Editorial

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

Yes

Leukotriene modifiers, that is, agents that inhibit the action of the cysteinyl leukotrienes at the $CysLT_1$ receptor (such as montelukast, pranlukast, and zafirlukast) or inhibit the action of the enzyme 5-lipoxygenase (such as zileuton), represent the first new class of antiasthma treatment in the past 20 years. Furthermore, they represent the first of what is likely to be many "designer" targeted asthma treatments, ones that have evolved from our understanding of the pathobiology of the disease rather than being discovered by screening, or by accident, to have salutary therapeutic effects. Because it has been so long since we had new asthma therapies, and because these are the first class of effective, specifically targeted asthma therapy, it is useful to consider how to position these agents in our asthma treatment armamentarium. Such consideration is particularly important as we consider the initiation of therapy for the largest group of patients whom the National Asthma Education Program (NAEP) classifies as requiring chronic administration of controller therapy—mild persistent asthmatics. We believe that it may be time to reconsider our approach to the administration of controller therapy as it applies to the mild persistent asthmatic.

Mild persistent asthma is defined by the United States National Asthma Education Program's *Guidelines for the Diagnosis and Treatment of Asthma II* (1) as asthma that occurs on a less than daily basis, with brief attacks; it is associated with nocturnal awakenings less than once a week but more than twice a month, and, most important, patients with this diagnosis have lung function that is essentially normal (FEV_1 or peak flow values $\geqslant$ 80% of that predicted). Although data on the prevalence of asthma of this severity are hard to find, most estimates are that this cohort represents 20 to 30% of the asthmatic population (2–4 million people in the United States alone). Considering the size of this cohort and the expectation that patients in this cohort should receive chronic controller therapy (1, 2), it is important to ask what one should expect of a first-line chronic controller treatment for this group of patients. We believe that there are two attributes of such treatment: it should produce effects that meet the NAEP guidelines for asthma control, and, considering the mild degree of these patients' asthma symptoms, it must be a treatment with which patients are likely to comply. Leukotriene modifiers meet both of these criteria as outlined below.

Leukotriene modifiers are effective antiasthma treatment. The basic and clinical physiology of the leukotriene modifiers is reviewed in detail elsewhere (3–7). In brief, the leukotriene modifiers block the effects of compounds that cause smooth muscle constriction, inflammatory cell recruitment, tissue edema, and mucus secretion. They reduce tissue and blood eosinophil numbers. With regard to clinical effectiveness, the NAEP guidelines define asthma control achieved with a controller medication as (*1*) prevention of symptoms, (*2*) improvement of physiological function and activity levels, (*3*) prevention of exacerbations, and (*4*) meeting of patient expectations. These attributes are to be achieved with "minimal or no adverse effects." The leukotriene modifiers meet requirements for efficacy and patient expectations as outlined by the NAEP. They have been shown to reduce symptoms and beta agonist use, block exercise- and cold air–induced bronchoconstriction, reduce exacerbations by 60 to 80% (6, 8), and nearly double symptom-free days and days without asthma while halving absence from school and work (9). There is no question that they are effective asthma treatment and meet the first four NAEP criteria.

Leukotriene modifiers are safe asthma treatment. Extensive premarketing studies have been performed on the three leukotriene modifiers available in the United States. The data demonstrate that this class of agents is remarkably well tolerated. Two issues have arisen that merit consideration. First, in patients receiving zileuton, monitoring of the serum alanine aminotransferase (ALT), a test of liver cell damage, has been recommended to identify the approximately 3.5% of patients in whom there will be a reversible increase in this marker. In patients receiving the recommended doses of montelukast or zafirlukast, hepatotoxicity has not been noted. In the case of montelukast, no adverse effects have been noted at doses many times the prescribed effective dose. Second, rare cases of Churg-Strauss syndrome—about one in 20,000 treatment years—were reported early on predominantly in patients with severe persistent asthma receiving zafirlukast treatment (10). Since these initial reports, over a million people worldwide have received this treatment with few additional reports of this phenomenon. Thus, this complication is simply not a consideration in the treatment of patients with mild-to-moderate persistent asthma.

