The Story of Corticosteroids in Asthma

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Abstract

Asthma is a common respiratory disease affecting patients of all ages and races. Up to the middle of the 20th century there was scarce knowledge regarding the biology of the disease and asthma was a potentially lethal disease with very limited therapeutic options. The introduction of corticosteroids revolutionized the management of asthma and improved the lives of millions of patients. Parental and later oral administration was the first treatment with remarkable effects on asthma symptoms and exacerbations but led to serious systemic effects. The invention of inhaled forms of corticosteroids that had minimal systemic absorption and adverse reactions, the enhancement of their efficacy by LABAs and the understanding of asthma pathophysiology were only a few of the significant advances in asthma management over the last 60 years. In this review we present these life-changing advances in asthma treatment, focusing on the evolutionary role of corticosteroids.

Keywords: asthma history, asthma treatment, OCS, ICS, LABA

Introduction: Historical Overview

Asthma is a chronic inflammatory airway disease affecting patients of all ages and races. It is characterized by heterogeneity which is defined by different underlying disease processes and pathophysiological characteristics (phenotypes).[1] This heterogeneity is reflected in therapeutic interventions that have been extensively evaluated during the last 20 years or so.

The term asthma is a Greek noun, άσθμα, which derives from the verb ασθμαίνω meaning to exhale with open mouth, to pant. The first written record of asthma appears around 2700 years ago in Homer's Iliad. The earliest text where the word asthma is found as a medical term is in the writings of the school of Hippocrates of Kos (460-360 B.C.).[2] In the writings of Hippocrates, however, the term probably refers to asthma as a symptom and not to the disease we know today. In the beginning of the 19th century, asthma was defined as an airway disease characterized by bronchospasm following invention of the stethoscope by Laennec (1781-1826).[3] The first reports of asthma as an extrinsic or intrinsic disorder caused by stress or animal dander are attributed to Henry Hyde Salter in 1860. In his treatise "On Asthma: its Pathology and Treatment", Salter describes asthma as a disease in which the airways narrow as a result of contraction of their smooth muscle.[4] A few years later Paul Ehrlich (1854-1915) described eosinophils and mast cells in asthmatic sputum using eosin and toluidine blue staining.[5] Sir William Osler (1849-1919),

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often mentioned as the Father of Modern Medicine, made a more precise definition of asthma connecting pathology, physiology, symptoms, and clinical findings, in the first edition of his Textbook Principles and Practice of Medicine.[6] Thus, it was in the 19th century that asthma was described as a distinct lung disease with specific etiology, clinical findings, and treatment.

Early Therapeutic Interventions

Therapeutic options for asthma were limited until the middle of 20th century and asthma was treated largely as a disease of bronchospasm.[7] Regimens containing *anticholinergics* were the first aetiologic treatment administered for asthma. Paul Ehrlich proposed black coffee for the treatment of bronchospasm, as this beverage contains theophylline and its derivative theobromine.[8] Henry Hyde Salter discusses "Asthma cigarettes" containing dried leaves and flowering of D. Stramonium as a treatment for asthma in his 19th century work.[9] Datura Stramonium contains alkaloids of belladonna which has anticholinergic action. William Osler in his eight edition of his textbook in 1914 suggests hypodermic injections of pilocarpine for asthma treatment.[10] *Adrenergic bronchodilators* were introduced as treatment for asthma in the beginning of 20th century. Initially both adrenaline and ephedrine were used subcutaneously at repeated intervals during asthma attacks.[11] In 1947, in Cecil's Textbook of Medicine, Rackemann presented the inhaled administration of ephedrine to relieve asthma symptoms.[12] Since then, inhalers were widely available for asthma and bronchodilators such as isoprenaline and orciprenaline.[13,14] The widespread use of those nonselective bronchodilators led to an increased ratio of deaths among asthmatics in England and Wales in the 1960s, possibly due to their cardiovascular adverse effects or as a result of inadequately treated asthma. In the 1970s, salbutamol[15] and terbutaline[16], relatively more selective β2- bronchodilators, were developed for inhaled use. Long-acting beta-agonists (LABAs - e.g., formoterol, salmeterol), introduced in middle '90s as an important drug in asthma management. They demonstrate a clear benefit in reducing asthma-related symptoms and improving lung function but only when used in combination with an anti-inflammatory agent.[17]

