REVIEW ARTICLE

Combination Therapy in Asthma: A Review

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Abstract

Background: *Asthma can be defined as a chronic inflammatory disease of the airways that is reversible either spontaneously or by treatment. Despite the exponential increase in asthma research, the prevalence of asthma is on the increase, especially in children and young adults in the western societies. Inhaled therapies are the mainstay of asthma management. This is often in the form of combined therapy using two drugs in a single device to ensure adjustable maintenance dosing.*

Method: *Relevant literature was reviewed using available medical journals, MEDLINE, Pubmed and Science direct via the Internet. The key words employed were: asthma, combination therapy, long acting beta agonists and corticosteroids. British Thoracic Society and The National Heart, Lung and Blood Institute websites were also used in sourcing information.*

Results: *Several studies have shown that combination therapy using long acting beta agonists (LABA) and inhaled corticosteroids (ICS) in a single inhaler device confers complementary and synergistic effect in the management of asthma. It further improves patient compliance and reduces the complexity of treatment and morbidity associated with the disease. Recent studies have shown the combination therapy to serve not only as maintenance but also a reliever therapy with same efficacy as the short acting beta agonists (SABA).*

Conclusion: *This review was able to show the advantages of using combination therapy in asthma patients. This has been a subject of review at both national and international levels as there is no single medication that is effective against both the inflammatory and bronchoconstrictive components of this disorder. Recent studies have shown that Budesonide/formoterol in a single inhaler has been found to be effective maintenance and reliever agent in both adults and children. It has also been found to be safe and more efficacious than fixed-dosing. In addition to convenience and patient compliance, combination devices also help towards individualized approach to asthma management and reduce the complexity of treatment; this appears ideal for adoption by the primary care physician with a view for the patient to effectively achieve control of his own condition.*

Key Words: *asthma, combination therapy, inhaled corticosteroids, long acting beta agonists.*

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Introduction

Asthma is a chronic inflammatory disease of the airways that is reversible either spontaneously or with treatment. It involves multiple cells and cellular elements including mast cells, eosinophils, T lymphocytes, neutrophils, and epithelial cells[1].

The prevalence of asthma has increased, especially in children and young adults, in the western societies despite the exponential increase in asthma research. Highest prevalence is seen in the western industrialized countries with temperate climate and low in rural developing communities[2-5] ; this tends to rise with the adoption of western life style in developing countries where greater economic and humanitarian effects are seen.

In a recent study to know the world wide trends on the prevalence of asthma symptoms (phase III of the international study of asthma and allergies in childhood) which aimed to allow worldwide comparisons of the prevalence of asthma symptoms, the findings indicate a reduction in the international differences in the prevalence of asthma symptom especially in the 13-14 year age group. However, it is also noted that there is a decrease in prevalence in Western Europe and other English speaking countries, with an exponential increase in prevalence in regions where prevalence was previously low[6].

In Nigeria, national prevalence on asthma is still lacking either due to under reporting, paucity of literature or both. Erhabor GE et al, showed that there is a relatively high prevalence of asthma among Ile-Ife university students with a male to female ratio of 10.4% (49) and 17.9% (78) in a study involving 127 respondents[7].

The symptoms seen in this disorder is as a result of the inflammatory response leading to abnormalities in

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autonomic neural control of airway tone, hypersecretion of mucus, mucociliary dysfunction, and hyperresponsiveness of the smooth muscle[1]. There may be recurrent episodes of breathlessness, cough, chest tightness and wheeze. Severity of the disease is directly related to the inflammation and the thickening of the subepithelial linings of the airway[8,9].

Allergic asthma can present for the first time at any age but higher incidence is seen in childhood[10]. In allergen-mediated asthmatics (atopics) there is a genetic predisposition unlike the non-atopics (idiopathic or precipitated by various factors); however, these two classes are not mutually exclusive as non-atopics may develop asthma later in life due to causes such as sensitisation to occupational agents or drug intolerance.

Diagnosis of asthma is usually straightforward and is based on a characteristic history and variability in lung function over time or improvement after a bronchodilator, prednisolone, or high-dose inhaled corticosteroid. Such variability can be measured with spirometry in the clinic or by regular peak-flow measurements at home, with regular peak-flow measurements usually giving a better overall measure of asthma severity. In young children presenting with cough, delay in diagnosis is not uncommon; in this situation, it can take sometime to ascertain whether it's a persistent asthma or wheezy bronchitis[11].

