



Research Article

# Addition of LABA to Low dose ICS in asthma-Is it justified?

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Received date: 5 May 2014; Accepted date: 19 August 2014; Published date: 25 June 2015

Academic Editor: Iwona Stelmach

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## Abstract

Most current guidelines to treat asthma recommend low dose inhaled corticosteroids (ICS) along with long acting  $\beta_2$  agonists (LABA) during step 3 and reduction in dose of ICS first (rather than stopping LABA) during step down. This has led to widespread use of LABA with low dose ICS, more so in fixed dose formulations. Since optimal dose of ICS in the initiation phase is not clearly defined and the safety of regular use of LABA with low dose ICS continues to be debatable, the rationale for use of fixed dose formulations of LABA with low dose ICS, needs to be re-assessed. The author has perused the current experimental and clinical data on ICS and LABA and is of the opinion that starting treatment with LABA and higher dose of ICS leads to better control of asthma in terms of clinical response, pulmonary functions, airway hyper reactivity (AHR) and surrogate markers of inflammation as compared to LABA with low dose ICS. Further, in the eye of the author, withdrawal of LABA first and subsequent lowering the dose ICS upon achieving persistent control should be more appropriate as compared to lowering the dose of ICS first and continuing LABA during step down. That being so, fixed dose formulations of LABA and low dose ICS should not find any place in the management of Chronic persistent bronchial asthma (CPBA).

**Keywords:** Chronic persistent bronchial asthma, long acting  $\beta_2$  agonists, Inhaled corticosteroids, Low dose ICS-LABA fixed dose formulations.

## Introduction

Surveys in several countries have revealed that the control of asthma continues to be poor despite the widespread availability of drugs and guidelines in its management

including that by Global Initiative for Asthma (GINA, 2012). These guidelines recommend low dose inhaled corticosteroids (ICS) & long acting  $\beta_2$  agonists (LABA) at step 3 and reduction in dose of ICS at step down. As a result, addition of LABA to low dose ICS is a

common practice in management of chronic persistent bronchial asthma (CPBA) and plenty of fixed dose formulations of low dose ICS & LABA are available in the market. However, there is no clarity on the optimal dose of ICS. Cates et al., (2008a) and Cates et al., (2008b) have also questioned the safety of regular use of LABA in view of the episodes of  $\beta$  agonists related morbidity and mortality in asthma patients. The author is reviewing the existing literature on ICS and LABA in CPBA and making prudent recommendations on the issue.

### **$\beta_2$ agonists in asthma**

$\beta_2$  agonists are currently the most effective bronchodilators. It causes smooth muscle relaxation through the activation of a large conductance  $Ca^{+}$  activated potassium channel (Maxi K channel). Other effects include inhibition of micro-vascular leakage and plasma exudation in airways and mast cell stabilization. Selective short acting  $\beta_2$  agonists (SABAs) albuterol and terbutaline decreased cardiac toxicity. But Kraan et al., (1985), Vathenen et al., (1988) and Wahedna et al., (1993) noted that regular use of these drugs led to tolerance and tachyphylaxis, rebound bronchoconstriction and decreased lung functions.

Long acting beta2 agonists (LABA), Salmeterol and formoterol were developed chiefly to overcome the short duration of action of SABAs. Better symptom control in asthma patients was indeed achieved with use of LABA along with ICS by Greening et al., (1994) and Ni et al., (2005) but meta analyses by Cates et al. (2008a) and Cates et al., (2008b) discovered that regular use of LABA too increased morbidity, mortality and frequency of nonfatal adverse events. Nelson et al., (2006) cautioned that regular use of LABA would mask signs and symptoms of an asthma exacerbation, but Jaeschke et al., (2008) and Sears et al., (2009) have failed to confirm this. Levenson et al., (2008) in a meta-analysis on the issue also observed that the increased risk of asthma-related events was confined to patients taking salmeterol

alone. But Food and Drug Administration was quick to issue a "black box" warning about the use of LABA and convened a joint meeting of committees (2008) on the issue. It was concluded that the risks of treatment with salmeterol or formoterol outweigh any benefits and these drugs should only be used along with ICS.

