5Should Antileukotriene Therapies Be Used Instead of Inhaled Corticosteroids in Asthma?

No

Asthma management is an evolving process which has culminated in the publication of numerous national and international guidelines for the treatment of the disease. Despite this, the concept of which drug or drugs should be used as the first-line agent for the treatment of mild persistent asthma remains under intense scrutiny. In evaluating the ability of any drug to fulfill that task, it is important to understand which properties should identify the "ideal" therapeutic agent for the "first-line" therapy of asthma, and then to discuss how certain drugs correspond to those ideal characteristics.

The following "ideal characteristics" are modified from suggestions from the most recent Expert Panel 2 report with a few additions based on long-term personal clinical experience in treating asthmatics (1).

Ideal characteristics. The drug should: (*1*) be easy to take; (*2*) improve symptoms of asthma; (*3*) improve pulmonary function; (*4*) improve bronchial reactivity; (*5*) decrease airway inflammation; (*6*) decrease exacerbation rates; (*7*) treat "all comers" with asthma; (*8*) improve long-term outcomes of the disease (i.e., be "disease-modifying"); and (*9*) have minimal side effects. These characteristics will be applied to the new antileukotriene drugs and to inhaled corticosteroids (ICS) in a point-by-point fashion to determine which more closely fits the ideal characteristics for first-line therapy for asthma.

1. Be easy to take. Numerous factors come into play when evaluating the ease of medicating and likelihood of compliance/adherence with certain compounds. These include the route of delivery, the frequency of dosing, complicating factors to delivery (with or without meals, etc.), interactions with other drugs, and the associated effects of dosing (i.e., taste, immediate side effects, and/or perceived "good" effects) (2). It is in this category that the leukotriene modifiers are the biggest winners. Leukotriene modifiers are oral agents, inhaled steroids are inhaled. Patients generally appear to prefer pills. In other aspects there appear to be lesser differences. Antileukotrienes can be dosed anywhere from 1 to 4 times per day, ICS are now generally dosed twice a day. In fact, one of the leukotriene modifiers (zafirlukast) has more "complicating factors to delivery" than inhaled steroids because of the directions to dose 1 h before or 1.5 h after meals (3). Additionally, zafirlukast and zileuton both have interactions with other drugs (coumadin, theophylline) which also have to be taken into consideration. The final subcategory here deals with the bad *and* good effects seen with dosing. The leukotriene modifiers probably also come out ahead here, primarily because they "may" have a perceived bronchodilating effect and do not have the potential to induce cough, laryngeal irritation or even candidiasis, which can be associated with the delivery of an ICS (4). However, the biggest factor here remains the somewhat nebulous and difficult to understand, but very clear reality, that patients seem to prefer pills. Hence, the antileukotrienes are the winners in this first category.

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ICS 0 Antileukotrienes 1

2. Improve symptoms. In all clinical trials to date, both ICS and antileukotrienes appear to decrease asthma symptoms. There are now several direct comparison studies of antileukotrienes with low doses of inhaled beclomethasone or fluticasone (5–7). The effects of the two drugs on symptoms have been variable, but except for a study of the antileukotriene pranlukast versus beclomethasone, the effect on symptoms has favored (although not always significantly) ICS.

There remain, however, questions regarding these comparison studies. Perhaps the most important is, had the ICS dose been higher, would a greater effect have been seen, as compared with the antileukotrienes? And, secondly, is there a difference between significantly different and clinically different in this setting? However, at our current level of data availability, it is likely that a point should be given to both drug categories, leaving the score:

ICS 1 Antileukotrienes 2

3. Improve pulmonary function. Both ICS and antileukotriene agents produce significant improvement in pulmonary function. However, the available head-to-head comparison studies consistently demonstrate a significantly greater impact of ICS on FEV_1 than that seen with the antileukotrienes (5–7). The differences do not appear to be subtle in this category, showing nearly twice as much improvement in FEV_1 with ICS as with the antileukotrienes. Similar, although not as consistent, comparison results have been shown with peak flows. Finally, as will be discussed later, there appears to be a greater percentage of patients whose FEV_1 responds well ($> 10\%$) to treatment with inhaled steroids, as opposed to the antileukotrienes (8). Therefore, when evaluating pulmonary function, the ICS remain the clear winner.

