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Revisiting the "FACET Study" is the Need of Hour

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Guidelines on treatment of chronic persistent bronchial asthma (CPBA) recommend low dose Inhaled Cortico Steroids (ICS) along with inhaled long acting b2 agonists (LABA) as the initial treatment. A recent meta-analysis on the issue has also established the safety of this approach [1].But control of asthma continues to be suboptimal in spite of these guidelines as has been revealed in several field surveys [2-4]. Lack of knowledge, underuse of guideline based treatment and poor compliance have emerged as the areas of concern. However, the guidelines itself may not be robust enough to control of asthma in field conditions, where compliance to therapy is relatively poor as compared to the trial conditions. In the eye of this author and may be several others, initiating therapy with High dose ICS and LABA may be much more rewarding than the guideline based approach. A revisit to the "FACET Study" [5] will reiterate the stand of this author.

The "FACET Study" [5] was carried out in the backdrop of the prevailing knowledge at that time i.e.: "1. ICS are the first-line treatment for CPBA, 2. Many patients taking ICS continued to have symptoms and needed additional treatment, 3. Regular use of inhaled β2-agonists is a subject of controversy, 4. Treatment with LABA's namely formoterol and salmeterol provides better control of symptoms 5. Combining LABA with ICS leads to a greater improvement in the control of symptoms and in lung function than doubling its dose and 6. Long-term treatment with LABA might result in tolerance to its effects or mask an increase in airway inflammation."

The authors of the study hypothesized that the addition of regular treatment of LABA to a lower or higher dose of ICS budesonide would result in improved control of symptoms and lung function, without any long-term deterioration in the control of asthma over a 12-month period. They enrolled 852 patients who were not controlled on low dose ICS alone. These patients were randomly assigned to one of four treatment regimens 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. Inhaled terbutaline was allowed as and when needed in all the patients. Frequency of exacerbations, symptoms of asthma, and lung functions were monitored.

There was greater improvement in symptoms of asthma and lung functions in patients where formoterol was added to budesonide. Severe exacerbations were reduced by 26%, 49% and 63% with formoterol plus lower dose of budesonide, higher dose of budesonide alone and formoterol plus higher dose of budesonide, respectively as compared to placebo. Mild exacerbations were reduced by 40%, 37% and 62% of the patients, respectively. The authors of the study concluded:

"Our results support therapeutic guidelines that recommend the addition of a long-acting inhaled β2-agonist to low doses of inhaled glucocorticoids in patients with persistent symptoms of asthma or less than optimal lung function. Increasing the maintenance dose of inhaled glucocorticoids might be a more appropriate initial therapeutic step in patients with repeated severe exacerbations of asthma."

What we have learnt from the "FACET Study": Addition of LABA to low dose ICS is as effective as the doubling the dose of ICS in control of asthma. Several other workers have also reiterated the same at a later date [6-8]. Jarjour et al. [9] marched a step ahead by observing that control of asthma and airway inflammation were maintained when patients requiring a medium-dose ICS were 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.

But……

What we failed to learn from "FACET Study: Addition of LABA to a higher dose of ICS leads to more effective control of asthma than addition of LABA and low dose ICS. This is being continuously ignored in spite of the fact that the above approach has been

reiterated in other studies also. Thus, Tukiainen et al. [10] and Inman et al. [11] have shown that higher doses of ICS led to more effective control of asthma i.e. better clinical response, improved pulmonary functions, decreased airway hyper-reactivity & decreased surrogate markers of inflammation. A recent Cochrane analysis by Cates et al. [12] has revealed that single maintenance and relieving therapy (SMART) leads to greater reduction in the risk of asthma exacerbations (needing oral corticosteroids) as compared to fixed dose maintenance ICS but at the same time, the average daily dose of budesonide was increased by 50% in the SMART patients as compared to the comparator arms.

These studies have not only reiterated the fact that initiating treatment with higher dose of ICS lead to better control of asthma than the lower dose but have also highlighted that symptomatic control of asthma does not necessarily mean the best control of asthma. Green et al. [13] have by now shown 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.

Why it is so that higher dose of ICS will lead to better control of the inflammation in the airways of asthma patients than the lower dose, along with LABA? Data from animal studies indicate that the relationship between b2 receptor activation or its blockade, airway inflammation, and airway responsiveness in asthma are complex. The effects of b2 agonists are not the same on their short term and long term use and timely use of ICS in optimal dose is critical. Otherwise, the threshold for adverse effects in relation to total β-agonist exposure might be crossed and once this has happened, even ICS may fail to protect [14-15].

The goals of asthma management have changed over the time and now the prevention of asthma deaths, acute hospitalizations or acute asthma episodes, is no longer regarded as sufficient treatment target. Focus has shifted on achievement of daily control and prevention of the consequences of insufficient control such as severe medical crises and day-to-day disability. A current GINA guideline [16] have also included control of asthma as important criteria in its step wise management of asthma but continues to rely on lower 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, thus ignoring the benefit of starting treatment with moderate to high doses of ICS along with LABA as a single step. Concerns regarding the risk of adverse effects with higher dose ICS have been raised time and again but can be checked by rinsing the mouth after the use of dry powder device or the use of a space haler device with the metered dose device during the initial phase of treatment and lowering the dose of ICS once control of asthma is achieved.

Meanwhile all the guidelines on asthma should include optimal dose of ICS along with LABA (At least 400 µgm of budesonide twice daily or its equivalent) as step 1 in its treatment protocol for all patients suffering from CPBA. This will not only prevent tolerance and other adverse effects of LABA but will also lead to more effective control of asthma. This was amply shown way back in the year 1997 by Powels et al. [5] and a revisit to the "FACET Study" is thus the need of the hour.

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