Review: Pharmacological Treatment of Airway Remodeling: Inhaled Corticosteroids or Antileukotrienes?

Graziano Riccioni, Carmine Di Ilio, and Nicolantonio D’Orazio
Unit of Human Nutrition, Department of Biomedical Sciences, D’Annunzio University, Chieti, Italy

Abstract. Chronic stable asthma is characterized by inflammation of the airway wall, with abnormal accumulation of basophils, eosinophils, lymphocytes, mast cells, macrophages, dendritic cells, and myofibroblasts. Airway inflammation is not limited to severe asthma, but is also found in mild and moderate asthma. This inflammation results in a peculiar type of lymphocytic infiltration whereby Th2 lymphocytes secrete cytokines that orchestrate cellular inflammation and promote airway hyper-responsiveness. The term “airway remodeling” in bronchial asthma refers to structural changes that occur in conjunction with, or because of, chronic airway inflammation. Airway remodeling results in alterations in the airway epithelium, lamina propria, and submucosa, leading to thickening of the airway wall. Consequences of airway remodeling in asthma include incompletely reversible airway narrowing, bronchial hyper-responsiveness, airway edema, and mucus hypersecretion; these effects may predispose subjects with asthma to exacerbations and even death due to airway obstruction. To avoid this progression, it is important to follow an adequate treatment aimed at interacting and modifying the inflammatory process. Inhaled corticosteroids remain the cornerstone of asthma management. Altough several drugs, such as ketotifen, sodium cromoglycate, sodium nedocromil, and theophylline have anti-inflammatory properties, they are less effective than corticosteroids. Anti-leukotrienes are a new class of anti-inflammatory drugs that interfere directly with leukotriene receptors. The aim of this brief review is to delineate the effects of inhaled corticosteroids and antileukotriene drugs on inflammation and remodeling.

Keywords: airway inflammation, remodeling, bronchial hyper-responsiveness, asthma, cytokines, inhaled corticosteroids, antileukotrienes, montelukast, zafirlukast, budesonide

Introduction

Bronchial asthma is a chronic inflammatory airway disease that involves many cells and mediators; it is characterized by reversible airflow obstruction, bronchial hyperresponsiveness (BHR), and allergic inflammation. The airway inflammation is considered to underlie the clinical disease expression (ie, variable airflow obstruction) and to contribute to the development of BHR [1-3]. Many epidemiological studies suggest that asthma is associated with an accelerated decline of pulmonary function. This decline is heterogeneous among patients and while it appears minimal in some, it is quite extensive in others, resembling that of patients with chronic obstructive pulmonary disease (COPD). Non-specific BHR is associated with airway remodeling and the accelerated decline in lung function [4-6].

Inflammatory process in asthma

Airway inflammation plays an important role in the pathogenesis of asthma, making it an important target for anti-asthma pharmacotherapy. The inflammatory process is often a consequence of allergic response to pollen, dust, and other antigens [7]. The allergic response involves infiltration of activated eosinophils (EOS), T-lymphocytes (T-lym), and degranulation of mast cells (MC); these
lead to the release of numerous chemical mediators that cause physiologic changes in the airways, such as smooth muscle contraction, edema, and increases in mucus secretion [3,8].

The inflammatory and remodeling process underlying asthma results from a highly complex interaction between various cell types (e.g., EOS, activated T-lym, MC, and macrophages, (MAC)) [9]. The cells of structural tissues (i.e., epithelial cells, fibroblasts, and smooth muscle cells) also play an important effector role by the release of mediators, cytokines, and chemokines. This leads to an acute inflammatory response characterized by vascular leakage, mucus hypersecretion, epithelial shedding, and widespread airway narrowing [10,11].

Through the release of mediators, cytokines, chemokines, and growth factors, these cells promote the development of a chronic inflammatory infiltrate and induce structural changes of the airway wall. These include increased thickness of the basement membrane, increased collagen deposition, changes in bronchial microcirculation, and smooth muscle hypertrophy and hyperplasia. The end result of airway inflammation and remodeling is an increased thickness of the airway wall, leading to a reduced baseline airway caliber and exaggerated airway narrowing [12-14].

Pharmacological option: inhaled corticosteroids and/or antileukotrienes?

Although the clinical relevance of airway remodeling to disease expression is incompletely understood, it appears that the treatment and prevention of remodeling are crucial elements in asthma management. The current NHLBI/WHO guidelines recommend inhaled corticosteroids (ICS) as a first-line control therapy in asthma, and emphasize its combination with symptom-controlling drugs, such as long-acting B2-agonists (LABA) [15]. The position of leukotriene receptor antagonist (LTRAs) drugs is not fully established. In the USA, montelukast and zafirlukast have both been approved as first line therapy for persistent asthma [16,17]. The NHLBI Expert Panel classifies LTRAs as a “alternative” to ICS for the treatment of patients with mild-persistent asthma (step 2) or worse, although indicating that ICS are the preferred option. In Europe, LTRAs are considered a third-line treatment and are licensed for use as additional therapy in patients already taking ICS [18,19]. A recent systematic review of randomized controlled trials regarding the ICS versus LTRAs as single agent asthma treatment concluded that ICS are more effective than LTRAs for treating adults with mild-moderate persistent asthma [20].