### **ICS in asthma**

ICS are currently the most effective anti-inflammatory drugs in the management of asthma. Blais et al., (1998) were first to report that regular use of ICS reduced the need for rescue bronchodilators and hospitalization, improved pulmonary functions and reduced bronchial hyperresponsiveness. By this time, Laitinen et al., (1997) had already reported that ICS reduced deposition of collagen and tenascin in the airway mucosa. Response to ICS, however, depends on several factors i.e. the time of intervention, co-prescription of  $\beta_2$  agonists and the dose of ICS. Type of inhaler used, Patient's compliance to the device/drug and his phenotype are the other factors of importance.

Selroos et al., (1995) noted that any delay in intervention of steroids led to irreversible or incompletely reversible changes in airway pathology. Early intervention of inhaled steroids is, therefore, a must for optimal control of asthma.

Powels et al., (1997) observed that ICSs give better clinical response when given along with  $\beta_2$  agonists. Renzi et al., (2010) and several others have confirmed this observation.

Earlier studies in asthma patients showed that when used with SABA, a daily dose of 400-800 $\mu$ g of inhaled beclomethasone dipropionate (or equivalent dose of other ICS) was enough but Toogood (1989), Salmeron et al., (1989) and Hummel et al., (1992) observed that patients with severe disease needed higher dosage. Lacronique et al., (1991) and Hummel et al., (1992) also

noted that high dose of ICS also allowed discontinuation of systemic steroid.

Newhouse (1993) suggested that the doses of inhaled drugs in infants and children has to be equal to that in adults as the lung deposition is poor in former due to limited penetration of drugs into their small sized airways.

Concerns have been raised regarding the risk of adverse effects with high dose ICS but it can be checked by rinsing the mouth after the use of dry powder device or the use of a spacer device with the metered dose device during the initial phase of treatment and lowering the dose of ICS once control of asthma is achieved (Agertoft and Pedersen, 1993).

#### **Addition of LABA to ICS**

It was Greening et al., (1994) who for the first time showed that addition of LABA to low dose ICS resulted in greater improvement in control of symptoms in asthma as compared to doubling the dose of ICS. Later, this was confirmed by Woolcock et al., (1996), Bouros et al., (1999), O'Byrne et al., (2001) and Laloo et al., (2003). Jarjour et al., (2006) observed that control of asthma and airway inflammation was maintained when patients requiring a medium-dose ICS are switched to a lower-dose ICS with a LABA implying that lower-dose ICS with a LABA is effective in controlling inflammation and providing clinical asthma control. This led to widespread use of LABA with low dose ICS, mostly in fixed dose formulations and this practice is continuing in spite of the fact that tolerance has been demonstrated to long term use of LABA by Cheung et al., (1992) and Bhagat et al., (1995).

Recently, 2 meta-analyses have been released on the subject. Ducharme et al., (2010) analysed data from all the identified randomised controlled trials comparing the addition of LABA to ICS versus increasing to a higher dose of ICS in asthmatic children and adults. They concluded that in adults, there was a modest advantage in adding LABA to ICS, compared with increasing the dose of

ICS, but in children there was a trend towards an increased risk of moderate and severe exacerbations. Cates et al., (2013) have analysed data from 20 studies in adults and 7 in children with participants having a range of asthma severity and most having been previously treated with regular ICS. Seven deaths were reported among 13,366 participants. Six of these deaths, including one related to asthma, were reported in adults taking formoterol and ICS and one death, in a participant taking ICS alone. Although the difference in mortality was not significant, they could not conclusively state that adding formoterol to ICS on regular basis carries no risk of increasing the number of deaths as compared to similar dose of ICS alone. With the addition of new studies in 2012, they found a lower risk of non-fatal serious adverse events attributed to asthma when formoterol was combined with ICS but there is no clarity on the dose of ICS used in these newer studies as compared to the rest.

However, literature cited above is not without flaws. Almost all of the studies discussed above, have examined addition of LABA to low baseline doses of ICS at which most of the therapeutic response of ICS has not been obtained. None of these studies have compared the effect of adding LABA to low dose ICS versus adding LABA with higher dose of ICS (Fluticasone 200 µgm or equivalent). Most of these studies have relied on control of symptoms rather than control of asthma. Several studies have shown that addition of LABA to low dose ICS led to a trend towards an increased risk of moderate and severe exacerbations in children. In the end, the results of these controlled trials cannot be automatically translated into field situations where defaults are common.

