential for additional treatment benefit with montelukast in the large population of asthmatics who have concomitant allergic rhinitis. Further study, including prospectively designed clinical trials, should be undertaken to evaluate this hypothesis.

REFERENCES


DEPOSITION OF EXTRA-FINE HYDROFLUOROALKANE-BECLOMETHASONE DIPROPIONATE INHALED VIA PRESSURIZED METERED-DOSE INHALER—SPACER IN ASTHMATIC CHILDREN

Based on an oral presentation by Roller CM,*† Owen JL,* Troedson RG,† LeSouef PN,* Devadason SG*

*University of Western Australia, Perth; †Princess Margaret Hospital for Children, Perth, Western Australia.

Using gamma scintigraphy, a team of Australian investigators has demonstrated that inhalation of an extra-fine aerosol formulation of beclomethasone dipropionate (smaller particles result by mixing beclomethasone with the hydrofluoroalkane propel- lant), delivered via metered-dose inhaler with an attached detergent-coated holding chamber, significantly decreases unnecessary oropharyngeal and gastrointestinal drug deposition while maintaining high levels of lung deposition in children with mild asthma.

Because airway targeting largely determines the efficacy of inhaled corticosteroids, maximizing the amount of drug that gets into the lung is a major fac-tor in optimizing inhalation therapy in asthmatic chil-dren. The smaller the particle size that is delivered by an aerosol device, such as an inhaler, the better the deposition into the airways. This issue is even more important in children because of their smaller airway diameters. Holding chambers are widely recommended for children in order to minimize unnecessary oropharyngeal and gastro-intestinal drug deposition, which can contribute to both local and systemic side effects.

To assess the total body deposition and distribution of extra-fine beclomethasone in children, the investiga-tors had 12 boys inhale 99 m technetium-radiolabeled drug via metered-dose inhaler and spacer. Eight boys, 5 to 10 years of age, took 5 tidal breaths through the spacer after each actuation, while 4 boys older than 10 years of age used a slow maximal inhalation followed by a 10-second breath hold. Simultaneous ante-rior and posterior planar gamma scintigraphic scans of the lungs were recorded.

Mean lung deposition, expressed as an attenuation-corrected percentage of the exactuated dose, was 35.1% in 4 boys between 5 and 7 years of age, 47.5% in 4 boys between 8 and 10 years of age, and 58.4% in 4 boys between 11 and 15 years of age. Gastrointestinal deposition was 25%, 10.3%, and 20.8%, respectively, in these same age groups. The percentage of the drug remaining in the spacer was 39.5%, 41.5%, and 20.3%, respectively. Lung deposition of extra-fine beclomethasone increased significantly with age (\(P < .04\)).

The extra-fine particle metered-dose inhaler–spac-er combination gave more efficient delivery of steroid by minimizing unwanted oropharyngeal and gastro-intestinal drug deposition while maintaining high drug deposition to the airways.
A DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED, CROSSOVER TRIAL OF MONTELUKAST IN ADULTS WITH NASAL POLYPOSIS

Based on a poster presented by Keith P, Ferrie P, Conway M, Wasserman S, Schmuck M, Denburg J
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In this study of 23 adults with bilateral nasal polyps, once-daily therapy with montelukast 10 mg for 4 weeks was significantly superior to placebo in improving global assessment of symptoms and quality of life. Active treatment also showed a trend toward reduction of blood eosinophil counts. These findings demonstrate that montelukast, a cysteinyl leukotriene receptor antagonist with clinical benefits for both asthma and allergic rhinitis, has beneficial effects for nasal polyposis, a chronic eosinophilic inflammatory condition.

Study subjects were randomized in this double-blind, placebo-controlled, crossover study to compare 4 weeks of montelukast therapy with placebo. There was a 4-week washout period between treatment periods. All subjects remained off intranasal steroids for at least 4 weeks prior to treatment and throughout the study. Global assessment of nasal polyp symptoms, quality of life assessment specific to patients with nasal polyps, and blood eosinophil counts were performed at the completion of each treatment period.

Nasal polyp symptoms were assessed on a +3 to −3 scale, with +3 being equivalent to “very much better,” 0 to “no better,” and −3 to “very much worse.” There was a significant improvement in symptom score for montelukast treatment compared with placebo, with scores of 1.8 for active treatment versus 0.4 for placebo after the first treatment period, and 1.3 for active treatment versus −0.8 for placebo after the second treatment period \( P = .001 \).

Similarly, quality of life, as assessed by a disease-specific questionnaire that employed a 7-point scale, was significantly better with montelukast compared with placebo, with an improvement of 0.6 for active treatment versus 0.21 for placebo after the first treatment period, and 0.6 for active treatment versus 0.0 for placebo after the second treatment period \( P = .01 \). The investigators conclude that montelukast treatment globally improves the symptoms of nasal polyposis and health-related quality of life.