Mechanism of Asthma

The symptoms of asthma are as a result of the interplay between inflammatory mediators (histamine, prostaglandins and leukotrienes), chemokines and cytokines[10]. The cascade gets activated as a result of immunogenic stimuli and cytokines. Type 2 helper T (Th2) cells, a CD4 helper T cell, plays a prominent role in the bronchial inflammation seen in asthmatics. The Th2 cells secrete interleukins that promote allergic inflammation thus stimulating B cells to produce IgE and other antibodies. In contrast, interferon-*g* and interleukin-2, is produced by type 1 helper T (Th1) cells, another class of CD4 T cells thus initiating the killing of viruses and other intracellular organisms by activating macrophages and cytotoxic T cells. These two subgroups of helper T cells constitute an immunoregulatory loop in which cytokines from Th1 cells (interferon-γ) inhibit Th2 cells and from Th2 cells (interleukin-4) inhibit Th1 in a vicious manner. This reciprocal imbalance aforementioned above explain the mechanism of asthma. However, studies have shown that when Th2 cells are freed from the restraining influence of interferon-γ, they provoke inflammation of the bronchial airway[12].

This concept was further supported by a study in which T-bet, a newly discovered transcription factor is necessary to induce helper T cells to differentiate into Th1 cells and for Th1 cells to produce interferon-γ. Thus, T-bet plays an important role in the mechanism of asthma as it is thought to be central to the feedback loops that regulate Th1 and Th2 cells[13]. Figure 1 describes the interplay (regulatory loop) between Th1 and Th2 cells.

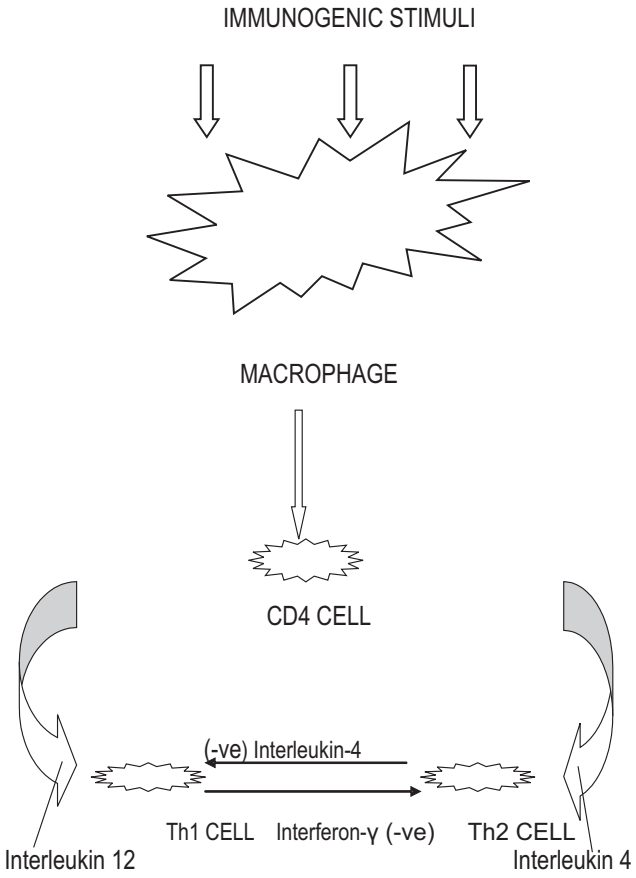

Figure 1 describes the interplay (regulatory loop) between Th1 and Th2 cells.

Combination Therapy

It cannot be disputed that inhaled therapies are the mainstay of asthma management. Several studies have supported the use of ICS and LABA because it improves asthma control and is recommended by guidelines as the optimal therapy for patients with moderate to severe asthma[14].

Table I: combination therapy devices

DRUG	BRAND	INHALERS	
		BAI*	MDI†
FORMOTEROL/BUDESONIDE	SYMBICORT®	TURBOHALER	-
SALMETEROL/FLUTICASONE	SERETIDE®	ACCUHALER	EVOHÆR AND VOLUMATIC

† Metered dose inhaler

* Breath actuated inhaler

(MIMS, APRIL 2004)

Combination therapy here denotes the use of LABA and ICS in a single inhaler device. By combining ICS with LABA in a single inhaler, physicians can provide coverage for both the inflammatory and bronchoconstrictive aspects of asthma without introducing any new or unexpected adverse consequences[15]. Provided there is flexibility to vary the ICS dose, a combination ICS and LABA in a single device represents important advances in the treatment of asthma. Furthermore, there is a compelling need to reduce the complexity of treatment, particularly in patients who require multiple therapies, and improve the likelihood of patient compliance[15].

