

The Treatment of Bronchial Asthma – A Multifaceted Approach

a report by

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The pathophysiology of bronchial asthma is characterised by three different but connected entities – chronic inflammation, smooth muscle dysfunction and remodelling of the airways.¹ Accordingly, the treatment of bronchial asthma should take into account the presence of these three entities and the fact that the disease is also associated with short-lived symptoms that can be prevented or reversed by bronchodilators. Another important factor is that asthma is characterised by the presence of exacerbations that can be treated or reversed by anti-inflammatory drugs, and the presence of airway remodelling also has to be considered in order for the identification of an appropriate treatment aimed at the prevention of its development.

Owing to their well-defined anti-inflammatory properties, inhaled corticosteroids (ICS) are considered by current management guidelines as a first-line treatment.^{2,3} However, optimal control of the disease can be achieved by the addition of long-acting β_2 -agonists (LABAs) to the ICS treatment.⁴ Moreover, the use of the leukotriene receptor antagonists (LTRAs) has been relatively recently licensed as first-line monotherapy or as add-on therapy in patients whose asthma is uncontrolled by ICS.² Finally, xantines, anticholinergic and anti-immunoglobulin E (IgE) agents are also used in the therapy of asthma, and new strategies, including the use of anti-tumour necrosis factor (TNF) agents, are currently under evaluation.^{5–7} This article will briefly review the effects of these therapeutic agents, both alone and in combination, on the major pathophysiological mechanisms that characterise the chronic inflammation, smooth muscle dysfunction and airway remodelling in bronchial asthma.

ICS and LABAs

Several studies have demonstrated the down-regulatory effect exerted by ICS on several inflammatory cells and mediators within the airways of patients with asthma. The number of mast cells, eosinophils, macrophages and T-lymphocytes is significantly reduced in bronchial biopsies from asthmatic patients after ICS treatment – this reduction is mainly related to the ICS-mediated inhibition of the

cytokines responsible for their recruitment from the blood circulation and for their activation.^{8,9} In this regard, it has been shown that ICS are potent inhibitors of TNF- α and interleukin (IL)-1, which are released by mononuclear phagocytes and are responsible for the expression of adhesion molecules – i.e. E- and P-selectins, intercellular adhesion molecule (ICAM)-1 and vascular adhesion molecule (VCAM)-1. These adhesion molecules actively contribute to the recruitment of neutrophils, eosinophils and basophils from the blood circulation to the site of inflammation.^{10,11} ICS are also able to downregulate the expression and the activities of cytokines IL-4 and IL-13, which are specific endothelial activators, and IL-3, IL-5 and granulocyte-macrophage colony stimulating factor, which all have the ability to prime and activate the eosinophils.^{10–12} Finally, ICS also up-regulate the release of IL-10, which has the ability to exert some anti-inflammatory effects including the downregulation of T-lymphocyte proliferation and the inhibition of some IL-1 and TNF- α activities.¹³ This evidence supports the concept that ICS have a broad spectrum of anti-inflammatory effects.

LABAs are currently used in combination with ICS to provide additional relief of airway obstruction and the prevention of asthma exacerbations.^{14,15} They exert an important bronchodilatory effect by the direct stimulation of β_2 -receptors on airway smooth muscles (ASMs), which leads to relaxation. These receptors are present on the smooth muscle of all airways from the trachea to the terminal bronchioles.^{16,17} The direct anti-inflammatory effect of LABAs is still controversial. Several studies reported that LABA treatment did not have any significant effect on the bronchoalveolar lavage (BAL) fluid differential cell counts, levels of mediators (histamine, tryptase and eosinophil cationic protein (ECP)) and T-lymphocyte activation, despite their ability to improve the peak flow rate.^{18,19} On the other hand, other studies have shown a significant decrease of ECP levels in BAL fluid and a reduction in *ex vivo* macrophage-stimulated oxidative metabolism, as well as a downregulation of serum ECP and a reduced tissue accumulation of mast cells and memory T-cells after LABA treatment.²⁰

It is now widely accepted that the combined administration of ICS and LABAs may target complementary aspects of asthma pathophysiology. It has been shown that LABAs, other than exerting effects on ASMs, are able to complement the effects of ICS on inflammatory cells and mediators. In this regard, LABAs have a direct influence on ICS action by exerting an effect on glucocorticoid receptors (GR), by priming GR for subsequent steroid binding and by promoting the translocation of the GR–steroid complex from the cytosol into the nucleus.²¹ Conversely, ICS can modulate β_2 -receptor density and function by a number of mechanisms, including protection against desensitisation/tolerance and inflammation-induced receptor downregulation and uncoupling.²² The author has recently demonstrated that the combined use of fluticasone propionate (FP) and salmeterol exerts a pro-apoptotic activity towards T-lymphocytes from asthmatics, which is significantly higher than that exerted by the use of FP alone;²³ therefore contributing to the downregulation of the number of pro-inflammatory cells in asthma.

