CURRENT STATUS OF LEUKOTRIENE ANTAGONISTS IN BRONCHIAL ASTHMA

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INTRODUCTION

Bronchial asthma or simply ‘asthma’ is a syndrome characterized by airflow obstruction that varies markedly, both spontaneously and with treatment. Asthma is one of the most common diseases globally and currently affects approximately 300 million people worldwide. The prevalence of asthma has risen in affluent countries over the last 30 years but now appears to have stabilized, with approximately 10-12% of adults and 15% of children affected by the disease.[1] As per National Family Health Survey of India, 2468 persons per 100,000 population are reported to be suffering from asthma, which is considerably higher in rural areas (2649 per 100,000 population) than in urban areas (1966 per 100,000 population).[2] According to the Global Burden of Asthma Report (GINA), over 50 million suffer from asthma in Central and Southern Asia and an absolute 2% increase in the prevalence of asthma in India would result in an additional 20 million people with this disease.[3] The epidemiologic observation suggests that there is a maximum number of individuals in the community, who are likely to be affected by asthma, most likely by genetic predisposition. In childhood, twice as many males as females are asthmatic, but by adulthood the sex ratio has equalized.

RISK FACTORS AND TRIGGERS

Asthma is a heterogeneous disease with interplay between genetic and environmental factors. Several risk factors have been implicated (Table 1).[4]

<table>
<thead>
<tr>
<th>Endogenous factors</th>
<th>Environmental factors</th>
<th>Triggers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic predisposition</td>
<td>Indoor allergens</td>
<td>Allergens</td>
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<tr>
<td>Atopy</td>
<td>Outdoor allergens</td>
<td>Upper respiratory tract viral infections.</td>
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<tr>
<td>Airway hyper responsiveness</td>
<td>Occupational sensitizers</td>
<td>Exercise and hyperventilation.</td>
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<tr>
<td>Gender</td>
<td>Passive smoking</td>
<td>Cold air</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Respiratory infections</td>
<td>Sulfur dioxide and irritant gases</td>
</tr>
<tr>
<td>Obesity</td>
<td></td>
<td>Drugs (β-blockers, aspirin)</td>
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<tr>
<td>Early viral infections</td>
<td></td>
<td>Stress</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Irritants (household sprays, paint fumes)</td>
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</table>

The allergens that lead to sensitization are usually proteins that have protease activity, and the most common allergens are derived from house dust mites, cat and dog fur, cockroaches, grass and tree pollens, and rodents. Atopy is genetically determined production of specific IgE antibody, with many patients showing a family history of allergic diseases.

LEUKOTRIENES

Leukotrienes (LTs) are unsaturated fatty acids generated by action of the 5-lipoxygenase (5-LO) enzyme on the cell membrane-bound arachidonic acid (AA). Two classes of LTs are derived from the 5-LO pathway, the nonpeptide LTs LTA4 and LTB4, and the cysteinyl-LTs LTC4, LTD4 and LTE4. Once secreted extracellularly, LTs act on specific receptors, after which they are rapidly degraded, with a very short half-life. In particular, the activation of the recently cloned Cys-LT1 receptor, whose expression has been demonstrated on bronchial smooth muscle cells and various inflammatory cell types in the lung, is responsible for the bronchoconstrictive and proinflammatory actions, including increased microvascular permeability with oedema and increased mucus secretion, possessed by cysteinyl-LTs.[5]

Pharmacological research for the identification and development of anti-LT drugs started towards the end of the 1970s and the beginning of the 1980s, soon after the discovery by Samuelson and his group at the Karolinska Institute in Sweden of the chemical nature and potent activity of LTs. Since 1987, clinical studies on various compounds with anti-LT properties were initiated, and just 10 years later the first anti-LT drugs zileuton, pranlukast, zafirlukast, and montelukast were almost contemporarily commercialized. Zileuton blocks the synthesis of LTs by inhibiting the 5-LO enzyme, whereas pranlukast, zafirlukast, and montelukast are all orally active cysteinyl-LT receptor antagonists (LTRA).