Although there is an argument that inhaled therapies might have limited drug penetration to the airways thus inability to treat systemic component of asthma, this can be avoided by the use of turbohalers or large volume spacers[16]. However, inhaled formulations are not without side effects but these are fewer both in children and adults especially if used at the therapeutic low-dose. The most common drug-related adverse events of the inhaler devices were those known to be attributable to the constituent medications[15]. Current evidence indicates that ICS do not cause important side effects if used in doses within the therapeutic window[17]. Some studies have question the safety of LABA as regular treatment with this class of drugs is associated with increased risks of severe exacerbations of the disease and death in a rather insignificant group of patients hence the need to use it in combination with inhaled steroids. However, manufacturers have argued that asthma-related mortality has not increased but rather decreased since the introduction of LABA in clinical practice[19]. In another studies, the exacerbation of symptoms in one third to one half of the asthmatics may be explained by poor compliance to therapy or coexistence of other ailments like the chronic obstructive pulmonary disease which are non-responsive to the beta agonists. Furthermore, close medical supervision, patient compliance and advice to seek medical attention when symptoms remain uncontrolled is vital[18,20,21].

Nevertheless, there is a growing concern that the use of the LABA alone may mask sub-clinical airway inflammation[22]; this is not seen when in combination with ICS at a therapeutic dose as it controls the underlying inflammation. The LABA have a slow onset of action but longer plasma half-life of up to about 12 hours as compared to the SABA that has a plasma half-life of about 3-6 hours. The exception to this is formoterol, which has a rapid onset of action that is comparable to the SABA but the same duration of action as salmeterol; it is licensed for used for short-term symptom relief[23]. Adverse effects of these drugs can be minimized by rinsing the mouth after each dose; this is presented in tables 1 (ICS) and 2 (LABA). Table 3 shows the commonly used combination therapy devices.

Different drugs employed in the management of asthma act at different cellular levels. It has been shown that ICS and LABA interact at a receptor level with resultant synergistic effect. ICS increase β2-adrenergic receptor transcription in the human lung and increase the synthesis of respiratory mucosal β2-receptors at clinical doses. Inhaled LABA also prime the inactive glucocorticoid receptor through a phosphorylation mechanism, rendering the receptor more sensitive to steroid-dependent activation[24,25,26].

Several studies advocating the use of LABA (salmeterol, formoterol etc) and ICS (Budesonide, fluticasone etc) using a single device has been carried out in the past decade or two. Ind PW et al conducted a study involving large group of patients. The study was based on the use of single combined formulation of formoterol/budesonide in the form of Symbicort® and this group is the first to report the use of guided self-management in patients receiving combination of ICS and LABA[27]. The study compared patient-guided management of asthma using adjustable-dosing of budesonide and formoterol to fixed-dosing in an open-label, multi-centre, randomised study across the United Kingdom. It was shown from the study that adjustable-dosing led to reduce usage of combination therapy thus reduced inhaled steroid consumption and also reduced inhaled β2-

agonist reliever. A small, but statistically significant, reduction in morning and evening PEF was seen in the adjustable-treatment arm compared to the fixed-treatment control group. The difference, however, is not clinically meaningful but worthy of note[27]. The study further emphasized the success of Bud/form in the overall shift from moderate- to mild-persistent or mild-intermittent asthma, as shown in the previous smaller studies[28,29].

Studies have shown that patients using formoterol as needed in addition to routine maintenance therapy with ICS have fewer exacerbations compared with those using terbutaline[30] or salbutamol[31] as needed. In particular, the rate of exacerbations defined by PEF criteria may be reduced because long-acting $ß_2$-agonists provide a longer duration of bronchodilation and bronchoprotection compared with short-acting $ß_2$-agonists[30]. In view of the attributes of formoterol, its rapid onset of action that is comparable to the SABA, same duration of action as salmeterol and its use as a reliever drug, recent studies on Bud/form combination (Symbicort®) have shown that it can be used as a maintenance and reliever drug; this is because it significantly reduces exacerbations of asthma in patients, exposure to oral steroids, use of reliever medication (SABA), night-time awakening symptoms and improves lung function. It has also been shown that adjustable dosing (AMD) is superior, safe and more efficacious than fixed-dosing (FD) in terms of overall asthma control; this involves adjustment of the maintenance dose in response to variability of asthma control over time. Furthermore, the convenience of this combination product is that it improves patient adherence and may therefore reduce the morbidity of asthma. In addition, an adjustable-dosing regimen inhaler device has been shown to provide a simpler, flexible, convenient and individualised approach to asthma management[23,27,32,33].

