Corticosteroids Still at the Frontline in Asthma Treatment?

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KEY POINTS

• Inhaled corticosteroids (ICS) have led to considerably improved asthma control and reduced asthma mortality in the Western world over the last 2 decades, particularly in combating T-helper type 2-driven inflammation featuring mast cell and eosinophilic airway infiltration.
• Their effect on innate immunity-driven neutrophilic inflammation is rather poor and their ability to prevent airway remodeling and accelerated lung decline is highly controversial.
• Although ICS remain pivotal drugs in asthma management, research is needed to find drugs complementary to the combination ICS/long-acting β2-agonist in refractory asthma and perhaps a new class of drugs as a first-line treatment in mild to moderate noneosinophilic asthma.

KEYWORDS : Eosinophilic asthma ; Corticosteroids ; Inflammation ; Mast cells ; Asthma phenotypes

INTRODUCTION

There was a time when asthmatics had their symptoms treated with a regular short-acting bronchodilator and theophylline, while reserving the use of systemic corticosteroids for severe exacerbations and for chronic maintenance treatment of the most severe patients. The emergence of corticosteroids suitable for the inhaled route in the 1970s followed by convincing clinical trials during the late 1980s has dramatically changed the picture of asthma treatment. The class of inhaled corticosteroids (ICS) has rapidly demonstrated its superiority over other classes of drugs used in asthma.[1] The first Global Initiative for Asthma consensus in the early 1990s further highlighted the importance of the role of ICS in asthma treatment.[2] There is no doubt that the reduced mortality and morbidity of asthma observed since the 1990s is, in a large part, related to the regular use of ICS as the mainstay of asthma treatment. Yet some studies have pointed out the variability of the response to ICS in patients with asthma, suggesting that ICS administered alone might not be the best drug for all patients.[3]

FROM EARLY PROMISE TO THE TIME OF CERTITUDE

The first studies using inhaled hydrocortisone and prednisone in asthma were disappointing. It became apparent that this was because of the inappropriate chemical structure of prednisone, which has first to be metabolized to become pharmacologically effective, and the lack of topical activity of these corticosteroids. The chemical transformation of prednisone to increase both lipophilicity and interaction with glucocorticosteroid receptor made it possible to find compounds that were suitable for the inhaled route. Early studies in the 1970s used inhaled beclomethasone dipropionate and triamcinolone acetate in moderate to severe asthma and showed that these drugs were effective in improving lung function and reducing symptoms despite tapering oral corticosteroids.[4-6] The introduction of ICS dramatically and effectively changed the conventional approach to asthma therapy. The institution of ICS made it possible to replace, in most of the patients, the chronic use of oral corticosteroids, thereby avoiding side effects that were often severe and debilitating.[7] Furthermore, it soon seemed to be an inverse relationship between the rate of hospitalization for acute asthma exacerbation and the sales of ICS. In a cohort study of more than 13,000 patients with asthma, ICS were shown to be more effective than theophylline in reducing the hospitalization rate as long as they were taken regularly.[8] In a population-based epidemiologic study it was found that the regular use of low-dose ICS was associated with a reduced risk of death from asthma.[9]

The interest of ICS in the milder form of the disease was established later. Thefirst pivotal study proving the superiority of ICS over β2-agonists as a maintenance treatment dates back to 1991. Haahtela and colleagues[10]