The Introduction of Corticosteroids on Asthma Management

The story of corticosteroids in asthma begins in the early 1950s, when cortisone was first administered to treat asthma successfully. Case series reporting the benefits of *parenteral administration* of cortisone in patients with allergic asthma were published: In 1950, Carryer presented 3 patients with seasonal asthma and hay fever who received sequentially 100 mg cortisone or cholesterol suspension daily over a 4-week period in a blinded manner. All three patients experienced prompt relief from symptoms of asthma and hay fever, which lasted a few days post administration.[18] In 1953, Burrage W. presented 14 cases of severe bronchial asthma treated with a mean daily dose of 50mg cortisone for a prolonged period. The author mentioned that "the use of cortisone in severe asthma involves a treatment of an as yet imperfectly understood disease with a potent hormone, whose mode of action remains a mystery" and that "no patient has remained asthma free on less than 25mg of cortisone daily".[19] Several other reports of parenteral administration of cortisone in patients with asthma were published over the following years.[20-22]

The difficulties of parenteral administration and the relapse of symptoms following discontinuation of treatment were extinguished with the initiation of *oral therapy*. In January 1951, Scwartz E. reported 3 cases of "intractable" asthma successfully treated with cortisone acetate tablets at initial doses of 50-100mg with gradual tapering

to maintenance dose of 25mg daily.[23] Sidney and Alex Friedlaender described a series of 12 patients who received an average daily dose of 150 to 200mg oral cortisone which produced a comparable effect to that obtained with intramuscular administration. Interestingly they mentioned reduction in eosinophil counts.[24] Savidge R. and Brockcbank studied 24 asthmatics with remarkable limitation in their daily activities in 1954: Using a partially blinded methodology, they started with an initial dose of 100mg cortisone daily or placebo, gradually tapering by 12.5mg every four to six weeks in an effort to avoid side effects. In all patients, there was remarkable improvement in symptoms and patient could return to their daily activities.[25] At that period, oral cortisone for asthma treatment was administered as long-term or intermittent basis with an effort to use the minimal needed doses.[26]

The following years, several forms of steroids such as hydrocortisone, prednisolone, triamcinolone and dexamethasone were used, providing an effective management for a disease that previous to their use, had been life threatening and had detrimental effect on patients' lives.[27,28] Unfortunately, oral steroids also have side effects. So, in asthma steroids have always been a double-edged sword, due to their systemic adverse reactions.[29] By 1960 all the systemic toxic effects of oral and parenteral treatment of corticoids had been described and OCS-sparing efforts were made in nearly every disease where OCS were used, not only due to safety issues but also to improve outcomes.[27,30–34] This effort was reflected in many published works on the administration of cortisone *by inhalation* which started shortly after intramuscular treatment was made an established choice for severe asthma. In 1951, Maxwell Gelfand reported 5 cases of bronchial asthma treated for two weeks with 5mg nebulized cortisone inhaled every hour for a period of ten hours daily. Discontinuation of treatment led to relapses, which though, were successfully treated with re-initiation of treatment. The medical community had not yet linked asthma with inflammation of the airways, so the author discusses a probable mechanism of cortisone action as follows: "*The direct application of cortisone to the bronchial mucosa may either interfere with the union of antigen and antibody or inhibit the liberation of histamine in the site of shock organ* (lung)".[35] Inhaled dexamethasone in a study of 64 patients resulted in withdrawal of oral steroids in 29 of these patients for a period from 2 to 120 months.[36] In the early 60s, the first studies evaluating the effects of inhaled steroids in lung function with the use of spirometry were published.[36] *Unfortunately, despite these advances, the systemic absorption of agents such as dexamethasone, even when administered by inhalation proved an insuperable problem.*[37]

The Break-through of ICS in Asthma Treatment

A milestone in asthma treatment was the invention of Beclomethasone dipropionate (BDP) which was patented in 1962 and was the first inhaled corticosteroid (ICS) marketed for use in the treatment of chronic asthma.[38] In 1972 Brown H.M, Storey G. and George W.H.S published the results of a study involving 60 asthmatic patients who received *Beclomethasone dipropionate* by means of a metered aerosol delivering 50 μg of micronized powder per puff.[39] (37 of these patients had been oral steroid dependent for up to 16 years). Two puffs four times daily, giving a total of 400 μg, was the usual dose, occasionally increased to three puffs four times a day. In 56 cases 400 μg was the optimum dose but four remained well controlled on 150 to 200 μg daily. In 28 out of 37 steroid-depended cases there was complete withdrawal of OCS. Besides, 19 out of 23 other asthmatics not dependent on steroids were also completely controlled. In that study Beclomethasone was the first inhaled steroid that had no biochemical

evidence of adrenal suppression. In other studies Beclomethasone dipropionate proved a safe and effective alternative to oral Prednisolone by means of patients' preference, use of rescue medications and lung function (PEFR, FEV1).[37,40]

