LEUKOTRIENE ANTAGONISTS: A NEW APPROACH IN THE TREATMENT OF ASTHMA

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ABSTRACT
Asthma is the most common respiratory disease encountered in clinical practice, affecting both children and adults. It is an important cause of mortality and morbidity. Inflammation plays an essential role in the genesis of airflow obstruction and bronchial hyper-reactivity in the early stages of clinical asthma. Amongst a number of inflammatory mediators leukotrienes occupy a privileged place by the power of their inflammatory and constrictor effect on bronchial smooth muscles. These properties justified the clinical development of specific antagonist to their receptors. Leukotriene receptor antagonists have been shown to protect against bronchoconstriction induced by antigen, exercise, cold air and aspirin. Challenge studies with these agents are reviewed. Clinical studies with leukotriene antagonists have confirmed the central role of leukotrienes in pathophysiology of asthma. In conclusion, we suggest that new generation of leukotriene receptor antagonists may be suitable as first line therapy in patient with mild to moderate asthma. Further studies are required to determine whether the leukotrienes antagonists will be equally effective or provide any additional anti-inflammatory benefit.

INTRODUCTION
Recent clinical and basic studies have demonstrated 5-lipoxygenese products to be major mediator in the pathophysiology of bronchial asthma (Isreal E. et al., 1993). Clinical trials of several selective cyst LT, receptor antagonist have demonstrated beneficial results in the management of patient with bronchial asthma (Drazen J.M. and Isreal E., 1995). It is now established that leukotrienes are pivotal mediator of airway obstruction in asthma. The leukotrienes were discovered in basic studies of arachidonic acid metabolism in leucocytes 20 years ago. They were found to display a number of biological activities, which may contribute to airway obstruction. Therefore antileukotriene drugs have been developed and treatment trials have been indeed established that this new class of drug has beneficial anti-asthmatic properties.

Although asthma was once regarded largely as a disease of airway smooth muscle leading to treatment with oral and inhaled broncho-dilators. Investigations over the last decades have shown asthma to be a chronic inflammatory disease complicated by periodic acute inflammatory changes (Barnes P.J., 1992). Indeed it is now clear that even patients with mild asymptomatic asthma have obvious inflammatory changes in their airways, characterized by infiltration of the mucosa and epithelium with activated T cells, mast cells and eosinophils (Beasley R. et al., 1993).

However, despite the well-recognized efficacy and safety of inhaled corticosteroids,
many patients will still have poorly controlled asthma and poor quality of life (Geddes D., 1992). In addition, there are rising trends in asthma prevalence, morbidity, severity and mortality rates (Burney P.J.G.J., 1992) and there is also concern about the long-term safety of inhaled corticosteroids, particularly in high doses and at the extreme of age. Numerous studies have pointed to poor patient compliance with therapy especially for inhaled preparation with which many patients also have a poor technique (Cockcroft D.W., 1993). These problems have prompted the search for alternative, well-tolerated and effective pharmacological agents that target airway inflammatory events.

The metabolism of arachidonic acid produces a family of substances that have diverse biological activities. Significant attention has been focused on the cysteinyl or peptidoLeukotrienes (LTs i.e. LTC₄, LTD₄, LTE₄) which are known to be responsible for physiochemical and biological properties of slow reacting substance of anaphylaxis, these metabolites are thought to be critical mediators in the pathophysiological state of several inflammatory diseases, most notable asthma (Piacentini G.L. and Kaliner M.A., 1991). The sources of leukotrienes include inflammatory cell that are implicated in the pathogenesis of asthma, such as mast cells, basophil, eosinophil and macrophages. Leukotrienes exert various effects on the pulmonary system that may contribute to the etiology of asthma. Although most widely recognized of this effect is bronchoconstriction, LTs also induce mucous secretion, inflammatory cell infiltration, micro-vascular permeability, airway smooth muscle proliferation, and neuronal input interactions. The blocking of these multiple effects is likely to be particularly relevant to the treatment of asthma (Hay D.W.P. et al., 1995).