demonstrated that the regular use of inhaled budesonide at the dosage of 1200 µg/d was by far superior to the regular use of terbutaline in improving the day-to-day peak expiratory flow rate and reducing asthma symptoms and as-needed relief bronchodilator usage. It is also by this time that the fundamental inflammatory nature of asthma was recognized even in the mildest form of the disease.[11] Asthma has then been regarded as a chronic airway inflammatory disease featuring eosinophil and mast cell airway wall infiltration as a consequence of a T-helper type 2 (Th2)-driven inflammatory process. The role of cytokines, such as interleukin 4 (IL-4) and IL-5, were highlighted as key cytokine in immunoglobulin E (IgE) synthesis from B cells and eosinophil survival respectively.[12] The role of chemokines for eosinophils, like eotaxin, was also demonstrated in asthma.[13] Regular treatment with ICS was shown to reduce the number of T-lymphocytes, eosinophils, and mast cells[14] and restore epithelial integrity[15] in bronchial biopsies. Numerous studies showed that regular treatment with ICS sharply and quickly reduces the percentage of eosinophils contained in the sputum from patients with asthma.[16-20] Therefore, corticosteroids were thought to be effective in asthma treatment because of their ability to repress the release of Th2 cytokine from lymphocytes[21] and eotaxin from epithelial cells,[22] thereby depleting airways from eosinophils and mast cells. More recently, it has been shown that corticosteroids are highly effective in inhibiting the transcription factor GATA3, which drives Th2 cells and the release of Th2 cytokines.[23] Therefore, ICS have been regarded as the perfect treatment of asthma leading to control for the peculiar airway inflammation while minimizing the systemic side effects because of their local action. Even in the mildest form of the disease, severe exacerbations may occur and ICS were shown to be extremely effective in preventing them.[24] This important property of ICS can lead us to think of this drug class as a disease-modifying drug in asthma. However, it soon appeared that ICS, even administrated at high doses, might not treat all facets of asthma or control all patients with asthma.

CORTICOSTEROIDS AND LOSS OF LUNG FUNCTION

Accelerated lung decline is a well-known feature of chronic obstructive pulmonary disease (COPD) and it is generally accepted that ICS fails to prevent it when patients continue to smoke.[25] The recognition that patients with asthma also have an accelerated lung function decline regardless of smoking[26,27] and despite regular treatment with ICS[24,28] has questioned the role of this class of drugs as a disease-modifying agent in asthma. In contrast to what has been shown for airway inflammation, it has been extremely difficult to convincingly demonstrate an effect of corticosteroids on airway remodeling. These effects require higher doses and sustained administration to show small changes in airway structure.[29,30] On the other hand, it has been demonstrated that in some young children, there is intense airway remodeling without any inflammation.[31,32] These observations led to the concept that airway inflammation and airway remodeling may be largely independent processes and, consequently, governed by different cytokine and growth factor networks, with corticoids being essentially active against the Th2 inflammatory component.[33] The recent observation that bronchoconstriction by itself may be a trigger for airway remodeling is of great importance because it may have potential significant implications for a treatment strategy to prevent lung function decrease.[34] In this view, it would seem logical to combine corticoids and long-acting-β2-agonist (LAESA) at the early stages of asthmatic disease to maximize the bronchopro-tecting effect and reduce the chance to evolve toward airway remodeling.

THE RECOGNITION OF REFRACTORY ASTHMA

The Gaining Optimal Asthma Control study showed that most patients with asthma can become largely asymptomatic when regularly treated by a combination ICS/LABA.[35] This therapeutic strategy also proved to be efficient in preventing asthma exacerbation in most patients. Yet a small fraction of patients with asthma, called patients with refractory or severe asthma, escape to that treatment. Severe or refractory asthma is generally thought to affect 1 % to 5% of all patients with asthma and accounts for most asthma costs.[35-39] This phenotype is defined by inadequate asthma control despite a high dose of inhaled corticosteroids or the need for oral corticosteroids, often associated with other controller medication, such as LABA, leukotriene receptor antagonist, or theophylline.[40,41] By itself, this phenotype clearly points out the inability of corticosteroids to control disease expression in some patients with asthma. Early studies showed that these patients had consistent persistent eosinophilic or neutrophilic airway inflammation despite regular antiinflammatory treatment,[42-46] indicating that corticosteroids were unable to control the underlying airway inflammation. These studies have certainly contributed to the emergence of the concept of an eosinophilic versus neutrophilic asthma phenotype, a concept that has extended beyond the sole group of refractory asthma (see later discussion). In severe asthma, this concept has proved to be useful in asthma management. It was clearly demonstrated that persistent eosinophilic inflammation may still be responsive to an increase in the dose of inhaled or systemic corticosteroids in terms of lung function and symptom improvement[47] and chiefly in terms of the reduction of exacerbation.[48,49] These important studies point to a reduced sensitivity rather than to a real resistance to eosinophilic inflammation to corticosteroids. Reduced eosinophil apoptosis in induced sputum despite a high

dose of inhaled corticosteroids was shown to be related to disease severity.[50] The molecular reason why severe eosinophilic inflammation may persist despite heavy treatment with corticosteroids remains unknown, but there are several molecular mechanisms for corticosteroid resistance in asthma.[51]

