

INHALED CORTICOSTEROIDS: THE ROLE IN THE PREVENTION OF ASTHMA, PATHOPHYSIOLOGICAL AND CLINICAL ASPECTS

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Abstract:

Asthma is a complex disorder that displays heterogeneity and variability in its clinical expression both acutely and chronically. Asthma is a problem worldwide, with an 300 million affected individuals. Prevalence of asthma varies from region to region but generally speaking it increases. Asthma is most common chronic disease in the childhood.

An understanding of the immunopathophysiology of airways in asthma has been markedly advanced with the use of bronchoscopy and biopsy.

Corticosteroids are the most efficacious treatment for airway inflammation associated with asthma. Current guidelines recommend long-term treatment with inhaled corticosteroids (ICS) in the prevention of asthma. There is considerable variation in corticosteroid response among asthmatic subjects. Understanding the genetic mechanisms that regulate corticosteroid response variability could allow determination of a subject's response to corticosteroid therapy, leading to more effective dosing, selection of single-drug or combination therapies, or both for treating asthma.

Key-words: inhaled corticosteroids, inflammation, asthma, prevention

Introduction:

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. Asthma is a problem worldwide, with an estimated 300 million affected individuals. Asthma is most common chronic disease in the childhood. Prevalence of asthma varies from region to region but generally speaking it increases.(1)

A number of factors that influence a person's risk of developing asthma have been identified. These can be divided into host factors (primarily genetics, e.g. genes pre/disposing to atopic, genes pre/disposing to airway hyper-responsiveness, obesity, sex) and environmental factors (allergens indoor: domestic mite, furred animals, cockroach allergen, fungi, molds, yeasts and outdoor: pollens, fungi, molds, yeasts), infections-predominantly viral, tobacco smoke (passive and active smoking), outdoor and indoor air pollution, diet. [1]

Asthma affects approximately 23 million American children and adults, resulting in almost 15 million physician office and hospital visits, and nearly 2 million emergency department visits each year. Despite the publication of National Asthma Education and

Prevention Program guidelines, asthma remains poorly controlled, with annual costs estimated at up to \$56 billion.

Asthma is a complex disorder that displays heterogeneity and variability in its clinical expression both acutely and chronically. Presently, no precise physiologic, immunologic, or histologic characteristics can be used to definitively make a diagnosis of asthma, and therefore the diagnosis is often made on a clinical basis related to symptom patterns (airways obstruction and hyperresponsiveness) and responses to therapy (partial or complete reversibility) over time. Although current treatment modalities are capable of producing control of symptoms and improvements in pulmonary function in the majority of patients, acute and often severe exacerbations still occur and contribute significantly to both the morbidity and mortality of asthma in all age groups. [2, 3]

Current guidelines recommend long-term treatment with inhaled corticosteroids (ICS) because of their superior effectiveness in managing the chronic airway inflammation that characterizes persistent asthma. Treatment with inhaled corticosteroids is considered the most potent and effective anti-inflammatory medica-

tion currently available for the achievement and maintenance control of persistent asthma. The anti-inflammatory effects of ICS have been reported to improve lung function, reduce asthma symptoms, and decrease exacerbations. The use of ICS has been associated with fewer asthma-related hospital admissions and deaths compared with placebo. [4, 5]

Pathophysiology of asthma

It is now known that asthma is a chronic inflammatory disorder that also causes bronchoconstriction of the airways. A key process is IgE-induced mast cell activation and release of various cytokines, chemokines, and other mediators including histamine, tryptase, and leukotrienes. This, in turn, causes an influx of T cells, eosinophils, and other inflammatory cells into the airways. In the past, a primary focus of asthma research has been on mechanisms of airway inflammation, in particular the role of type 2 helper T (Th2) cell cytokines in directing the inflammatory response, but recent attention has been given to the investigation of the structural changes involved in asthma, known as airway remodeling. [6]

The airway epithelium, while playing an important role as a physical barrier, is now recognized to be fundamental to asthma pathogenesis. There are characteristic structural changes with collagen deposition under the epithelium, described as basement-membrane thickening and thickening of the airway smooth-muscle cell layer as a result of hyperplasia and hypertrophy. The process is accompanied by an increased number of mucus-secreting goblet cells in the epithelium, enlargement of submucosal glands, and raised number of blood vessels. This indicates that the epithelium is chronically injured and unable to repair properly, mostly in patients suffering from severe asthma. The permeability of the asthmatic epithelium is greatly increased, leading to greater access of inhaled allergens, pollutants, and other irritants to basal cells and the underlying airway tissue. [6]