Recommended adult doses are 20–40 mg twice daily for zafirlukast and 10 mg once daily for montelukast. Only montelukast is licensed for use in children, with a 5-mg dose for children 6–12 years of age and a 4-mg dose (only in USA) for children 2–5 years of age. A number of studies have demonstrated that LTRAs show bronchodilating and anti-inflammatory properties, that make these drugs ideal candidates for the treatment of asthma.[6]

In fact, they are capable of blunting both the early and late bronchoconstrictive response and the cellular inflammatory response to inhaled allergen, and to prevent the exercise induced and the aspirin induced bronchoconstriction, without evidence of tolerance with prolonged use.[2] Finally, long-term treatments with LTRAs are able to reduce both the blood and sputum eosinophilia in both adults and children with asthma.[4]

Cysteinyl leukotrienes are important pro-inflammatory and bronchoconstrictor mediators in the pathogenesis of asthma, while leukotriene receptor antagonists (LTRAs) demonstrate hybrid anti-inflammatory and bronchodilatory properties.[5] Current international guidelines[6] recommend using an LTRA as first-line therapy in patients with mild, persistent asthma, or as second-line therapy in conjunction with inhaled corticosteroids, as an alternative to increasing the dose of inhaled corticosteroids. Cells that do not express 5-LO, including platelets, erythrocytes, endothelial cells and epithelial cells, also have the capacity to produce cysteinyl-LTs and/or LTB4 through the transcellular metabolism of LTA4 synthesized by activated neutrophils.[7] After their intracellular formation,
cysteinyl-LTs and LTB4 are released to the extracellular space through specific carrier-proteins that are potential targets for future antileukotriene drugs.\textsuperscript{[8]}

Cysteinyl-LTs are functionally involved in airway remodeling that includes eosinophil cell inflammatory response, airway smooth muscle cell hyperplasia, mucus gland hyperplasia, mucus hypersecretion, and collagen deposition beneath the epithelial layer and in the lung interstitium at sites of leukocytes infiltration.\textsuperscript{[9, 10]}

LEUKOTRIENE RECEPTOR ANTAGONISTS

Selective CysLT1 receptor antagonists that have been approved for clinical use in asthma include montelukast, zafirlukast and pranlukast (Table 2).\textsuperscript{[11]} Zileuton, a 5-LO inhibitor, has been approved for the prevention and chronic treatment of asthma in adults and children 12 years of age and older in the United Kingdom and USA. Montelukast is the most prescribed CysLT1 receptor antagonist in Europe and the USA, whereas pranlukast is only marketed in Japan and other Asian countries. Zafirlukast was the first anti-LT that was approved in Europe, but it is not frequently prescribed due to possible food and drug interactions, and its twice daily administration regimen.\textsuperscript{[11, 8]} The fact that selective CysLT1 receptor antagonists and 5-LO inhibitors have similar efficacy in short-term treatment studies and challenge models indicates that most of the antiasthmatic effects of anti-LTs are due to CysLT1 antagonism.\textsuperscript{[8]} The use of zileuton is limited because of a small, but distinct, incidence of hepatic enzyme elevation, which is not observed with montelukast, and the short half-life, requiring four daily administrations.\textsuperscript{[8]} A twice-daily controlled-release formulation of zileuton has been approved by the U.S. Food and Drug Administration (FDA).\textsuperscript{[12]}

At least two aspects of selective 5-LO inhibitors concerning the inhibition of LTB4 synthesis deserve further investigation: their effects on airway hyper responsiveness (AHR) in patients with asthma \textsuperscript{[13, 14]} that is slightly affected by CysLT1 antagonists \textsuperscript{[15]}; the potential efficacy of 5-LO inhibitors in rhinitis and rhinoposy as these drugs are very effective in reducing nasal symptoms in patients with aspirin-sensitive asthma (ASA).\textsuperscript{[13]}

Table 2: Salient pharmacological characteristics of antileukotrienes\textsuperscript{[11]}.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Drug</th>
<th>Mechanism of action</th>
<th>Benefits</th>
<th>Side effects</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Montelukast</td>
<td>CysLT1 receptor antagonism</td>
<td>As monotherapy in children with mild persistent asthma; particularly effective in exercise-induced asthma, ASA, allergen-induced asthma; as add-on therapy with ICS</td>
<td>Headache, abdominal pain; possible association with Churg-Strauss syndrome.</td>
<td>Adults: 10 mg o.d., Children 6 to 14 years of age: 5 mg o.d., children 2 to 5 years of age: 4 mg o.d.</td>
<td>Most widely prescribed CysLT1 receptor antagonist.</td>
</tr>
<tr>
<td>2.</td>
<td>Pranlukast</td>
<td>CysLT1 receptor antagonism</td>
<td>Particularly effective in exercise-induced asthma, ASA, allergen-induced asthma; as add-on therapy with ICS</td>
<td>Abdominal pain, liver enzymes elevations; possible association with Churg-Strauss syndrome</td>
<td>Adults: 225 mg b.i.d.</td>
<td>Only marketed in Asia.</td>
</tr>
<tr>
<td>3.</td>
<td>Zafirlukast</td>
<td>CysLT1 receptor antagonism</td>
<td>Particularly effective in exercise-induced asthma, ASA, allergen-induced asthma; as add-on therapy with ICS</td>
<td>Headache, abdominal pain, liver enzymes elevations; possible association with Churg-syndrome</td>
<td>Children ≥ 12 years of age and adults: 20 mg b.i.d., Children 5 to 11 years of age: 10 mg b.i.d.</td>
<td>First CysLT1 receptor antagonist to be approved; food and drug interactions virtually abandoned because of poor compliance and hepatic toxicity.</td>
</tr>
<tr>
<td>4.</td>
<td>Zileuton</td>
<td>5 – LO inhibition</td>
<td>Particularly effective in exercise-induced asthma and ASA</td>
<td>Headache, abdominal pain; liver enzymes elevations (5%)</td>
<td>Adults and children 12 years of age and older: 600 mg q.i.d.</td>
<td></td>
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Abbreviations:
ASA = aspirin-sensitive asthma; CysLT = cysteiny-leukotrienes; ICS = inhaled corticosteroids.