SINGLE-INHALER THERAPY WITH BUDESONIDE/FORMOTEROL

Three of the posters presented at the World Allergy Organization Congress in Vancouver described studies evaluating fixed and adjustable dosing with budesonide/formoterol, an inhaled glucocorticosteroid and a long-acting fast-onset beta-adrenergic agonist, in a single inhaler device. Because all 3 studies evaluated the same combination, and because 2 of the studies used the same design and patient population, they are presented here as a unit. The first, by FitzGerald et al, assesses the effects on asthma exacerbations. The second, by Sears et al, examines the effects on symptom severity in the same patient population. The third, by Aalbers et al, compares adjustable versus fixed dosing with budesonide/formoterol and adjustable dosing with budesonide/formoterol versus fixed dosing with salmeterol/fluticasone.

BUDESONIDE/FORMOTEROL ADJUSTABLE MAINTENANCE DOSING REDUCES ASTHMA EXACERBATIONS COMPARED WITH FIXED DOSING: A 5-MONTH STUDY IN CANADA

Based on a poster presented by FitzGerald JM,* Boulet LP,† McIvor A,‡ Becker A,§ Sears MR,‖ Ernst P,¶ Georgijev NS,# Lee J#
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In this 5-month, randomized, open-label, parallel-group study involving 995 patients with asthma at 95 healthcare and hospital centers in Canada, adjustable maintenance dosing with budesonide/formoterol in a single inhaler was significantly more effective than fixed dosing with the same agents in reducing asthma exacerbations.

Patients were 12 years of age or older (mean, 40.6 years in the adjustable-dosing group and 42.8 years in the fixed-dosing group), met American Thoracic Society criteria for asthma, had postbron-
Patients were considered symptomatic if they used a short-acting beta-agonist on at least 2 occasions in the previous 7 days, had asthma symptoms on at least 2 days in the previous 7 days, or had at least 2 nighttime awakenings due to asthma in the previous 30 days.

After a 1-month run-in period during which all patients received fixed-dose budesonide/formoterol (80/4.5 µg or 160/4.5 µg, 2 inhalations twice daily) to gain control of their asthma, patients were randomized to receive an additional 5 months of treatment with either fixed dosing or adjustable dosing. In the adjustable-dosing protocol, patients could step down from 2 inhalations twice daily to 1 inhalation twice daily if patients felt their asthma was well controlled in the previous 7 days, used reliever medication no more than 2 times during this period, and had no nighttime awakenings due to asthma during this interval. Patients could step up from 1 inhalation twice daily to 4 inhalations twice daily if they had 2 consecutive nights with awakenings due to asthma or 2 consecutive days with morning peak flow values that were below 85% of their mean baseline value, or with the need to use reliever medications 3 or more times daily. Patients could again step down after 7 or 14 days of step-up treatment, from 4 inhalations twice daily to 1 inhalation twice daily, if they met all of the step-down criteria presented above.

Exacerbation was defined as the need for additional inhaled and/or oral corticosteroids for asthma, emergency department treatment due to asthma worsening, an asthma-related serious adverse event, and/or withdrawal from the study due to the need for additional asthma maintenance therapy. Severe exacerbation was defined as the need for oral corticosteroids due to asthma worsening, emergency department treatment or hospitalization due to asthma worsening, and/or an asthma-related serious adverse event.

Patients in both study groups were well matched regarding age, sex, mean postbronchodilator FEV1, peak expiratory flow during the run-in period, inhaled corticosteroid and long-acting beta-agonist use at study entry, and stratification by budesonide/formoterol dose during the fixed-dose run-in phase. Of those receiving the 80/4.5-µg fixed dose during the run-in phase, 140 were randomized to adjustable dosing and 129 to fixed dosing. Of those receiving the 160/4.5-µg fixed dose during run-in, 359 were randomized to adjustable dosing and 367 to fixed dosing.

At the end of the 5-month randomization phase, significantly fewer patients in the adjustable-dosing group experienced exacerbations, with the mean number of exacerbations reduced by 57% compared with the fixed-dosing group (P = .001). This was accomplished at an overall lower dose of the budesonide/formoterol inhaler (mean, 2.5 vs 3.9 inhalations daily) and cost (mean savings, $141 Canadian) compared with fixed dosing. In addition, fewer patients in the adjustable group had 1 or more severe exacerbations, with the mean number of such exacerbations reduced by 47% compared with the fixed-dosing group. Time to first exacerbation was significantly prolonged in the adjustable-dosing group (P = .001) compared with the fixed-dosing group.