THE MOLECULAR CONCEPT OF CORTICOSTEROID RESISTANCE

It has been well demonstrated that corticosteroids have a positive interaction with β2-agonists at the molecular level. Indeed, corticosteroids increase the transcription of the β2-agonist receptor, resulting in increased expression of the receptor at the cell surface.[52,53] On the other hand, there is growing evidence to show that β2-agonists enhance the action of corticosteroids, particularly through enhancing the translocation of glucocorticoid receptor (GR), therefore, increasing the binding of GR to the glucocorticoid response element at the gene level.[54] However, patients with severe asthma have a poor response to corticosteroids, even when combined to β2-agonists, which necessitates the need for high doses and a few patients are completely resistant. Patients with asthma who smoke are also relatively corticosteroid resistant and require increased doses of corticosteroids for asthma control.[55] Several molecular mechanisms have now been identified to account for corticosteroid resistance in severe asthma.[51] In smoking patients with asthma and patients with severe asthma, there is a reduction in activity and expression of the critical nuclear enzyme histone deacetylase-2, which prevents corticosteroids from switching off activated inflammatory genes.[56-58] In steroid-resistant asthma, other mechanisms may also contribute to corticosteroid insensitivity, including the reduced translocation of GR as a result of phosphorylation by p38 mitogen-activated protein (MAP) kinase[59] and abnormal histone acetylation patterns.[60] A proposed mechanism is an increase in GR-β, which prevents GR binding to DNA,[61] but there is little evidence that this would be sufficient to account for corticosteroid insensitivity because the amounts of GR-β are too low.[62] Th17 cells may be involved in driving neutrophilic inflammation in some patients with severe asthma and these cells seem to be largely corticosteroid resistant.[63,64]

COMPLEMENTARY TREATMENT TO CORTICOSTEROIDS IN REFRACTORY ASTHMA

Although abundantly used in COPD, tiotropium has been poorly validated in asthma treatment. A recent study conducted in patients with uncontrolled asthma, despite a moderate dose of inhaled beclomethasone, showed that tiotropium was at least equivalent to salmeterol in improving asthma lung function and symptoms.[65] Further studies focusing on patients with more severe asthma and looking at exacerbations as the major outcome are now warranted to validate the use of a long-acting anticholinergic in refractory asthma.

In those patients with refractory asthma, with moderately elevated total serum IgE and sensitization to a perennial allergen, omalizumab, a humanized monoclonal antibody against IgE, has proved to be effective in reducing the exacerbation rate and improving quality of life,[66,67] although part of the effect seen in clinical practice in quality-of life-improvement is likely to be caused by a placebo effect and a careful follow-up of patients inherent in the mode of drug administration.[68] Like for corticosteroids, the clinical benefit of omalizumab might be partly explained by a reduction of eosinophilic inflammation.[69,70] The major drawback of this currently available treatment is the high cost, which weakens the cost-effectiveness relationship.[71] Cost-effectiveness, however, depends on how hospitalization for exacerbation may be prevented; a drug that may reduce the hospitalization rate in high-risk patient is likely to be cost-effective.

Some studies indicate a continuous synthesis and release of Th2 cytokines, such as IL-4 and IL-5, both at a systemic[72] and airway level[73] despite the regular treatment with inhaled corticoids. Yet there is no sign of reduced activity of corticosteroids in vitro to inhibit cytokine release from circulating leukocytes in those patients with refractory asthma.[72] The importance of IL-5 in driving the persistent systemic and airway eosinophilic inflammation has recently been demonstrated by the efficacy of mepolizumab, an anti-IL-5 monoclonal antibody, to further decrease eosinophilic inflammation in those patients with refractory asthma despite a high dose of corticosteroids.[74,75] The clinical relevance of the persistent eosinophilic inflammation is demonstrated by the reduction in the exacerbation rate and the improvement in quality of life observed in those patients receiving mepolizumab,[74] even if no effect is observed on airway caliber and bronchial hyperresponsiveness,[74] which is confirmatory of earlier studies with other anti-IL-5 antibodies.[76,77] Importantly, mepolizumab made it possible to taper and sometimes suppress the use of oral corticosteroids.[75] A recent 16-week study using reslizumab, a new monoclonal antibody against IL-5, has shown a significant improvement in forced expiratory volume in the first second of expiration in patients with moderate to severe eosinophilic asthma displaying prominent reversibility to a β2-agonist.[78]