Budesonide, the second broadly used inhaled ICS, was patented in 1973.[41] The first studies on asthmatic patients showed a comparable action with beclomethasone in asthma control in both adults and children.[42,43] In vivo studies have shown different pharmacodynamic properties and although beclomethasone has higher receptor affinity, Budesonide has higher in vitro potency.[44] Like Beclomethasone, the introduction of Budesonide in corticosteroid dependent patients with severe asthma seemed to offer an improvement, allowing substantial reduction or withdrawal of oral prednisolone without systemic absorbsion.[45] *Fluticasone propionate* was patented in 1980 and approved for medical use in 1990.[46] In a large international study fluticasone propionate 1mg/day was as effective as 2mg/day beclomethasone dipropionate in the control of severe asthma, better effect on lung function with less effect on adrenal function.[47,48] The results were similar in lower doses of both medications.[49] Other studies also demonstrated that both the dry powder and aerosolized formulations of fluticasone propionate had twice the efficacy of beclomethasone dipropionate via a pressurized inhaler, introducing an alternative dry powder device (Diskhaler) for asthma drug delivery.[50]

In the last 30 years, three more inhaled steroid agents were introduced: Mometasone Furoate, Ciclesonide, and Fluticasone Furoate. *Mometasone furoate* is a highly potent synthetic glucocorticoid initially used as a topical dermatologic agent proved to be an effective treatment for patients with mild-to-moderate persistent asthma previously taking only inhaled β2-adrenergic agonists when administered either as a once daily or twice daily regimen.[51,52] *Ciclesonide* is a prodrug glucocorticosteroid which itself is inactive and needs to be cleaved by esterases in the lung to bind to the glucocorticoid receptor. In the majority of clinical trials, it was administered as a single dose.[53–55] *Fluticasone Furoate* is the newest discovered inhaled corticosteroid that demonstrates prolonged action up to 26 h in asthma patients.[56]

Pilot Studies on Asthma Pathophysiology: The Role of Inflammation

Understanding the pathophysiology and *inflammatory triggers and processes* of asthma *as well as the effects of ICS* on the control of inflammation and bronchial mucosal infiltration was a milestone in asthma management. Laboratory and clinical studies *established inhaled steroid treatment as the main therapeutic option for asthma, dethroning bronchodilator monotherapy*. In 1991 Laitinen LA and coworkers compared the effect of budesonide and terbutaline, on clinical symptoms, lung function, and airway epithelium (on biopsies obtained with bronchoscopy) in 14 adult patients with newly diagnosed asthma. Budesonide improved lung function and bronchial hyperreactivity but most importantly was more effective in *ameliorating abnormalities of the bronchial epithelium and decreasing inflammation in the airways.*[57] One year earlier Haahtela and coworkers had shown that early anti-inflammatory treatment with ICS in newly detected asthma resulted in greater improvement of symptoms and lung function than treatment with terbutaline and that the improvement lasted through the entire two-year study period.[58] In a follow-up study, patients who had been assigned to terbutaline were assigned to ICS and experienced less improvement than those who had started on ICS, suggesting that *early treatment was more effective than delayed treatmen, ie treatment later into the course of asthma.*[59,60]

Despite these advances, the information on whether *inhaled corticosteroids prevent deaths from asthma* remained sparse and inconclusive. Suissa S. and coworkers conducted a population-based epidemiologic study to determine whether and to what extent the use of inhaled corticosteroids prevents death from asthma. The cohort consisted of 30596 subjects who were followed from 1975 through 1997 and the results were published in 2000. Authors concluded that regular use of low dose inhaled corticosteroids was associated with a decreased risk of death from asthma and that the rate of death from asthma decreased by 21 percent with each additional canister of inhaled corticosteroids used in the previous year.[61] Unfortunately, to this day, we see patients receiving bronchodilators only and deaths associated with excessive bronchodilator use.

