



# Antileukotrienes, asthma pathogenesis and the pharmaceutical industry

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In the early 1940s Kellaway and Trethewie<sup>1</sup> identified a biological activity that caused slow-onset but very prolonged constriction of smooth muscle, an activity that was not antagonized by antihistamines. They called the causative agent for this activity "slow-reacting substance."<sup>1</sup> Twenty years later, Brocklehurst<sup>2</sup> demonstrated release of slow-reacting substance from lung segments that had been obtained from an asthmatic subject and exposed to allergen; he modified the name to slow-reacting substance of anaphylaxis. This finding generated great excitement among researchers interested in the pathogenesis of asthma, mainly because the substance was a potent constrictor of smooth muscle in the airways and had a much longer duration of action than other smooth-muscle constrictors, such as histamine. It was therefore thought to be important in causing bronchoconstriction and symptoms in asthmatic patients after inhalation of allergens. In 1979 Samuelsson and investigators in his laboratory at the Karolinska Institute in Stockholm — including a Canadian, Pierre Borgeat (who played an important part in this discovery) — found that the slow-reacting substance of anaphylaxis consisted of arachidonic acid metabolites, which they called "leukotrienes."<sup>3</sup> The biological activity is now known to be caused by the cysteinyl leukotrienes C<sub>4</sub>, D<sub>4</sub> and E<sub>4</sub>. Samuelsson later won the Nobel Prize in Medicine and Physiology, in part for this discovery.

Identifying a role for any mediator in asthma or another inflammatory disease depends on various types of evidence. Often, when the structure of a mediator (such as one of the leukotrienes) is identified and the compound synthesized, the mediator is given (usually by inhalation) to people with asthma, to determine whether it can mimic some component of the asthmatic response. Then, when assays for the mediator become available, efforts are made to measure it in biological fluids, to determine whether it is released (and excreted) during asthmatic responses. However, this evidence is indirect and can be misleading. For example, the *in vivo* asthmatic response may involve

local release of mediators at concentrations too low to allow systematic measurement; alternatively, a mediator may be released but not have a measurable biological effect until hours later.

The most compelling evidence of the importance of a particular mediator in asthma comes from selective antagonists, which block the action of the mediator on its receptor, and from inhibitors of synthesis of the mediator, which prevent its production. These compounds can be used to evaluate the role of the mediator in causing components of the asthmatic response. The final, and most difficult, hurdle is to determine whether the antagonists or synthetase inhibitors of the mediator can be used to treat asthmatic patients; if so, the mediator's important role in the pathogenesis of asthma is proven.

This stepwise experimental approach is possible only if the pharmaceutical industry invests resources in developing these compounds and evaluating their safety for use in asthmatic patients. The development of the antileukotrienes is an excellent example. The pioneering research that started with a serendipitous discovery reported in 1940 led several pharmaceutical companies to establish leukotriene programs in the early 1980s. Indeed, one of these, Merck Frosst of Dorval, Que., played a particularly important role by making synthetic leukotrienes available, free of charge, to asthma researchers around the world, so that they could conduct studies on the biological role of these compounds. By the early 1990s several potent and selective compounds had been developed, which were then used to demonstrate the critical role of leukotriene generation and release in the airways in causing exercise-induced,<sup>4</sup> allergen-induced,<sup>5</sup> cold-air-induced<sup>6</sup> and ASA-induced<sup>7</sup> bronchoconstriction in asthmatic patients. This work has represented an important and satisfying collaboration between academia and industry, one that has greatly improved the understanding of the pathogenesis of asthma and resulted in potential new drugs for the treatment of this disease.



The antileukotrienes have now been extensively evaluated in clinical trials involving patients with persistent asthma, as is comprehensively reviewed by Paolo Renzi elsewhere in this issue (page 217).<sup>8</sup> These drugs have been shown to be efficacious, and they have a good safety profile in patients with moderately severe asthma. Two of these compounds, the receptor antagonists accolate and montelukast, were released in Canada in 1998 and represent the first novel treatment in asthma management in more than 25 years.

However, the responsibility of academia and industry has not ended with the launch of this new class of drugs. In some regards, the most difficult work lies ahead: determining how best to use these new treatments, how to evaluate their effectiveness and cost-benefit ratio, and how to monitor their safety as larger populations of patients are treated. These are issues that Renzi has fully elucidated in his review. At present, there does not appear to be any indication for the use of antileukotrienes in patients with very mild, intermittent asthma, in whom infrequent use of inhaled  $\beta_2$ -agonists is adequate to control symptoms. The antileukotrienes are effective in patients with moderate or severe persistent asthma, for many of whom symptoms are not optimally controlled with low to moderate doses of inhaled corticosteroids; in this population, the antileukotrienes will be one of several treatments recommended in asthma consensus guidelines. In patients with milder but persistent asthma, in whom disease control is not achieved with the infrequent use of  $\beta_2$ -agonists, currently available consensus guidelines on the management of asthma suggest that low doses of inhaled corticosteroids are the most effective treatment.<sup>9</sup> It is likely that the antileukotrienes will also be effective in some of these patients; however, because low doses of inhaled corticosteroids are highly effective in this patient population, the antileukotrienes cannot be recommended as the preferred treatment (unless the patient cannot, or will not, use inhaled corticosteroids). If an antileukotriene is chosen as the next line of treatment, a therapeutic trial of 2–4 weeks will allow a decision to be made about treatment efficacy. If the treatment is ineffective, it should not be continued beyond this time.

There are many examples in asthma management of how the use of drugs has changed markedly over time. For example, inhaled corticosteroids were introduced in 1972 mainly as oral steroid-sparing agents, but they are now the first-line treatment for persistent asthma.<sup>9</sup> For 2 decades, inhaled short-acting  $\beta_2$ -agonists were advocated for use 4 times daily or more often, but current recom-

mendations indicate that they should be used as infrequently as possible.<sup>9</sup> Establishing the correct position of a new class of treatment, even one with as selective an action as the antileukotrienes, within 1 year of release is not possible. However, it is appropriate to give some advice, based on an evaluation of the available clinical studies, which Renzi has done admirably. The lack of certainty will be resolved only by well-designed studies to compare antileukotrienes with currently available therapy, to establish whether they are disease-modifying drugs (as inhaled corticosteroids appear to be) and to carefully monitor patients for unwanted effects. This means continuing collaboration between industry, academia and those physicians who are using antileukotrienes in the management of patients with asthma.

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**Competing interests:** Dr. O'Byrne has been a member of several pharmaceutical company advisory boards concerned with the development of drugs to treat asthma. In addition, he has received research funds and honoraria from several companies for work in this field.

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