The Evolving Role of Leukotriene Modifiers as First Line Therapy in Mild Chronic Asthma: Modifying the Stepped Care Approach to Asthma

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Abstract

The National Asthma Education and Prevention Program (NAEPP) guidelines (1) were developed by consensus by experts in the field to provide a logical approach to asthma therapy based on asthma severity as assessed by clinical symptoms and pulmonary function data. These guidelines are a good starting point to begin the treatment of asthma, but it must be remembered that the guidelines are based on a combination of clinical practice, some studies, and a general rationale for the mechanism of action of the drugs and understanding of the disease in 1997. Currently, the leukotriene modifying drugs might be considered in a different light based on evolving knowledge and clinical experience related to these drugs.

THE EVOLVING ROLE OF LEUKOTRIENE MODIFIERS

Patients with mild persistent asthma, ie normal pulmonary function as measured by peak expiratory flow (PEF) and FEV_1 and either nocturnal symptoms greater than twice a month but less than once a week or symptoms greater than twice a week but not daily, would be recommended to start low dose inhaled corticosteroids twice a day and short-acting inhaled B_2 -agonists as needed for symptoms. The rationale for this approach is that all persistent asthma should be treated with an anti-inflammatory medication, since the underlying basis of chronic asthma is inflammation. The triad of the asthma phenotype, airway inflammation, airway hyperresponsiveness, and airway obstruction ([2]) are all improved with corticosteroids.

An alternative to inhaled corticosteroids for mild persistent asthma would be a leukotriene modifier ([1]). Leukotriene modifiers, both 5-lipoxygenase inhibitors and leukotriene receptor antagonists, are considered acceptable alternatives in mild persistent asthma, although it is felt their place in the step approach to asthma is not yet entirely clear (1). Theoretically, the leukotriene modifiers are a logical first choice when mild intermittent asthma crosses over to mild persistent asthma. First, these agents are anti-inflammatory agents, which satisfy the requirement for a controller medication that is anti-inflammatory in controlling a disease with an inflammatory basis. Second, leukotriene production is increased in asthma ([3], [4]), and the leukotrienes are well known to cause bronchospasm, increased mucus production, mucosal edema, and stimulate eosinophil recruitment to the airways. Third, corticosteroids do not seem to completely affect leukotriene synthesis or release, making the leukotriene pathway a somewhat steroid independent pathway in causing inflammation and bronchospasm in asthma ([4],[5],[6]). Last, treatment with leukotriene modifiers in mild asthma can control disease. Studies reveal that these agents improve mild to moderate asthma as related to symptoms and asthma free days compared to short acting B_2 -agonists or placebo ([7],[8],[9]), decrease airway and peripheral eosinophilia ([10]), attenuate the early and late asthmatic response to allergen, and may decrease airway hyperresponsiveness ([11],[12]).

The leukotriene modifier agents available in 1997 were zileuton and zafirlukast. Zileuton, a 5-lipoxygenase inhibitor, requires four times a day dosing and can cause liver function abnormalities. Zafirlukast, a leukotriene receptor antagonist, is dosed twice a day and is known to cause Warfarin drug interactions. The agent of choice, currently, is montelukast. This medication requires once a day dosing, has no serious side effects noted at the 10 mg daily dose for adults or 5 mg daily dose for children age 5 and over, has no known drug interactions, and has been

shown to be better than placebo at improving pulmonary function and controlling asthma symptoms ([13]). It should be noted that asthma symptom control and pulmonary function were improved more with inhaled corticosteroids than with montelukast, although both were much better than placebo (13). Additional advantages of montelukast compared with the other main controller medication, inhaled steroids, are better compliance with oral agents compared to inhaled medication ([14]), ease of use, once a day dosing, onset of action within hours versus one week or more with inhaled steroids (13), and no corticosteroid side effects such as oral candidiasis, hoarseness, or decreased bone mass over time ([15]).

Two other subgroups of asthmatics may benefit specifically from treatment with leukotriene modifiers, exercise- and aspirin-induced asthma. Multiple studies have shown an improvement in some but not all patients with exercise-induced asthma when treated with leukotriene modifiers (4,[16,17,18]). These studies reveal protection varying from 20 to 80% in reducing the maximal bronchoconstrictor response, in decreasing the loss of area under the pulmonary function curve versus time after exercise challenge versus placebo, and improving the recovery time versus placebo (16, 17,18,[19,20]). This protection maintains itself for up to 24 hours after the last dose of medication (19,20).

Aspirin-induced asthma (AIA), present in at least 10% of asthmatics, appears to be associated with an increased basal level of leukotriene production, which increases further after aspirin challenge ([21,22]). Commonly proposed mechanisms for AIA include a LC_4 synthase promotor polymorphism ([23]) resulting in increased expression of LC_4 synthase in eosinophils and mast cells of aspirin sensitive asthmatics, increased expression of LC_4 synthase in inflammatory cells of AIA compared to controls ([24,25]), release of an inhibitory effect of PGE_2 on leukotriene production with the use of cyclooxogenase blockers ([26]), a combination of all previous mechanisms, and others. Proof of these hypotheses across populations is lacking, however ([27]). Consistent with the increased basal level of leukotriene production in AIA, one study revealed an 18% improvement in pulmonary function with the addition of a leukotriene receptor antagonist to AIA subjects who were not challenged with aspirin ([28]). Other studies reveal a decrease in bronchial hyperresponsiveness and decreased sensitivity to aspirin products with leukotriene receptor blockers ([29]), partial inhibition of the reduction in pulmonary function ranging from 43 to 74% in some AIA with leukotriene receptor antagonists ([30,31]), and complete inhibition of the AIA response with a 5-lipoxogenase inhibitor ([32]).

Leukotriene modifying drugs, and in particular the leukotriene receptor blocker montelukast, should be considered as first line therapy in mild persistent asthma, especially if exercise- or aspirin-induced. Montelukast's once a day dosing, anti-inflammatory effects, absence of side effects, ability to use in children and adults, clinical effects occurring within hours, and clinical efficacy in some but not all asthmatics make it an ideal drug for a short trial of therapy. Leukotriene modifying drugs clearly do not work in all asthmatics, possibly related to the varied underlying physiology in different asthmatics. Therefore, if a short trial of several weeks or a month does not work, inhaled corticosteroids can be substituted or added to the leukotriene modifier.

CONCLUSION

Possible future roles for the leukotriene modifiers include adding to currently used corticosteroid therapy to reduce the steroid dose and the attendant side effects, the development and addition of a once or twice per day dosing of a 5-lipooxygenase inhibitor without side effects since these drugs appear superior to leukotriene receptor blockers in AIA and possibly asthma in general, and the addition of leukotriene modifier therapy to other asthma treatment combinations such as long acting B2-agonist therapy or inhaled corticosteroids to determine whether these combinations are better than the available regimens to date. It is an exciting time in the treatment of asthma as we watch the unfolding of the use of leukotriene modifier therapy in this disease.

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