Development of MK 0591: An Orally Active Leukotriene Biosynthesis Inhibitor with a Novel Mechanism of Action

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Introduction

Asthma is a chronic inflammatory condition characterized by bronchial hyper-responsiveness and reversible airway obstruction. A number of mediators have been implicated in the pathophysiology of this complex disease, including leukotrienes (LTs) (Ford-Hutchinson, 1989; Chanarin and Johnston, 1994). The biological effects of these arachidonic acid (AA) metabolites, including smooth muscle contraction, vasoconstriction and vascular permeability mimic the pathological changes seen in asthma (Ford-Hutchinson et al., 1980; Samuelsson, 1983; Jones et al., 1989). Furthermore, baseline LT production is higher in asthmatic subjects and is increased significantly during asthmatic attacks (Isono et al., 1985; Lam et al., 1988; Tagari et al., 1990; Knapp et al., 1992; Picado et al., 1992). The pro-inflammatory effects of LTs have also implicated these compounds in inflammatory bowel disease (IBD) (Rask-Madsen et al., 1992). The demonstration that LTs have properties associated with asthma and IBD has stimulated the development of many potential therapeutic agents to block the effects of these compounds.

LT biosynthesis inhibitors represent one of the most interesting new classes of compound for the treatment of asthma and IBD in development at present. Here, we would like to describe one of the approaches to the development of such an entity taken at Merck Frosst, which resulted in the discovery of our clinical candidate MK 0591. During this process,
elucidation of the mechanism of action of MK 0591 and its predecessor MK-886 provided novel insights into the cellular synthesis of LTs.

The enzyme 5-lipoxygenase (5-LO) catalyzes the first two steps in the synthesis of all LTs from AA, namely the oxidation of AA to 5-hydroperoxyeicosatetraenoic acid (5-HPETE) followed by an LTA₄ synthase activity which converts 5-HPETE to LTA₄ (Rouzer et al., 1986; Shimizu et al., 1986) (Figure 8-1). LTA₄ can be further metabolized to the pro-inflammatory compound LTB₄ or to the bronchoconstrictive peptido leukotrienes LTC₄, LTD₄, and LTE₄, with the amounts and ratios of these products depending upon the cell type being studied (Maycock et al., 1989). 5-LO has therefore been the focus of intense efforts to develop inhibitors of LT biosynthesis. Various whole cell and isolated enzyme assays have been used to identify a number of potent inhibitors of 5-LO (Fitzsimmons and Rokach, 1989). Some of these compounds, including zileuton (Carter et al., 1991), MK 0591 (Brideau et al., 1992) and D 2138 (McMillan et al., 1992) are currently in clinical development.

The Early Years

Early in our search for inhibitors of 5-LO we proposed that, as AA is a substrate for both 5-LO and cyclooxygenase enzymes, examination of cyclooxygenase inhibitors may reveal compounds with 5-LO inhibitory activity, particularly if these compounds are AA mimetics or active site inhibitors. Indeed, study of the indole-2-alkanoic acids, indomethacin-like molecules, such as 1 yielded compounds possessing moderate activity (IC₅₀ ~ 5 μM) for the inhibition of LT synthesis in human polymorphonuclear leukocytes (HPMN). This compound also possessed thromboxane receptor antagonist activity. Medicinal chemistry effort was initiated to dissociate these two activities. This effort was successful and led to the discovery that by appropriate manipulation of the indole substitution as well as constraint of the alkanoic side chain, it was possible to derive specific thromboxane receptor antagonists with high potency, such as (-)-L-670,596 (Ford-Hutchinson et al., 1989). Introduction of bulky substituents on the indole nucleus resulted in potent inhibitors of LT biosynthesis which were essentially devoid of thromboxane receptor antagonist or cyclooxygenase activity. Optimization of this activity led to the discovery of MK-886 (Gillard et al., 1989).

MK-886 was a potent inhibitor of LT synthesis in a variety of cell types, including human and rat PMN with IC₅₀ values of approximately of 3 nM. However, the compound was essentially inactive in broken cell 5-LO assays or when tested against purified enzyme (IC₅₀ > 10 μM). In