Rabe KF et al[34] were the first to underscore the importance of using Bud/form combination in a single inhaler device to serve as both maintenance and reliever drug. Bud/form for both maintenance and relief was more effective than traditional asthma therapy using a higher dose of budesonide alone as demonstrated by improved lung function, reduction in severe exacerbations, and improvements in daily asthma-control measures. The study was a 6-month randomized double blind involving 697 subjects with mean age of 38 years having mild to moderate asthma. The patients were randomized to receive either bud/form (80µg/4.5µg, two inhalations qd) as maintenance and additional inhalations as needed for relief of symptom, or budesonide (160µg, two inhalations qd) for maintenance medication plus terbutaline (0.4mg) as required. PEF was used as the primary efficacy variable. Those receiving bud/form showed greater improvements in morning PEF than patients receiving budesonide (increases of 34.5 l/min vs 9.5 l/min, respectively; $p < 0.001$), low incidence of severe exacerbation, marked improvement in morning PEF and reduction in use of oral steroids for asthma amongst others. The study concluded that Bud/form combination as both maintenance and reliever improves asthma control with a lower steroid load compared with a higher dose of budesonide plus terbutaline.

O'Byrne PM[23] et al further supports the use of Bud/form combination in a single device as both maintenance and reliever. This study involved was a double-blind, randomized, parallel-group study involving 2,760 asthma patients aged 4-80 years (FEV1 60-100% predicted) received either terbutaline 0.4mg as SABA with bud/form 80/4.5µg twice a day or bud 320µg twice a day or bud/form 80/4.5µg twice a day with 80/4.5µg as-needed. A once-nocte maintenance dose was given to children. Bud/form maintenance plus relief prolonged time to first severe exacerbation ($p < 0.001$; primary end point), resulting in a 45-47% lower exacerbation risk. Furthermore, Bud/form maintenance plus relief also prolonged the time to the first, second, and third exacerbation requiring medical intervention ($p < 0.001$). On the overall, there was an improvement in symptoms exacerbation rate, night awakenings, and lung function compared with both fixed dosing regimens.

In an effort to establish the use of Symbicort® in children to serve both as maintenance and reliever agent, Bisgaard H et al[36] has proven that combination of this sort greatly reduces asthma exacerbations as compared to ICS alone. They conducted a 12-month, double-blind, randomized study involving 341 children between the age group of 4 to 11 years with asthma uncontrolled on ICS. It has also been established that children as young as four years can generate enough inspiratory force to use a Turbohaler. The study showed that using Bud/form for maintenance and reliever therapy (Symbicort® maintenance and relief therapy [SMART]) could reduce exacerbations. The patients received SMART (budesonide/formoterol 80/4.5µg qd maintenance plus additional inhalations for symptom relief), budesonide/formoterol 80/4.5µg qd for maintenance (fixed combination), or higher-dose budesonide 320µg qd (fixed-dose budesonide).

Blinded as-needed medication (terbutaline 0.4µg) was provided in both fixed-dose groups. The study revealed that SMART reduced exacerbation requiring medical attention by 70 to 79%, night awakenings, yearly growth improved by 1.0 cm. It was concluded that combination regimen using bud/form in a single inhaler device is useful for both maintenance and as-needed symptom reliever in children with asthma.

Conclusion

This review was able to show that combination therapy using ICS with LABA in a single inhaler in the form of adjustable maintenance dosing have some complementary and synergistic effect which can provide coverage for both the inflammatory and bronchoconstrictive aspects of asthma without introducing any unexpected adverse consequences. Recent studies have shown that Budesonide/formoterol in a single inhaler has been found to be as effective as SABA for relief of acute asthma attacks. It has also been found to be safe and more efficacious than fixed-dosing, thus the modern concept is its use as both maintenance and reliever therapy in asthmatics. Furthermore, children as young as four years old can as well be managed comfortable on combination therapy device unlike in the past. In addition to convenience and patient compliance, combination devices also help towards individualized approach to asthma management and reduce the complexity of treatment; this appears ideal for adoption by the primary care physician as the single-inhaler strategy represents one of the most significant advances in asthma management in recent years. The importance of establishing a partnership between patients and health care professional(s) cannot be over emphasized. This is with a view for the patient to effectively achieve control of his own condition.

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