Pauwels et al., (1997) in a landmark study, more popularly called as the "FACET Study", compared the effect of adding LABA to low dose ICS as well as high dose ICS. Eight hundred fifty two patients who were not controlled on low dose ICS alone were randomly assigned to one of four treatments given twice daily by means of a dry-powder

inhaler: 100 µg of budesonide plus placebo, 100 µg of budesonide plus 12 µg of formoterol, 400 µg of budesonide plus placebo or 400 µg of budesonide plus 12 µg of formoterol. Terbutaline was permitted as needed in all the patients. Frequency of exacerbations, symptoms of asthma, and lung functions were monitored. Severe exacerbations were reduced by 26 percent, 49 percent and 63 percent with formoterol plus lower dose of budesonide, higher dose of budesonide alone and formoterol plus higher dose of budesonide, respectively. Mild exacerbations were reduced by 40 percent, 37 percent and 62 percent, respectively, albeit there was greater improvement in symptoms of asthma and lung functions on addition of formoterol to budesonide. The authors concluded that the addition of formoterol to budesonide therapy or the use of higher dose of budesonide was beneficial in patients not controlled on lower dose of ICS and the addition of formoterol to budesonide improved symptoms and lung functions without lessening the control of asthma. However, also evident from the above data is the fact that the control of asthma (reduction in exacerbations) was much better on higher dose of budesonide, more so with add on formoterol, as compared the lower dose of budesonide with add on formoterol i.e. the addition of LABA to higher dose ICS is superior to that to low dose ICS, in control of asthma.

Studies done by Tukiainen et al., (2000) and Inman et al., (2001) have supported the work of Pauwels et al., (1997). They showed that higher doses of ICS led to more effective control of asthma, not only in terms of better clinical response and pulmonary functions but also in terms of decreased AHR and surrogate markers of inflammation. Further, Green et al., (2002) showed that when sputum eosinophilia was used as criteria for control of asthma (as compared to control of symptoms alone), there were fewer exacerbations and hospitalizations. This study established that symptomatic control of asthma does not necessarily mean the best control of asthma.

### **Single maintenance and reliever therapy (SMART)**

Since formoterol was found to have early onset of action, SMART was evolved simultaneously and compared with the conventional approach. O'Byrne et al., (2005) and Rabe et al., (2006) reported that the time to first severe exacerbation was delayed in the SMART group as compared to the conventional combination therapy. Studies conducted by Selroos et al., (2007), Barnes (2007) and Humbert et al., (2008) also showed that SMART approach, besides being convenient to patients, reduced the risk of exacerbation, increased the likelihood of rapid control and provided better improvements in several other outcomes than the traditional approach but Bousquet et al., (2007) and Bateman et al., (2007) failed to confirm these results. A recent Cochrane analysis by Cates et al., (2009) revealed that SMART reduced the risk of asthma exacerbations (needing oral corticosteroids) as compared to fixed dose maintenance ICS but it is worthy to note that the average daily dose of budesonide was increased by 50% in the SMART patients compared to the comparator arms.

These observations by Cates et al., (2009) only reiterates the fact that higher dose of ICS lead to better control of asthma than the low dose.

### **β<sub>2</sub>agonists controversy**

β<sub>2</sub> agonists are known to cause smooth muscle relaxation and mast cell stabilization but its regular use may cause increased morbidity and mortality. How it is than possible that the drugs, which hitherto are known friends in our fight against asthma, can turn foes with passage of time?

Experimental studies have, however, now unrevealed the pro-inflammatory effects of β<sub>2</sub> agonists. Thus, Panina-Bordignon et al., (1997) showed that albuterol inhibited IL-12 production by human monocytes and modified the development of the Th-1 inflammatory pathway. In another study,

Agarwal et al., (2000) showed that when monocytes were incubated with increasing concentrations of terbutaline, there was an increased release of IL-4/IL-5 and decreased release of interferon- $\gamma$  i.e. an enhancement of the Th-2 pathway. Aldridge et al., (2000) and Lazarus et al., (2001) showed that regular use of SABA and LABA led to increase in inflammatory cells in induced sputum. McGraw et al., (2005) and (2007) showed an increase in AHR with an increase in  $\beta_2$ receptor activation and gain in contractile signaling with chronic  $\beta_2$ agonist exposure.