**Leukotriene (LT) Receptors**

LT receptors are located in the plasma membranes of smooth muscle cells in the airway and in other types of cells (Cristol J.P. et al., 1989). A single class of receptors in human airway smooth muscle appears to mediate contractions induced by LTC₄, LTD₄ and LTE₄ (Jones T.R. et al., 1989). Although unique binding sites for LTC₄ have been reported, they appear to be non-specific S-alkylglutathione binding sites (Coffin A.M. and Nguyen A., 1989). No compelling evidence has been reported for the existence of a distinct LTE₄ receptor. The existence of single class of receptor in human airway smooth muscle has important implications for drug development, because it suggests that a single LTRA would antagonize bronchoconstriction induced by all three LTs. Some evidence exists for different LT receptor sub-types that are tissue specific. Further molecular biological and biochemical studies are likely to reveal critical characteristics of LT receptor and perhaps will lead to differentiation of the variousLTRAs on the basis of their relative affinities for distinct LT receptors.

**Effect of Cysteinyl LT Antagonist in Challenge Studies**

To date, clinical trials with LTRAs have focused almost exclusively on their ability to inhibit bronchoconstriction elicited by several stimuli, including LTD₄, antigen, exercise, cold air and aspirin. However clinical investigation of the influence of LTRAs on effect other than bronchoconstriction are ongoing. In the future, significant efforts should be directed toward assessing the clinical significance of the non-bronchoconstrictor influences of the LTs that have been demonstrated in pre-clinical research.

Only few reports have been published on effects of the LTRAs in asthma. In the first published study, a multi-centre, trial of chronic asthma produced a small gradual improvement in pulmonary function (Cloud M.L. et al., 1989). More impressive results were obtained when pranlukast was administered over a six-month period to patient who had bronchial asthma (Spector S.L. et al., 1994). FEV₁ and bronchial hyper responsiveness to histamine improve
significantly in 12 and 24 weeks after pranlukast treatment began, and decrease use of β₂-adrenoceptor agonist was noted. Severity score of asthma symptoms was reduced significantly after two weeks of therapy and remain reduced for another 22 weeks. Recent studies with pranlukast and other LTRAs also demonstrated improvement in both objective and subjective measures of asthma severity in patients with asthma.

**EXERCISE**

Broncho-constriction in asthma provoked by exercise is, to a large extent, mediated through the release of bronchoconstrictor substances from the inflammatory cells in the airway wall. LTs seem to play a particularly important role in this response. A single 20mg oral dose of zafirlukast produced marked protection against exercise induced bronchoconstriction in majority of patients. Thus in the study by Finnerty et al. (1992), the mean maximum percent fall in FEV₁ after exercise was 36% in patients treated with placebo and 21.6% in patients treated with active drug, with a maximum effect being observed 5 to 30 minutes after stimulation. When 400 µg of the drug was administered by inhalation, it also produces a similar degree of protection against bronchoconstriction although this varied among individuals (Makker H.K. et al., 1993).

Another marker of airway hyper-responsiveness related to exercise induced asthma is bronchoconstriction provoked by cold air. Cysteinyl-LT antagonists on cold air induced bronchoconstriction in asthma. Glass et al. (1994) showed that inhaled zafirlukast-attenuated bronchoconstriction in patients with mild to moderate disease.

**Platelet Activating Factor (P.A.F.)**

Another stimulus that is shown to be LT-dependent is the bronchoconstriction produced by inhalation of PAF. Single doses of inhaled PAF increase the excretion of the cysteinyl LT metabolite LTE₄ in the urine. Thus a single dose of 40mg of zafirlukast inhibited PAP-induced bronchoconstriction in normal volunteers by 59% when compared with placebo (Kidney J.C. et al., 1993).

**Antigen Provocation**

Various clinical studies have demonstrated suppressive effects of LTRAs against both the early-phase asthmatic response (EAR) and late-phase asthmatic response induced by antigen provocation in subject who have asthma (Findlay S.R. et al., 1992). The overall effects of LTRAs on EAR confirm pre-clinical observation that LTRAs inhibit antigen induced contraction in isolated airways of human and guinea pigs and they attenuate the broncho-spasm (Early and Late phase) produced by antigen challenge in guinea pigs and monkeys in vivo. The late phase asthmatic response is thought to be the effect other than contraction of airway smooth muscle; e.g., edema, secretion of mucus, influx and activation of inflammatory cells; as such, late phase asthmatic response may be more representative than EAR of the mechanisms underlying chronic asthma.