Anti-tumor necrosis factor (TNF)-α is an established treatment in chronic inflammatory diseases, like Crohn disease or rheumatoid arthritis. Despite early promising pilot studies,[79-82] treatments that target TNF-α have

generally proved to be disappointing in improving asthma control in patients with refractory asthma. This finding has been demonstrated with drugs, such as golimumab[83] and etanercept.[84]

The studies focusing on neutrophilic inflammation in refractory asthma have been limited so far. One study using clarithromycin has shown a significant reduction of sputum neutrophil count and sputum elastase together with an improved quality of life.[85] However, there was no improvement in asthma control or airway caliber. On the other hand, targeting neutrophils may theoretically prove to be a dangerous strategy in patients with refractory asthma by increasing their susceptibility to infections.[86] A recent study in COPD, another disease with prominent neutrophilic inflammation,[87,88] has shown a reduction of the exacerbation rate by regular treatment with azithromycin.[89] The mechanisms by which macrolide antibiotics might be effective remain elusive. Whether it is through antiinflammatory activity or by limiting airway colonization with typical or atypical bacterial pathogens remains to be investigated.[90] Clearly, in refractory asthma, further studies conducted on a longer-term period are needed to investigate the impact of macrolides on asthma exacerbation rate. Other treatments in development, mainly for COPD, also target neutrophilic inflammation, including antagonists against the chemokine receptor CXCR2, phosphodiesterase-4 inhibitors, and p38 MAP kinase inhibitors.[91]

Bronchial thermoplasty (BT) is an innovative non-pharmacologic treatment approach to reduce the bronchoconstrictor response in asthma. Although technically demanding, BT has been shown to improve asthma control and quality of life and to be safe in patients with moderate to severe asthma.[92-94] A recent multicenter study confirmed the ability of BT to improve control and quality of life in patients with refractory asthma and showed that BT resulted in a reduced severe exacerbation rate in the posttreatment period.[95]

EMERGENCE OF THE CONCEPT OF ASTHMA PHENOTYPE IN MILD TO MODERATE ASTHMA

The development of the technique of induced sputum has been a key step in the appearance of the concept of inflammatory phenotype in asthma. Although it confirmed the eosinophilic inflammation as a prominent feature of asthma,[96] which relates to disease severity,[43,50,72] it also showed that up to 50% of patients with asthma failed to exhibit this eosinophilic phenotype.[97,98] Almost half of them are characterized by intense neutrophilic inflammation[99] but the other half fails to show any abnormal granulocytic inflammation despite excessive lung function variability. The importance of these phenotypes is that the underlying molecular mechanisms are different. Although the eosinophilic phenotype is likely to reflect ongoing adaptive immunity in response to an allergen with Th2 cytokine IL-4, IL-5, and IL-13 playing a key role, the neutrophilic phenotype is thought to reflect innate immune system activation in response to pollutants or infectious agents.[100,101] Therefore, it is conceivable that the 2 phenotypes actually require different therapeutic molecular approaches.

Exhaled nitrous oxide (NO) is increased in patients with asthma[102] and particularly in those with eosinophilic inflammation.[103] A large-scale study conducted in routine has shown that a fractional exhaled NO threshold of around 40 ppb (measured at an exhaled flow of 50 mL/s) is predictive of eosinophilic inflammation in patients with asthma even though this threshold may be decreased by smoking and a high dose of ICS. The threshold was 27 ppb in smoking asthmatics and 28 ppb in those receiving at least 1000 µg/d of fluticasone (considered as high dose ICS). Moreover the threshold can be as low as 15 ppb in a non atopic smoking patient receiving high dose of ICS.[104] However, we lack an equivalent noninvasive marker for neutrophilic inflammation. The development of breath print by chromatography and mass spectrometry is a promising tool to approach these cellular phenotypes.