Bronchial asthma is a common immune-mediated disorder characterized by reversible airway inflammation, mucus production, and variable airflow obstruction with airway hyperresponsiveness. Allergen exposure results

in the activation of numerous cells of the immune system, of which dendritic cells (DCs) and Th2 lymphocytes are of paramount importance. Although the epithelium was initially considered to function solely as a physical barrier, it is now evident that it plays a central role in the Th2-cell sensitization process due to its ability to activate DCs. Cytokines are inevitable factors in driving immune responses. To the list of numerous cytokines already known to be involved in the regulation of allergic reactions, new cytokines were added, such as thymic stromal lymphopoietin (TSLP), IL-25, and IL-33. IgE is also a central player in the allergic response. The activity of IgE is associated with a network of proteins, especially with its high- and low-affinity Fc receptors. Understanding the cellular and molecular mechanisms of allergic reactions helps us not only to understand the mechanisms of current treatments, but is also important for the identification of new targets for biological intervention. [6, 7]

Pharmacological management of asthma

Medications to treat asthma can be classified as controllers and relievers. Controllers are medications taken daily on a long-term basis to keep asthma under control chiefly through their anti-inflammatory effects. They include inhaled and systemic corticosteroids, leukotriene modifiers, long-acting inhaled beta2-agonists in combination with inhaled corticosteroids, sustained-release theophylline, cromones, and anti-IgE. [1]

The aim of asthma management is control of the disease. Complete control of asthma is defined as:

- no daytime symptoms
- no night-time awakening due to asthma
- no need for rescue medication
- no exacerbations
- no limitations on activity including exercise
- normal lung function (in practical terms FEV1 and/or PEF > 80% predicted or best).
- minimal side effects from medication.

A stepwise approach aims to abolish symptoms as soon as possible and to optimise peak flow by starting treatment at the level most likely to achieve this. Patients should start treatment at the step most appropriate to the

initial severity of their asthma. The aim is to achieve early control and to maintain by stepping up treatment as necessary and stepping down when control is good. Before initiating a new drug therapy practitioners should check adherence with existing therapies, inhaler technique and eliminate trigger factors.

Inhaled corticosteroids are the most effective preventer drug for adults and older children for achieving overall treatment goals. [8, 9] Understanding the genetic mechanisms that regulate corticosteroid response variability could allow a priori determination of a subject's response to corticosteroid therapy, leading to more effective dosing, selection of single-drug or combination therapies, or both for treating asthma.

Because the corticosteroid receptor functions as part of a large protein hetero-complex, Hawkins et al assessed whether variants in the genes of the intracellular corticosteroid receptor hetero-complex (HSPCB, HSPCA, stress-inducible protein 1 [STIP1], HSPA8, DNAJB1, PTGES3, FKBP5, and FKBP4) affect corticosteroid response.

The authors concluded that STIP1 genetic variations might play a role in regulating corticosteroid response in asthmatic subjects with reduced lung function. [10]

There is an increasing body of evidence demonstrating that, at recommended doses, they are also safe and effective in children less than five years with asthma. [11, 12]

Inhaled steroids should be considered for adults, children aged 5-12 and children under the age of five with any of the following features: using inhaled β_2 agonists three times a week or more, symptomatic three times a week or more or waking one night a week. In addition, inhaled corticosteroids should be considered in adults and children aged 5-12 who have had an exacerbation of asthma requiring oral corticosteroids in the last two years.

Starting dose of inhaled corticosteroid

In mild to moderate asthma, starting at very high doses of inhaled steroids and stepping down confers no benefit. Start patients at a dose of inhaled steroids appropriate to the severity of disease. In adults, a reasonable starting dose will usually be 400 micrograms budesonide (BDP) per day and in children 200 micrograms BDP

per day. In children under five years, higher doses may be required if there are problems in obtaining consistent drug delivery. Titrate the dose of inhaled steroid to the lowest dose at which effective control of asthma is maintained.

Children

Administration of inhaled corticosteroids at or above 400 micrograms budesonide (BDP) a day or equivalent may be associated with systemic side effects. These may include growth failure and adrenal suppression. Isolated growth failure is not a reliable indicator of adrenal suppression and monitoring growth cannot be used as a screening test of adrenal function. [13]

Good asthma control can be achieved in most patients, even those with moderate-to-severe asthma. [14, 15] There is compelling evidence that despite the availability of asthma treatment guidelines and very effective treatment, asthma remains undertreated. [16,17] There is evidence that starting with a moderate dose of ICS and then reducing the dose once asthma control has been achieved is as effective as starting with a very high dose. [18]

Asthma Treatment: ICS Monotherapy as the Gold Standard

Current guidelines recommend long-term treatment with inhaled corticosteroids (ICS) because of their superior effectiveness in managing the chronic airway inflammation that characterizes persistent asthma. Additionally, the US Food and Drug Administration (FDA) issued a warning in February 2010 that long-acting inhaled β_2 -agonists (LABA) should never be used alone to treat asthma, specifying that when they are used, they should be administered only for the shortest duration possible and then discontinued. This warning resulted from analyses showing that LABA use was associated with an increased risk of severe exacerbations leading to hospitalization in both children and adults, with a possibility of death.