Zafirlukast, administered by inhalation in a dose of 400µg, blocked the early phase of the antigen induced airway response (Nathan R.A. et al., 1994). But had a lesser effect on the late-response. A second study showed that a larger 1600 µg inhaled dose of zafirlukast also inhibited the early reaction but again failed to influence the late response. These results suggest that cysteiny1-LTs released in the lung during early response may have a systemic role, possibly promoting leukocyte chemo-attraction during the late response, which in turn is associated with a further bout of airway obstruction. Evidence for this view come from a recent study in which oral Zafirlukast was given to 11 patients with mild to moderate asthma, who had a segmental allergen challenge performed after 5 days of treatment and BAL after an additional 2 days (Caloon W.J. et al., 1995) compared with placebo, Zafirlukast produces a dramatic reduction in basophil count in BAL fluid,
accompanied by significant reduction in lymphocyte counts and histamine level, a trend toward reduction in eosinophil count and reduction in superoxide production in alveolar macrophages ex vivo.

Aspirin Induced Asthma

For many years it has been known that in 5% to 10% of patients with asthma, cyclooxygenase inhibitors including aspirin produce profound bronchoconstriction particularly in patients with so-called late onset intrinsic disease. Recently studies have shown that patients with aspirin sensitive asthma have an increase production of cysteinyl LTs and increase airway sensitivity when challenged with these agents. The cysteinyl LT receptor antagonists improve lung function and inhibit bronchoconstriction induced by aspirin in patients with aspirin sensitive asthma (Dahlen B. et al., 1993).

Effects of Cysteinyl-LT Receptor Antagonist on Baseline Lung Functions in Asthma/Clinical Asthma

A particularly interesting observation made in several studies investigating the efficacy of cysteinyl LT antagonists in stable asthma has been, the ability of these drugs to produce broncho-dilatation, suggesting that cysteinyl LT contribute to the baseline airway tone in this disease (Gaddy J.N. et al., 1992).

Preliminary studies in patients with mild to moderate disease showed a definite therapeutic benefit with cysteinyl LT antagonist. A double-blind randomized placebo-controlled parallel group study in outpatients with mild to moderate asthma, examined the effects of oral Zafirlukast at three doses (5, 10, 20 mg) twice daily for 6 weeks. Approximately 60 patients were randomized to each group. Efficacy of objective and subjective measures inpatient with symptom was dose dependent and great improvement was achieved with 40 mg dose. When compared with placebo, significant improvement in evening peak flow, a 30% reduction in rescue use of inhaled β2-agonist, a 46% reduction in night waking and 26% improvement in morning asthma. These observations have increased the confidence in the efficacy of these drugs for the treatment of clinical asthma (Spector S.L. et al., 1994). Zafirlukast doses up to 80 mg twice daily have been given to 285 patients with asthma for 13 weeks, with beneficial effect increasing still further at higher doses.

CONCLUSION

There is now overwhelming evidence that the cyst LTs play an important role as inflammatory mediator in the pathogenesis of asthma. Clinical studies with selective cyst LT receptor antagonist have been critical in confirming this role. The most widely investigated antagonist, Zafirlukast has been shown to protect against broncho-constriction, provoked by inhaled LTD4, exercise, cold air, PAF, and allergens. In addition cyst LT antagonists inhibit the late asthmatic response to inhaled allergen and subsequent increase in bronchial responsiveness, suggesting that they may have effects on the inflammatory cascade. Preliminary studies in patients with mild, moderate and severe asthma have shown that LT antagonists exert significant therapeutic benefits.

With these factors in mind, the new generation of cyst LT receptor antagonist may be suitable as first line therapy for patients with mild to moderate asthma when used alone or in combination with β2-agonist as required. Cyst LT receptor antagonist represent a step forward and new direction in targeted drug therapy for asthma and will be the first new class of anti-asthmatic introduced in nearly 25 years.

Although further clinical studies are necessary and the evidence to-date support the concept that cyst LT antagonists are safe and efficacious in the treatment of asthma, whether assessed in various challenge model or in the clinics. Furthermore knowledge about the pathogenesis of asthma and the pharmacological characteristics of the LTRAs
will be enhanced as clinical experience with those compounds increases.

REFERENCES


on bronchoalveolar lavage fluid (BAL) after segmental antigen bronchoconstriction (SBP) in patients with mild to moderate asthma. (Abstract) Am J Respir Care Med. 151: A42.