PREDICTING FACTORS OF CLINICAL RESPONSE TO CORTICOSTEROIDS

The results of large, randomized controlled clinical trials have perhaps masked for too long the fact that the response of ICS is variable in patients with asthma.[105] As pointed out earlier, the response to ICS is characterized by a high intraindividual repeatability and a high interindividual variability, with up to 40% of patients showing no short-term response to the treatment.[3] The presence of a persistent airway eosinophilic inflammation seems to be a good predicting factor for a short-term response to ICS 105-109 Alternatively, a high exhaled NO level (>47 ppb according to the studies) is predictive of a good response to ICS in patients with chronic respiratory symptoms regardless of the disease label.[110] Furthermore, the presence of a Th2 cytokine profile in the airways seems to be needed to have rapid lung function improvement with ICS.[111] Even if a convincing response may be sometimes observed[112] in those with high exhaled NO (>33 ppb),[107] noneosinophilic asthma generally exhibits a limited response to ICS[113] and the response seems to be particularly poor in those patients exhibiting intense airway neutrophilic inflammation,[99] which is reminiscent of the inability of ICS to control airway inflammation in COPD.[114,115] A recent study has highlighted the importance of the genetic background in the improvement of lung function following chronic treatment with ICS. A functional variant of glucocorticosteroid transcript 1 gene

was found to be associated with a decreased response to ICS in several randomized clinical trials.[116] In the studies published so far, the corticosteroid response has been assessed either by lung function or quality-of-life improvement over a short-term period (a few weeks). There is, however, a lack of evidence to support that denying treatment with ICS over a long-term period in some patients does not place them at risk of severe exacerbation. Clearly, new long-term prospective studies with asthma exacerbation as the main outcome are needed to clarify this important point.

CORTICOSTEROIDS IN CLINICAL PRACTICE

Like in many chronic diseases, poor compliance to maintenance treatment has been shown to be a major issue in asthma.[117] Poor inhalation technique is a further impediment in achieving a successful treatment with inhaled therapies in patients with asthma.[117] Because corticosteroids do not bring acute relief for asthma symptoms, it is likely to play a role in poor compliance. Although ICS have clearly demonstrated superior efficacy to leukotriene receptor antagonists with respect to most clinical outcomes in randomized controlled trials, a recent field study conducted in the United Kingdom has not confirmed this superiority in terms of asthma control.[118] The emergence of the SMART concept (Symbicort as a maintenance and relief therapy) has been an interesting paradigm that allows patients to inhale a dose of corticosteroids whenever he or she feels the need to use a rapid-acting bronchodilator. The concept that has been extensively validated in randomized controlled clinical trials[119] has also been shown to be valid in daily clinical practice.[120] The SMART approach has been shown to be particularly efficient in reducing the rate of severe asthma exacerbation.

NEW CLASS DRUG IN DEVELOPMENT

There are several new drugs for asthma currently in development that may be suited more for patients who do not respond well to corticosteroids.[91] Several cytokines are involved in the pathophysiology of asthma, including Th2 cytokines. Anti-IL-5 antibodies (mepolizumab, reslizumab) are currently in clinical trials for severe eosinophilic asthma that is resistant to corticosteroids, as discussed earlier. IL-13 is increased in severe asthma and causes corticosteroid resistance, so it is a logical target. Currently, anti-IL-13 antibodies, such as lebrikizumab, have been disappointing with little physiologic effect and no effect on symptoms or exacerbations.[121] Blocking antibodies to other cytokines, including IL-9, IL-25, IL-33, and thymus stromal lymphopoietin, are also in development for asthma. Small molecule antagonists of inflammatory mediators have been disappointing in asthma, but there has recently been great interest in blocking prostaglandin (PG) D_2, which is released from mast cells and attracts Th2 cells and eosinophils via the receptor chemoattractant homologous receptor expressed on Th2 cells (CRTH2) (or DP_2 receptors). PGD_2 seems to be increased in patients with severe asthma who are not controlled on inhaled therapy.[122] Several oral CRTH2 antagonists are now in development and have shown some clinical benefit.[123] As discussed earlier, there are several broad-spectrum antiinflammatory treatments that target neutrophilic inflammation, so they may be effective in patients with severe asthma who do not respond well to corticosteroid therapy.[124] Mast-cell activation is found in patients with severe asthma, suggesting that mast-cell inhibitors may be useful in these patients. As discussed earlier, omalizumab is useful in some patients with severe asthma and reduces exacerbations[66,67] but cannot be used in patients with high circulating IgE concentrations, so antibodies with a higher affinity are now in development. Other drugs that target mast cells include c-kit and Syk inhibitors.