Inhaled corticosteroids

ICS have been shown to produce profound effects on inflammatory cells, cytokines, and mediators in numerous studies; the effect of ICS on airway remodeling is also well established [21-23]. For these reasons, the ICS remain the “gold standard” of anti-inflammatory therapy for asthma. Even though many studies documented the efficacy of ICS in asthma, the role of ICS on airway remodeling needs to be better assessed. In fact, current data suggest that treatment with ICS does not enhance tissue remodeling in patients with established asthma [24].

Many ICS, such as beclomethasone dipropionate (BDP), budesonide (BUD), or fluticasone propionate (FP), are able to decrease airway inflammation [25]. FP has been shown to have high topical potency and low clinical systemic activity at a moderate dose [26]. In particular, FP has approximately twice the potency of BDP in the McKenzie skin vasoconstriction assay in humans [27]. Few data are available on the effects of ICS on airway remodeling, despite their importance in asthma prophylaxis [28].

Two cross-sectional studies have showed that airways in subjects with asthma untreated with ICS have more vessels and a greater than normal percentage area of vasculature in the lamina propria immediately below the epithelium [29,30]. The increased vascularity indices in asthma were found to be related to functional changes in regard to lung function, BHR, and ICS dose. ICS treatment was associated with a relatively normalized airway wall vascularity in subjects with asthma, at least in terms of the percentage area of airway wall occupied by vessels, although the absolute number of vessels per unit area remained high [31]. Increased vascularity
may therefore be a relatively easily quantifiable index of the generalized airway remodeling process and its response to medications [32].

One study showed that, if the dosage of inhaled corticosteroids is adjusted to the degree of BHR, a reduction of lamina reticularis pseudothickening can be achieved [33]. The ICS doses used in that study were higher than usually recommended, and such high doses of ICS can significantly reduce airway vascularity [29]. These morphological data suggest that prolonged treatment with ICS improves both hypersensitivity and hyper-reactivity of the airways, exerting an effect on the components of remodeling. However, in most studies BHR improves, but does not return to the normal limits, indicating that ICS cannot fully reverse remodeling [34,35]. The ICS do not completely block the pro-inflammatory effects of cysteinyl-leukotrienes and provide inadequate asthma control because of a significant proportion of clinical non-responders, which may reach 50% [36-39].

Antileukotrienes drugs

Antileukotrienes are the first novel anti-asthma drugs that have been approved for chronic treatment of asthma. These drugs include LTRAs such as montelukast and zafirlukast, which block the Cys-LT1 receptor and are available world-wide, and biosynthesis inhibitors, such as zileuton, which is a 5-lipoxygenase inhibitor and is available in the USA. LTRAs have efficacy similar to low doses of ICS in improving lung function and preventing symptoms of asthma [40-44]. The pharmacological mechanism of LTRAs is different from and complementary to that of ICS [45,46]. Our studies have demonstrated a similar efficacy of various doses of budesonide (800 vs 1600 µg), and an additional effect on bronchial reactivity with the administration of montelukast in patients that had been treated with only budesonide [47,48]. Combined administration of montelukast and budesonide reduced the bronchial inflammation and consequently the BHR. These findings confirm the anti-inflammatory properties of budesonide and montelukast and the possible role that a combination of these drugs may have on airway remodelling [47-49].

Conclusions

Most of the long term experience in treating patients with asthma is with ICS. However, inhaled corticosteroids have disadvantages compared to LTRAs, which offer convenient oral delivery and a more favorable tolerability profile. These properties, coupled with the considerations that the LTRAs provide effects additive to those of ICS and permit long-term reduction of ICS dosage, indicate that LTRAs are an attractive option for complementary therapy of patients with chronic persistent symptoms who have a suboptimal response to low-to-moderate doses of ICS and who show poor compliance with this therapy.

Future studies of asthma therapy with LTRAs should investigate the role that chronic treatment with LTRAS plays in airway remodelling. Currently, low dose ICS is the reference therapy for control of mild-moderate persistent asthma. LTRAs are an additional option, although in asthma, as in every chronic disease, use of multiple therapies complicates treatment regimens, tending to lower compliance. Montelukast may offer clinical benefits by improving patient compliance, maintaining symptom control, reducing the dose of ICS, and thus minimizing possible ICS adverse effects [50].

Large clinical studies are needed to address the pharmacological treatment of airway remodelling in patients with bronchial asthma, including evaluations of therapeutic efficacy, the incidence of side-effects, and relevant pharmaco-economic issues.

References

36. O’Shaughnessy KM, Wellings R, Gillies B, Fuller RW. Differential effect of fluticasone propionate on allergen- evoked bronchoconstriction and increased urinary leuko-