Callaerts-Vegh et al., (2004) were first to observe that  $\beta$  adrenoceptor agonists and  $\beta$  blockers with inverse properties may exert reciprocating effects on cellular signaling in a murine model, depending on the duration of its use. Both the airway inflammation and AHR increased after acute treatment with beta blockers but it decreased, significantly so, after its chronic use (28 days). Hanania et al., (2008) examined the safety and effects of a non-selective beta-blocker, nadolol, in subjects with mild asthma and observed that most patients tolerated the dose-escalating administration of beta-blocker, nadolol and that the drug might have beneficial effects on AHR in these patients.

These data indicate that the relationship between  $\beta_2$  receptor activation or its blockade, airway inflammation, and airway responsiveness in asthma are complex. The effects of  $\beta_2$  agonists are not the same on their short term and long term use. It has been argued that timely use of ICS in optimal dose is critical else the threshold for adverse effects in relation to total  $\beta$ -agonist exposure might be crossed. Once this has happened, ICS may fail to protect against the adverse effects of  $\beta$  agonists even if the patients are now put on seemingly adequate doses of anti-inflammatory treatment.

### **Rationale for adding LABA to low dose ICS in CPBA?**

The goals of asthma management have evolved over the time. The prevention of asthma deaths, acute hospitalizations or acute asthma episodes, is no longer regarded as sufficient treatment targets. The main focus has now shifted on achievement of daily control and prevention of the consequences of insufficient control such as severe medical crises and day-to-day disability. It is also being emphasized now that the control of asthma should be assessed on validated parameters. The recently introduced "Asthma control test" by Nathan et al., (2004) could be one such test.

GINA guidelines (2012) have now included control of asthma as important criteria in the step wise management of asthma but it continues to rely on "Step-up and step-down" approach and advocates initiating therapy with low dose of ICS alone at step 2 and low dose of ICS along with LABA or moderate dose of ICS alone at step 3 of the plan of management. It allows higher dose of ICS only at step 4 of the treatment plan. Further, GINA and other guidelines on asthma continue to rely on reducing the dose of ICS as a first step and continuing with LABA during the maintenance phase ("step-down") in adults.

The existing guidelines, however, are overlooking the benefit of starting treatment with moderate to high doses of ICS along with LABA as a single step. Optimal dose of ICS (At least 200  $\mu$ gm of fluticasone or equivalent) will lead to optimal control of asthma, besides, preventing tolerance and other adverse effects of LABA.

Further, regular use of LABA along with lowered dose of ICS during step-down, as recommended in these guidelines, may invite increase in airway inflammation, that too, without being noticed by the patient or his physician due to the masking effect of the former drug on symptoms of asthma. This places such patients at risk of excess

morbidity/mortality as has been observed by Cates et al., (2008a) and (2008b). FDA in its report (Fanta 2009) also recommended that, as far as possible, LABA should be withdrawn first during step down.

The existing experimental and clinical data also favored tapering of dose of ICS only after achieving a sustained control of asthma, may be 25-50% initially and then to maintain the therapy on lowest possible dose of ICS, along with SABA as 'on demand' basis. Fear of loss of control should not deter us from this policy as it is a known phenomenon during maintenance phase, regardless of the mode of step-down. More important is to recognize it with ease and at the earliest so that it can be managed in time. Both the patient and his physician are likely to recognize the loss of control in the patients who are not on LABA during maintenance phase as it is likely to be symptomatic. This is in contrast to those patients who are on LABA during maintenance phase who will continue to remain asymptomatic and any loss of control remains hidden in them for long. This is likely to make their asthma worse. Loss of control can be easily countered by re-introduction of LABA, albeit, along with a simultaneous increase in the dose of ICS.

Based on the above, the author's opinion is that the therapy in CPBA should be initiated with optimal dose ICS (At least 200 µgm of fluticasone or equivalent) along with LABA and the latter drug should be withdrawn first during step-down. Initiating therapy with moderate to high dose of ICS along with LABA and withdrawal of LABA first during step-down in the management of CPBA has been assigned as "STEP I- STEP II" approach by Gupta and Jain (2013).

Also evident from the above facts is that there appears to be no place for the fixed dose formulations of low dose ICS and LABA in the management of CPBA and its use should be discouraged, both in the initiation phase as well as during the step down phase. However, further studies are needed to confirm this view point of the author.

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