These effects, together with the known ability to improve the control of symptoms and the quality of life,^{14,24} support the use of ICS and LABAs in combination as first-line therapy for asthma.

Anti-leukotrienes

Leukotrienes play a part in the pathogenesis of asthma. Leukotriene receptor antagonists (LTRAs) directly inhibit bronchoconstriction and may have some anti-inflammatory effects,¹ although the extent to which inhibiting one set of inflammatory mediators attenuates the inflammatory response is questionable. Studies comparing the effects of ICS and LTRAs have tended to focus on clinical outcomes.^{25,26} There have been few direct comparisons between ICS and LTRAs with regards to their effects on anti-inflammatory mediators. Some studies that compared the clinical effects of ICS and LTRAs concluded that there was significantly greater improvement in pulmonary function generated by the use of ICS when compared with LTRAs.¹ In this regard it has been shown that the addition of LTRAs to the ICS therapy allowed the reduction of moderate to high doses of ICS while maintaining clinical effectiveness in patients with chronic asthma.²⁶ Some other studies confirm that the addition of LTRAs to ICS therapy can provide additional benefits.^{27,28}

Xantines

Xantines are the most widely prescribed drugs in the world for acute attacks of asthma. Theophylline inhibits the adenosine receptor at therapeutic concentrations. Inhaled adenosine causes broncho-

constriction in patients with asthma and this effect can be prevented by therapeutic concentrations of theophylline.²⁹ Moreover, theophylline has some anti-inflammatory effects including the inhibition of the expression and release of TNF- α and IL-1 β from human peripheral blood and the downregulation of the number of eosinophils in the airway mucosa.^{30–32} Their use for maintenance asthma therapy is limited by the possible presence of side effects and by the necessity to maintain a precise range of blood drug concentrations.

Anticholinergic, Anti-IgE and Anti-TNF Agents

The strategy of using anticholinergic agents in asthma is to block the muscarinic receptor M3, generating a bronchodilatation in turn. The use of these drugs was superseded by the introduction of the β -adrenergic agonists. In the last decade, molecules including ipratropium bromide or oxitropium bromide have been successfully used in the therapy of asthma despite their weak ability to selectively block the M3 muscarinic receptor and despite their short duration of bronchodilator action of six to eight hours.³³ The use of tiotropium has recently been proposed as this has the advantages of long duration of bronchodilator action (more than 36 hours).³⁴

The use of anti-IgE agents represents a new approach in the therapy of severe asthma. A recent multicentre randomised study has evaluated the efficacy and safety of omalizumab in patients with concomitant moderate to severe asthma and has demonstrated that this drug is well-tolerated and effective in preventing asthma exacerbations and improving the quality of life in these patients.⁶

Severe bronchial asthma is frequently steroid resistant and may be characterised by the involvement of neutrophils (rather than eosinophils) and specific cytokines, including TNF- α , in the scenario of an altered asthma inflammatory profile.⁷ It has recently been demonstrated that TNF- α is increased in steroid-dependent asthmatics, at both mRNA and protein levels, and that a 12 week treatment with a TNF- α antagonist was able to improve asthma symptoms, lung function and bronchial hyper-responsiveness.⁷ These results suggest that anti-TNF- α agents might be used in the near future in the therapy of severe asthma.

Conclusions

Although the precise mechanism of the action of ICS and of several other drugs used in the asthma therapy is not completely known, in recent decades the management of the treatment of asthmatic patients has been successfully improved. This has been

possible because the cellular and molecular mechanisms involved in the bronchial inflammation have been widely studied and characterised. Several drugs are now available to interact with these mechanisms in order to provide the asthmatic patient with a better quality of life. This goal can be achieved only by a multifaceted approach to the therapy of bronchial asthma. ■

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