COMPARATIVE ASPECTS

CysLT1 receptor antagonists are less effective than inhaled glucocorticoids as first-line agents in both adults \textsuperscript{[16]} and children with asthma.\textsuperscript{[17]} In patients with asthma who are not sufficiently controlled with a constant dose of inhaled budesonide alone, add-on therapy with montelukast improves asthma control\textsuperscript{[18]} to a level comparable to that achieved by doubling the dose of budesonide.\textsuperscript{[19]} The advantage of this therapeutic strategy would be the reduced risk of side effects due to long-term administration of high-dose inhaled glucocorticoids.\textsuperscript{[19]} In patients whose symptoms remain uncontrolled with inhaled fluticasone alone, the addition of montelukast is a therapeutic option \textsuperscript{[20]}, although the addition of a long-acting β2-agonist is generally more effective than a CysLT1
receptor antagonist for preventing exacerbations requiring systemic steroids, and for improving lung function, symptoms and the use of rescue β2 agonists. In patients with well-controlled asthma based on symptoms and lung function testing, the addition of pranlukast to the combination of inhaled glucocorticoids and long-acting β2-agonist gives better control of airway inflammation compared with therapy with the combination of inhaled glucocorticoid/long-acting β2-agonist alone.

LTRAs show some anti-inflammatory activity and, in this context, montelukast is able to prevent in asthmatic patients both the early and late asthmatic response to inhaled allergen and to reduce with long-term treatments the eosinophil levels both in the blood and in the airways. Oral montelukast, 10 mg once a day, with inhaled beclomethasone, 200 mg twice a day, for 12 weeks has demonstrated inhaled beclomethasone to be slightly superior to montelukast in improving clinical and functional indexes in patients with mild to moderate asthma.

There are limited prospective, comparative studies examining the safety of CysLT1 receptor antagonists in pregnancy. Montelukast does not appear to increase the baseline rate of major malformations. The lower birth weight observed in infants born to women treated with montelukast could be attributed to severity/control of the maternal asthma.

Treatment with inhaled fluticasone (100 µg b.i.d. for four weeks) reduces LTE4 concentrations in EBC by 18% in children with intermittent and mild persistent asthma. The therapeutic response to CysLT1 receptor antagonists as well as to inhaled glucocorticoids in both adults and children with asthma is variable. In children with mild persistent asthma, montelukast withdrawal can result in enhanced airway inflammation, as reflected by increased fractional exhaled nitric oxide concentrations (FeNO) and worsening of lung function.

CONCLUSIONS AND FUTURE PERSPECTIVES

Bronchial asthma is a multifaceted disease with respect to its etiology as well as its treatment. Most of our knowledge of the pathophysiological role of LTs in asthma is currently limited to CysLT1 receptor-mediated effects, whereas the role of the CysLT2 receptor is largely unknown. The identification of responders to CysLT1 receptor antagonists might be relevant for a more rational therapy of patients with asthma. The bottom line is that regular treatment with LTRAs have proved to be beneficial in asthmatic patients by improving airway function, asthma symptoms, as-needed use of rescue medications, and quality of life. At present, international guidelines for asthma management recommend that LTRAs should be used for regular treatment in patients with moderate asthma not completely controlled by inhaled corticosteroids in order to improve the asthma control, in patients with moderate asthma well controlled by inhaled corticosteroids in order to try to reduce the dose of inhaled corticosteroids, and, as monotherapy, in patients with mild persistent asthma in order to reduce airflow inflammation and minimize symptoms and use of rescue medications.

REFERENCES