The National Asthma Education and Prevention Program (NAEPP) Expert Panel Report (EPR)-3 Guidelines recommend a stepwise approach to asthma treatment: [15]

1. ICS monotherapy as first-line controller treatment for persistent asthma (mild, moderate, and severe) for both adults and children.

2. If asthma remains uncontrolled with low-dose ICS monotherapy, only then should physicians consider a medium-dose ICS or adding a LABA to a low-dose ICS regimen.
3. Increasing the ICS dose may reduce the risk of severe exacerbations and hospitalizations compared with approaches that involve adding a LABA

Although ICS treatment is the gold standard for treating asthma, aerosol particle size is crucial, with only small, less dense particle sizes having the ability to reach the small airways. Particles between 0.6 and 0.3 mm are likely to be exhaled, and therefore of less therapeutic benefit. Although delivery method and dosage vary between ICS products, most traditional ICS therapies are aerosols that deliver large particle sizes (2.4 to 4.5 mm) to the central airways, resulting in relatively low total lung deposition. Large-particle metered-dose inhalers, pressurized inhalers, or dry-powder inhalers have not shown great efficiency, delivering drug to the smaller airways at no more than 30% of the administered dose.

There is general consensus that the following recommendations are useful:

- When ICS are being used alone in medium to high doses, a 50% reduction in dose should be attempted at 3-month intervals.
- Where control is achieved at a low dose of ICS alone, treatment may be switched to once-daily dosing.
- When asthma is controlled with a combination of ICS and long-acting inhaled β_2 -agonist (LABA), the preferred approach is to begin by reducing the dose of inhaled ICS by 50% while continuing the LABA. When a low dose of ICS is reached and the patient remains stable, the LABA may be stopped. An alternative is to switch the combination treatment to once-daily dosing with an ICS and long-acting inhaled β_2 -agonist (LABA) combination.
- ICS treatment may be stopped if the patient remains well controlled on the lowest dose of ICS for 1 year.

Patients with moderate-to-severe asthma obtain greater benefit from the combination of ICS and LABA than from ICS therapy alone, both in achieving current control and in reducing severe asthma exacerbations.

Drug	Low	Medium	High
Beclomethasone dipropionate	200-500	500-1000	1000+
Budesonide	200-400	400-800	800-1600+
Ciclesonide	80-160	160-320	320-1280
Flunisolide	500-1000	1000-2000	2000+
Fluticasone propionate	100-250	250-500	500-1000+
Mometasone fuorate	200-400	400-800	800-1200+
Triamcinolone acetonide	400-1000	1000-2000	2000+

What are Considered Low, Medium and High Dosages for Adults? [1]

All dosages are daily, in micrograms (MCG).

Conclusion:

ICS are the mainstay of asthma treatment and can usually provide ideal asthma control and reduce the risks of severe asthma exacerbations in both children and adults with asthma. Once asthma control is achieved, efforts should be made to reduce the dose of ICS, and occasionally patients with mild asthma can discontinue regular ICS treatment. However, symptoms will often recur over a variable period of time if ICS are discontinued. In patients with mild asthma, intermittent ICS therapy at the time of an exacerbation has also been suggested to be an effective treatment strategy for mild persistent asthma, but it is less effective than low-dose regular therapy for most outcomes. [19, 20] Studies have demonstrated that beclomethasone dipropionate is clinically effective and cost efficient compared with other asthma monotherapies or combination therapies.

In adult patients, the combination of ICS and LABA (usually in a single inhaler) is better than doubling the dose of ICS to achieve better asthma control and reducing exacerbation risks. One of the combinations of ICS and LABA available to treat asthma has been evaluated as both maintenance and reliever therapy in patients with moderate-to-severe disease, and it has been shown to further reduce the risk of severe exacerbations. In patients with milder asthma, a combination of ICS and LABA in a single inhaler, used as needed, was as effective as regular low-dose ICS for many asthma outcomes. However, further evaluation of intermittent use of ICS or combinations of ICS and β_2 -agonists in a single inhaler in mild asthma is needed before these treatment approaches are recommended as appropriate therapy. [21, 22]

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