ICS 2 Antileukotrienes 2

4. Improve nonspecific bronchial hyperreactivity. For many years, the definition of asthma has included an increase in nonspecific bronchial hyperreactivity (NBR). Although the mechanisms which underlie this increased reactivity are unclear, it has been felt to be driven at least minimally by eosinophilic inflammation (9). Further evidence for inflammation as a driving force behind bronchial reactivity has been provided by the known impact of ICS on the provocative dose causing a 20% fall in FEV_1 (PD_{20}).

With this background in mind, whereas numerous studies with ICS have demonstrated long-term improvement in NBR, in the range of 2 to 3 doubling doses, the impact of antileukotrienes on NBR has been minimal to nonexistent (10, 11). Additionally, antileukotrienes have only minimal effects on the increase in NBR seen after allergen challenge, another area where ICS have known efficacy (12).

ICS 3 Antileukotrienes 2

5. Improve airway inflammation. In the last 20 yr, there has been an increased appreciation of the significant role that inflammation plays in the pathogenesis of asthma. As this appreciation increases, the emphasis on eradicating that inflam-

mation has taken on increasing importance. Over the last 10 years, there have been a multitude of bronchoscopic biopsy and lavage, as well as sputum studies, demonstrating the far-reaching anti-inflammatory effects of ICS (13–15). These studies have shown profound effects on inflammatory cells (eosinophils, lymphocytes), cytokines (interleukins and growth factors), and mediators, such as nitric oxide, after treatment with ICS. This conglomerate of studies has led to the concept that ICS are the "gold standard" of anti-inflammatory therapy for asthma.

In contrast, only a minimal amount of data exist on the anti-inflammatory effects of antileukotrienes. The published and abstracted data are limited to a handful of bronchoalveolar lavage (BAL) and sputum studies, without any biopsy studies. The effect on inflammation is generally limited to a small but significant effect on BAL or sputum eosinophils and/or basophils (16–18). The effect on BAL eosinophils has only been demonstrated in nocturnal and allergen-induced asthma, with no bronchoscopic studies evaluating the effect on eosinophils in chronic asthma. There is very limited information on the effect of antileukotriene agents on other aspects of inflammation, such as cytokines or growth factors. Although there are data to suggest an effect on the cytokine, tumor necrosis factor alpha, the effect is marginal when compared with the effects of ICS (17). Finally, the effect of antileukotrienes on exhaled nitric oxide remains questionable. Therefore, at least until further information becomes available, the evidence supporting the anti-inflammatory effect of inhaled steroids far outweighs the evidence supporting the anti-inflammatory effect of the leukotriene modulators.

ICS 4 Antileukotrienes 2

6. Decrease exacerbation rates. In addition to improving the day-to-day symptoms and pulmonary function, prevention of exacerbations of asthma is of considerable importance from many perspectives. Decreasing exacerbations will decrease morbidity and mortality, likely improve quality of life, and substantially diminish economic costs of the disease. Although truly "long term" ($>$ 1 yr) studies of inhaled corticosteroids are rare, there are a multitude of 1-yr studies (including a handful of prospective studies) which have suggested decreases in exacerbations, emergency room visits, and hospitalizations following inhaled steroid use (19, 20). Similar to many of the previous points, there are generally much more limited data regarding the efficacy of the antileukotrienes, partly owing to the significantly shorter duration of clinical experience associated with any new drug. The studies with the antileukotrienes that do exist include 3-mo studies with zafirlukast and montelukast, which demonstrate a decrease in the need for oral steroids, and 6- and 12-mo studies with zileuton which demonstrate similar effects (21). Interestingly, in the comparison study of montelukast with low-dose beclomethasone, there is no significant difference in exacerbation rates over the short (3-mo) duration of the study (8). Therefore, although evidence exists that antileukotrienes have some preventative effects on exacerbation rates (hence, the awarding of one-half point), more long-term data are needed to determine whether the effect is equal to that of the ICS. In this context, a point is awarded to the ICS, whereas the more limited experience (even though positive) with the antileukotrienes merits 0.5 points.

ICS 5 Antileukotrienes 2.5

7. Treat "all-comers" with asthma. Although asthma is often discussed as a single disease, it is much more likely to be accurately described as a group of syndromes, all of which lead to the same or a similar clinical phenotype. Inhaled steroids are broad-spectrum anti-inflammatory agents, such that they likely will cover the differences in inflammation which may exist among the different subgroups.

