

LEUKOTRIENE

- 1- Leukotrienes result from the action of 5-lipoxygenase on arachidonic acid**
- 2- and are synthesized by a variety of inflammatory cells in the airways, including eosinophils, mast cells, macrophages, and basophils.**
- 3- Leukotriene B₄ (LTB₄) is a potent neutrophil chemoattractant,**
- 4- and LTC₄ and LTD₄ exert many effects known to occur in asthma, including :**
 - a- bronchoconstriction,**
 - b- increased bronchial reactivity,**
 - c- mucosal edema, and mucus hypersecretion.**
 - d- inhalation of leukotrienes causes not only bronchoconstriction but also an increase in bronchial reactivity to histamine that persists for several days.**

Two approaches to interrupting the leukotriene pathway have been pursued: inhibition of 5-lipoxygenase, thereby preventing leukotriene synthesis; and inhibition of the binding of LTD₄ to its receptor on target tissues, thereby preventing its action. Efficacy in blocking airway responses to exercise and to antigen challenge has been shown for drugs in both categories:

- 1- zileuton**, a 5-lipoxygenase inhibitor,
- 2- and zafirlukast and montelukast**, LTD₄-receptor antagonists.

- 3- All have been shown to improve asthma control and to reduce the frequency of asthma exacerbations in outpatient clinical trials.
- 4- Their effects on symptoms, airway caliber, bronchial reactivity, and airway inflammation are less marked than the effects of inhaled corticosteroids,
- 5- but they are more nearly equal in reducing the frequency of exacerbations. Their principal advantage is that they are taken orally; some patients—especially children—comply poorly with inhaled therapies.

Montelukast is approved for children as young as 6 years of age.

- 1- In the USA, **zileuton** is approved for use in an oral dosage of 400-800 mg for administration 2-4 times daily;
 - **zileuton is the least prescribed because of the former requirement of**
 - - a- four-times-daily dosing (a formulation for twice-daily use has recently been developed)
 - b- and because of occasional liver toxicity
- 2- **zafirlukast**, 20 mg twice daily;
- 3- and **montelukast**, 10 mg (for adults) or 4 mg (for children) once daily.
- 5- Trials with leukotriene inhibitors have demonstrated an important role for leukotrienes in **aspirin-induced asthma**.
- 4- Due to shifting arachidonic acid metabolism from the prostaglandin to the leukotriene pathway.
- 5- The receptor antagonists appear to be safe to use.
- 6- appear to have been coincidental, with the syndrome unmasked by the reduction in prednisone dosage made possible by the addition of zafirlukast or montelukast.