SUMMARY

There is no doubt that ICS have led to considerably improved asthma control and reduced asthma mortality in the Western world over the last 2 decades. ICS are particularly effective in combating Th2-driven inflammation featuring mast-cell and eosinophilic airway infiltration. Their effect on innate immunity-driven neutrophilic inflammation is poor and their ability to prevent airway remodeling and accelerated lung decline is highly controversial. Although ICS remain pivotal drugs in asthma management, research is needed to find drugs complementary to the combination ICS/LABA in refractory asthma and perhaps a new class of drugs as a first-line treatment in mild to moderate noneosinophilic asthma **(Fig. 1).**

Fig. 1. *Proposed strategy for asthma mainstay treatment according to the degree of severity and the sputum inflammatory phenotype. CRTH2, chemoattractant homologous receptor expressed on Th2 cells, also known as DP_2 receptor, a receptor for PGD_2; ICS, inhaled corticosteroids; LABA, long-acting β2-agonists; LTRA, leukotriene receptor antagonist; PDE4, phosphodiesterase 4 inhibitor.*
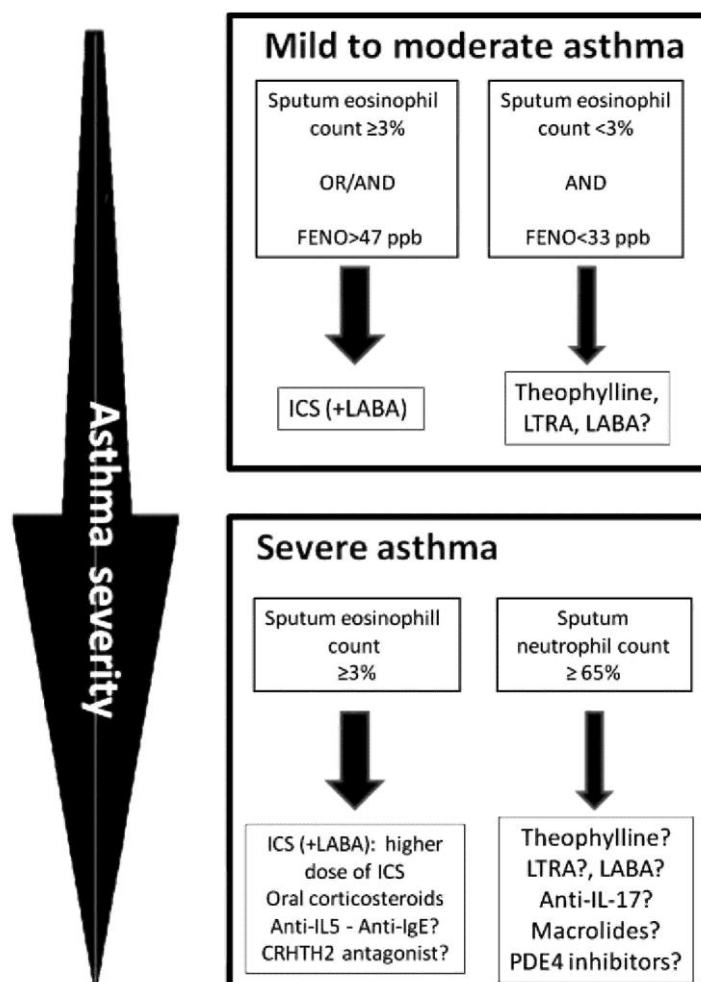
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