INHIBITORS OF LEUKOTRIENE ACTION: POTENTIAL USE IN ASTHMA, INFLAMMATORY BOWEL DISEASE, AND CUTANEOUS INFLAMMATION

Hoffmann-La Roche, Inc.
340 Kingsland Street
Nutley, NJ 07110

INTRODUCTION

Research carried out in numerous laboratories has led to the hypothesis that metabolites of the \( \Delta^5 \)-lipoxygenase (\( \Delta^5 \)-LO) pathway (e.g., leukotrienes and 5-HETE) may play an important role in mediating a number of inflammatory diseases including asthma, inflammatory bowel disease, and diseases associated with cutaneous inflammation. The purpose of this chapter is to briefly review the rationale supporting this hypothesis and to present the results of some experimental studies with promising \( \Delta^5 \)-LO inhibitors and leukotriene antagonists which would support the clinical evaluation of these types of drugs in the three disease states.

Asthma

The scientific rationale in support of a role for the peptidoleukotrienes (LTC\(_4\)/D\(_4\)/E\(_4\)) in mediating asthma is composed of a variety of observations such as:

a) Peptidoleukotrienes are very potent constrictors of isolated, in vitro preparations of guinea pig and ferret tracheal and parenchymal smooth muscle, and human bronchial smooth muscle (1-4).

b) The prolonged contraction induced by antigen in passively-sensitized human bronchi in vitro is antihistamine resistant (3) suggesting that other mediators, such as the leukotrienes, are primarily
responsible for inducing the smooth muscle contraction. In addition, antihistamines have not proven useful yet in treating asthma.

c) Peptido-leukotrienes produce bronchoconstrictions when administered in vivo to guinea pigs and primates (5-8).

d) The peptido-leukotrienes induce bronchoconstriction, coughing, wheezing, chest tightness, and a reduction in maximum expiratory air flow when administered by inhalation in man (9-16). LTC₄ and LTD₄ are approximately 1000-times and LTE₄ approximately 100-times more potent than histamine and their onset of action is slower and their duration of action is more prolonged than histamine (15-16).

e) Peptido-leukotrienes are formed when sensitized human lung is challenged with antigen in vitro in quantities sufficient to elicit a bronchoconstrictive response (17, 18). Leukotrienes are also synthesized in vitro by human mast cells and eosinophils upon antigen challenge (19, 20).

f) Leukotrienes have been detected in sputum (21) and plasma (22) collected from patients with acute asthma and in the nasal washings (23) taken from atopic individuals following antigen challenge; and

g) Leukotrienes have a wide spectrum of biological activities which may contribute to asthmatic symptomatology in addition to contracting airway smooth muscle. These include the ability to contract pulmonary vascular smooth muscle (24), increase vascular permeability (4, 5) and increase mucus secretion in lung tissue (25).

Based on the circumstantial but convincing evidence detailed above, a number of pharmaceutical companies launched programs several years ago to identify peptido-leukotriene antagonists or Δ⁵-LO inhibitors for evaluation in asthma reasoning that such compounds could prove to be new therapeutic agents for the treatment of this disease. Tables 1 and 2 describe the in vitro activity in our assay systems of a few of the most promising drug candidates to evolve from these efforts. Studies to evaluate the effects of known Δ⁵-LO or dual Δ⁵-LO/CO inhibitors on arachidonic acid metabolism in ionophore (A23187)-stimulated rat peritoneal macrophages were performed according to techniques described previously (26-28). The ³H-LTD₄ binding studies on recently described LTD₄ antagonists were performed as indicated in Table 2.