Enhancing Efficacy of ICS with LABA: Past and Present

A major advance in asthma management was *also the discovery that LABAs enhance the clinical efficacy of inhaled corticosteroids in asthma*[62]. In 1997 Pauwels R A and coworkers in the game-changing *FACET study,* evaluated the effects of adding inhaled formoterol to both lower and higher doses of the inhaled glucocorticoid budesonide and showed that combining ICS and LABAs, resulted in better outcomes, required lower doses of ICS and resulted in better lung function, less activity limitation and better quality of life. In short, 852 patients treated with glucocorticoids were randomly assigned to one of four treatments (low or high ICS with or without LABA) given twice daily for one year. The study showed that, in patients who have persistent symptoms of asthma despite treatment with inhaled glucocorticoids, the addition of formoterol to either the lower or the higher dose of budesonide also improved asthma-symptom scores and lung function and reduced exacerbations and the need for rescue medications.[63]

During the first decade of 21st century, effort was made to achieve control of asthma symptoms and exacerbations with the use of ICS and LABA combinations. *In the Gaining Optimal Asthma Control (GOAL) study*, Bateman and colleagues have assessed how frequently total asthma control or well controlled asthma control can be achieved. Stepping up the treatment to higher doses of Fluticasone alone or Fluticasone/Salmeterol resulted in a higher proportion of patients with controlled asthma. Similarly to the FACET study, more patients rapidly achieved totally or well-controlled asthma with the combination of inhaled salmeterol/fluticasone and at a lower dose of corticosteroid than with inhaled fluticasone alone.[64] Another option for gaining asthma control was the use of fixed Budesonide/Formoterol combination both for maintenance and relief, the *Symbicort Maintenance And Reliever Therapy (SMART) approach*. In 2007 Bousquet J and colleagues showed that in the treatment of uncontrolled asthma, budesonide/formoterol maintenance and reliever therapy reduced the incidence of severe asthma exacerbations and hospitalization/ER treatment with similar daily symptom control compared to sustained high-dose salmeterol/fluticasone plus SABA. This benefit war achieved with substantially less ICS exposure.[65] Over the following years several studies supported the MART strategy in asthma treatment.

Over the last 20 years the combination of LABA with ICS remained the main option for the treatment of moderate to severe asthma.[66] On the contrary, guidelines recommended, until recently, that most adults and adolescents with mild asthma use regular daily low dose ICS as maintenance treatment to reduce airway inflammation, symptoms, and the risk of exacerbations.[67] However, in clinical practice patients show poor adherence to asthma medications, particularly inhaled

glucocorticoids and rely on SABAs for symptom relief, a phenomenon more intense in mild asthma. However, SABAs do not address the underlying inflammatory process and they do not protect against exacerbations. On the contrary *SABA overuse* is related to high asthma mortality.[68,69]

SYGMA 1 and SYGMA2 are both multicenter, phase III, randomized, double-blind, 52-week, placebo-controlled studies, involving asthma patients who were assessed as needing GINA step 2 treatment. In the SYGMA 1 study, patients were randomly separated into three subgroups: i) terbutaline as needed group, ii) budesonide-formoterol as needed group, and iii) budesonide-formoterol regular maintenance group.[70] This study showed that, budesonide-formoterol as needed treatment was superior to terbutaline in outcomes as asthma control and severe exacerbations and equivalent to maintenance budesonide, but with an 83% lower median daily ICS dose. In SYGMA 2, the regular use of low dose ICS budesonide plus SABA as needed was tested against low dose budesonide-formoterol as needed in asthmatics with mild asthma. In this study, BUD/FORM as needed was non-inferior to BUD alone for reducing severe asthma exacerbations but resulted in 75% lower median daily ICS dose.[71] These data resulted in fundamental changes in the treatment of intermittent and mild asthma, the biggest changes since the initial development of GINA recommendations almost three decades ago (1995): The 2019 guidelines proposed that adults and adolescents with *mild asthma should preferably be treated with ICS-containing regimens: as-needed low-dose ICS-formoterol in Step 1 and as needed low-dose ICS plus as-needed SABA or as-needed low-dose ICS-formoterol in* Step 2. And this was the last major advance in asthma treatment confirming the essential role of ICS in treatment even in mild stages of the disease.[72]

Summary

The long journey of corticosteroids in asthma started in early 1950s. Despite their severe adverse effects, the parenteral and oral forms of these agents were a life changing medication for asthmatics, whose treatment options were almost non-existent until then. Twenty years later, the first inhaled steroids proved to be effective and safer, limiting the use of oral agents to more severe stages of disease and during asthma exacerbations. Personalized, phenotype-based treatment approaches using combinations of ICS with LABA, newer inhalation devices and, when needed, biologics for severe asthma are the new reality for all asthma patients. For the majority of patients, the target is to obtain control of asthma with the least (optimal) dose of ICS that each patient requires. ICSs combined with LABAs remain the cornerstone of asthma therapy.

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