The study demonstrates that adjustable dosing improves patient outcomes in asthma, a disease with fluctuating symptoms and periodic exacerbations, and reduces the potential for periods of undertreatment or overtreatment associated with fixed dosing.

BUDESONIDE/FORMOTEROL ADJUSTABLE MAINTENANCE DOSING EFFECTIVELY IMPROVES ASTHMA SYMPTOM SEVERITY: A MULTICENTER CANADIAN STUDY

Based on a poster presented by Sears MR,* McIvor A,† Becker A,‡ FitzGerald JM,§ Boulet LP,¶ Ernst P,¶ Georgijev NS,* Lee J#

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Using the same study design, dosing regimens, step-up and step-down criteria, and patient population as the study described by FitzGerald et al (see above), this report showed that adjustable maintenance dosing with budesonide/formoterol in a single
ADJUSTABLE DOSING WITH BUDESONIDE/FORMOTEROL REDUCES THE RATE OF ASTHMA EXACERBATIONS COMPARED WITH FIXED-DOSING SALMETEROL/FLUTICASONE

Based on a poster presented by Aalbers R,* Backer V,† Kava TTK,‡ Welte T,§ Omenaas E,|| Bergqvist PBF,¶ Sandström T#

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This 7-month study is the first to compare adjustable maintenance dosing with budesonide/formoterol in a single inhaler with fixed dosing with the same agents, as well as with fixed dosing with salmeterol/fluticasone. The investigators concluded that adjustable maintenance dosing with budesonide/formoterol is more effective in reducing exacerbations than fixed dosing with the same agents and more effective in controlling the variability of asthma than fixed dosing with salmeterol/fluticasone.

The randomized, 2-phase, multicenter study, which involved a total of 658 patients and included a 1-month double-blind phase and a 6-month open-extension phase, was preceded by a 2-week run-in phase during which patients continued their usual inhaled corticosteroids and were then randomized to adjustable-dose (n = 219) or fixed-dose budesonide/formoterol (n = 215) or fixed-dose salmeterol/fluticasone (50/250 µg, 1 inhalation twice daily; n = 224). During the 1-month double-blind phase, in which patients who were randomized to either scheme of budesonide/formoterol therapy received the fixed dose (160/4.5 µg, 2 inhalations twice daily), the fixed-dose combinations were compared with each other.

At the end of the double-blind phase, patients initially randomized to adjustable dosing who met the criteria for dose adjustment stepped down to 1 inhalation...
twice daily; those who did not remained on 2 inhalations twice daily. Patients were eligible for a step-down adjustment if, during the last 7 days of the double-blind period, they had no nighttime awakenings due to asthma and if they used reliever medication no more than once per day for not longer than 2 days.

During the open-extension phase, patients randomized to adjustable dosing with budesonide/formoterol could increase their dose temporarily, up to 4 inhalations twice daily, if their symptoms worsened (i.e., if they required reliever medication on 2 consecutive days on 3 or more occasions, or if they had nighttime awakenings due to asthma on 2 consecutive days). All patients were permitted to use short-acting beta2-agonists (terbutaline or salbutamol) as needed for symptom relief throughout the study.

Study participants were at least 12 years of age (mean age, 47 years in the adjustable-dosing group and 46 years in both fixed-dosing groups), with symptomatic asthma despite current medications, prebronchodilatory forced expiratory volume in 1 second (FEV1) value 50% or more of predicted, and mean peak expiratory flow between 50% or higher and 85% of postbronchodilatory peak expiratory flow. All were taking inhaled corticosteroids for at least 3 months before study entry and at a constant daily dose of 500 µg to 1200 µg during the month before the run-in phase. All had total daily symptom scores that were above 0 on at least 4 of the last 7 days of the run-in period. Patients in each of the 3 treatment groups were well matched regarding age, sex, mean asthma symptom score, mean dose of inhaled corticosteroids at study entry, beta2-agonist use at study entry, and mean FEV1.

During the study, exacerbations—defined as oral steroid treatment for at least 3 days and/or emergency department visits with or without hospitalizations—were recorded. Asthma symptoms and reliever medication use were recorded on patient diary cards.

At the end of the study, there was a 40% reduction in the rate of exacerbations in the group receiving adjustable-dose budesonide/formoterol compared with the group receiving fixed-dose salmeterol/fluticasone. The difference was even more impressive in the last 100 days of treatment (4-fold decrease in the number of exacerbations). There were also fewer exacerbations, fewer hospitalizations and/or emergency department visits, and less use of extra inhaled steroids in the group receiving adjustable-dose budesonide/formoterol than in both groups receiving fixed-dose treatment.

Study drug use was somewhat higher in the adjustable-dose group (average daily budesonide, 550 µg) compared with the fixed-dose group (average daily fluticasone, 500 µg).