Leukotriene modifiers are easy to administer. An important therapeutic advantage of the leukotriene modifiers is that all marketed forms of these drugs are taken orally. Studies of oral and inhaled asthma treatments show that patient acceptance and compliance are significantly greater for oral than for inhaled preparations (11). A patient whose asthma has undergone the transition from mild intermittent asthma to mild persistent asthma, suddenly finds that he or she now needs chronic controller treatment. If such a patient is started on inhaled corticosteroids, they will require, in addition to an explanation of the difference between intermittent and persistent asthma, extensive education about the proper use of inhalers. Such education, which is quite costly in terms of health care provider

Drs. Drazen and Israel, or their laboratories, have received significant financial support from the following commercial entities in the health care marketplace over the past 5 years: Abbott, Boehringer Ingleheim, Eli Lilly, Forest Laboratories, Genetics Institute, Merck, Pfizer, Roche Bioscience, Schering-Plough, Smith-Kline Beecham, Sepracor, Wyeth-Ayerst, Zeneca. Neither Dr. Drazen nor Dr. Israel hold an equity interest in any of the above entities.

time, must be continuously reinforced if proper inhaler use is to be maintained; without this maintenance, inhalers are of minimal therapeutic benefit. In contrast, no patient in our practice has ever required education on how to take a pill!

This point is especially important as one considers the relative efficacy of the leukotriene modifiers and inhaled corticosteroids. Many physicians believe inhaled corticosteroids to be the most effective, and thus first-line agents, for use as controller therapy in asthma. In our mind, there is little question that corticosteroids are the most potent antiasthma medications currently available. Administration by inhalation, although more complicated, allows us to capitalize on the salutary effects while decreasing, but not eliminating, concerns about untoward systemic effects such as those related to growth, cataracts, glaucoma, and osteoporosis (12–14). For the moderate persistent asthmatic who has frequent symptoms and/or impaired lung function, they are an appropriate controller therapy. However, for the mild persistent asthmatic who is barely symptomatic, an effective, less complicated albeit less potent, initial alternative now exists—the leukotriene modifiers.

The difference that ease-of-compliance can make in the therapeutic outcome for this mild group of patients should not be discounted. The data comparing inhaled corticosteroids and leukotriene modifiers show that the difference in mean response is driven by about 15% of patients receiving inhaled corticosteroids who had a substantial (more than 30%) increase in FEV_1 (15). Consider these data in the context of patient compliance. If you treat 100 patients with mild-to-moderate persistent asthma with an inhaled steroid, 50 of them will show an improvement in the FEV_1 of more than 11%. If you treat the same 100 patients with leukotriene modifiers, 42 will show a similar improvement in FEV_1. If we apply the findings of Kelloway and colleagues (11) with respect to treatment compliance, after 3 months of treatment, 35 patients taking leukotriene modifiers will still show benefit, compared with only 32 patients taking inhaled corticosteroids.

Thus, we believe that it makes sense for patients with mild persistent asthma receiving chronic controller therapy to use a stepped approach to treatment akin to that used in hypertension—the better tolerated, if less potent, drug is used first for chronic treatment unless control cannot be achieved. This approach recognizes the critical effect of ease-of-use on compliance with chronic therapy. If control cannot be achieved with this therapy, then we advocate the addition or substitution of an inhaled corticosteroid. Furthermore, for patients with more severe disease (not in the category under discussion), we agree with a step-down approach to therapy as advocated by numerous expert panels.

Does it make sense to use your most potent, but hard to administer, asthma treatment in patients whose lung function is near normal? We do not think so. We think that, for the patient with mild persistent asthma, potency is not what is needed. What is needed is an effective asthma controller treatment regimen that the patient is likely to use. Given their convenience of administration and their proven effectiveness, there is no question that leukotriene modifiers are the logical first choice antiasthma treatment for patients with mild persistent asthma. Patients prefer pills—it's that simple!

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