Antileukotriene agents impact a single pathway which may or may not be important in every subtype of asthma. Studies with exercise-induced bronchospasm would indicate that not all forms of exercise-induced asthma are secondary to leukotriene production, as 25% of these exercise asthmatics are not protected by these agents (22). Similar evaluations have been performed with long-term dosing and seem to indicate that somewhere in the neighborhood of 50 to 55% of patients respond to these drugs with a greater than 10% improvement in FEV_1 (6). The response rate to low doses of inhaled corticosteroids is not only higher, percentage wise, but there appears to be more individuals who develop a marked ($>$ 25%) improvement in FEV_1 with ICS than with antileukotrienes (6). These direct comparison results would support the concept that ICS, with their broader range of anti-inflammatory effects, will be more effective among the heterogenous inflammatory subtypes that make up asthma.

ICS 6 Antileukotrienes 2.5

8. Improve long-term outcomes (i.e., be "disease-modifying"). The use of ICS as disease-modifying agents is supported by several studies, and includes both clinical and pathologic approaches. Perhaps the best studies in this regard are those which followed FEV_1 over a 2-yr treatment period. Mild-to-moderate asthmatics began treatment with either a beta agonist alone, or moderate dose ICS. At the end of 1 yr, the group treated with ICS had better pulmonary function than the group receiving terbutaline. However, what is potentially more important is that when the group that received terbutaline for 1 yr was switched to budesonide, that group never obtained the same FEV_1 or peak flows as the group did that was treated with inhaled steroids from the start. This suggests that the inhaled steroids improved the "natural history" of the disease, and that the earlier they are used, the more of an effect they can have (23, 24).

Pathologic studies over 10 yr of treatment with inhaled steroids support this effect by demonstrating the near resolution of inflammation in patients treated with inhaled steroids (25). Additionally, there is some evidence to suggest that ICS may improve some of the airway "remodeling" (sub-basement membrane thickness) seen with asthmatic inflammation, and the injury and repair processes associated with it (26, 27).

In contrast, the antileukotrienes, by nature of their very young age, have almost no long-term data, and certainly have no long-term data in relation to ICS. Also, as inflammation is felt to be a major contributor to the long-term course of the disease, the "proven" anti-inflammatory effects of the ICS, as compared with the minimal anti-inflammatory evidence that exists with antileukotrienes, further support the superior role of ICS as disease-modifying drugs.

ICS 7 Antileukotriene 2.5

9. Have minimal side effects. As with the disease-modifying effects, a true understanding of the long-term side effects of treatment requires long-term experience with the compound in question. Once again, ICS have been clinically utilized for over 20 yr, with minimal side effects at low doses. Although there are reports of osteoporosis, growth retardation in children, and glaucoma from inhaled steroids, the effects generally follow a dose-related response. The antileukotrienes have no safety information for any longer duration than 3 yr; and this is in a very small numbers of patients. In addition, the an-

tileukotrienes have a modest amount of immediate side effects, in the form of gastrointestinal discomfort; longer term side effects, in the form of elevated liver enzymes; and finally, potentially devastating side effects in the form of Churg-Strauss and other hypereosinophilic syndromes in a very small number of potentially predisposed individuals (28). Based on this information and lack of information regarding the antileukotrienes, the final point must be awarded to the ICS.

FINAL SCORE

ICS 8 Antileukotriene Drugs 2.5

In conclusion, a careful analysis of the existing data on these two drugs strongly suggests that for the vast majority of patients, ICS are the "first-line" drugs of choice. With today's understanding of the disease and the activity of corticosteroids, ICS are by and large superior to antileukotriene drugs in: (*1*) improvement in pulmonary function; (*2*) improvement in NBR; (*3*) improvement in airway inflammation; and (*4*) percentages of patients improved by treatment. Based on the limited long-term experience with the antileukotriene drugs, the data support the superiority of the ICS in long-term outcomes and side effects as well. Further comparison studies are needed regarding the effect on exacerbations. It is only in the category of "ease of delivery" that the antileukotrienes appear to have the clear lead. However, long-term comparison studies of antileukotrienes and ICS should be performed to determine whether the increased likelihood of patient compliance/adherence is enough to outweigh the many other advantages of the ICS.

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