Asthma Step-Down Strategies

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Asthma step down strategies: Perhaps the patient should decide?

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There have been some concerns regarding the potential for long acting beta-agonist (LABA) to adversely affect asthma control, despite inhaled corticosteroid and long acting beta-agonist (ICS/LABA) combination therapy being a commonly used option at step 3 and above of asthma guidelines.[1] In vitro data have shown LABA to exhibit pro-inflammatory activity due to activation of beta-arrestin and extracellular signal regulated kinases via non-canonical G protein cyclic adenosine monophosphate (Gs-cAMP)-independent pathways.[2] Hence in vivo exposure to formoterol results in an inflammatory asthma phenotype in mice depleted of endogenous epinephrine.[3] Furthermore tachyphylaxis of response occurs rapidly to the canonical effects of LABA on airway smooth muscle and inflammatory cells due to down-regulation and uncoupling of Gs-cAMP. [4]

National and international guidelines advocate a process of assessment, stepwise adjustment of treatment, and review of response, to achieve the lowest effective maintenance therapy over the long term. Clinicians are always more inclined to step up therapy from ICS to ICS/LABA as opposed to performing the converse. For patients who are controlled on ICS/LABA combination, Global Initiative for Asthma (GINA) recommends continuing LABA while reducing concomitant ICS dose, while the US Food and Drug Administration (FDA) suggests that LABA should be stopped while continuing with the same dose of ICS alone.

There are some data to suggest that patients well controlled on ICS/LABA may do less well if they stop their LABA. A meta-analysis of five trials revealed impaired asthma control and quality of life when stepping off LABA [5], but did not clearly show an increase in exacerbations. The FDA mandated safety studies examining adding a LABA verses maintaining the same dose of ICS, observed that patients who had entered the trial who were initially maintained on ICS/LABA had an increased exacerbation risk when they were randomized to ICS alone as compared to ICS/LABA.[6, 7] However, there are no studies that can provide guidance regarding the conflicting recommendations as to whether patients well controlled on ICS/LABA should first have their ICS reduced or their LABA discontinued.

Against this background of uncertainty Rogers et al [8] randomized patients stable on medium-fixed dose ICS/LABA to receive reduced fixed- dose ICS/LABA, medium dose ICS alone ,or to continue the same medium dose combination treatment for 48 weeks . Using as a primary outcome a composite of control that included exacerbations, there were no significant differences in treatment failures between

any of the three strategies. However, LABA step off was associated with a 70ml mean decline in FEV1 compared with reducing ICS. There were five hospitalizations for asthma exacerbations all of which occurred after LABA step off, although systemic corticosteroid use did not differ between groups. Patients who were taking reduced dose ICS/LABA fared no worse on any outcomes compared to those taking a medium dose. A responder analysis for asthma control score (ACT) over 48 weeks was similar between groups when comparing the cumulative proportion of events with a score below 19 or with a decrease of at least 3.

While these data at first sight appear to be reassuring, it is important to understand that none of the groups did substantially worse than the other. This leads one to the possible interpretation that the patients in this study were being over-treated prior to enrollment and thus they were equally able to come off extra ICS or a possibly superfluous LABA. Perhaps these patients were already on more ICS than they needed? In an observational community study of ICS tapering it was possible to achieve a 37 % dose reduction without any deterioration in inflammatory markers in the majority of individuals in conjunction with a commensurate improvement in quality of life[9]. Thus, we are still unclear as to whether patients who truly required combination therapy will be better able to tolerate ICS reduction or LABA elimination.

With this caveat in mind, it might help to consider the Rogers study as more of a pragmatic study. It suggests, that in the context of current prescribing patterns, when faced with patients who are well controlled on moderate dose ICS/LABA, reducing ICS may be a reasonable first choice. However, in settings where prescribing may be more “parsimonious” these results may not hold. Further, it is important to point out that carrying this line of reasoning to the next step is not advisable. Namely, it is not reasonable to eliminate ICS in patients on low dose ICS/LABA. That strategy results in increased exacerbations and is therefore not recommended[10].

Are there patients in whom one should favor one type of reduction versus the other? Adverse effects might guide the clinician. There was more hoarseness in the group maintained on moderate dose ICS in the Rogers study. Are there biomarkers that can assist with this decision? Several come to mind. Patients who posses one or two copies of the arginine allele at the 16th amino-acid position of the beta-2 receptor have been shown to develop worsening of airway hyperresponsiveness when treated with ICS and formoterol [11] . ICS naïve patients with elevated exhaled nitric oxide have been shown to develop loss of bronchoprotection with regular use of salmeterol

[12]. It is interesting to speculate whether these, or other, biomarkers could guide us in making the step-down decision.

The issue of overtreatment raised by the Rogers study, brings us to the issue of variable use of controller therapy. Single inhaler maintenance and reliever therapy (SMART) using combinations containing formoterol and ICS, has repeatedly been shown to be accompanied by improved overall control and lower overall ICS exposure compared to fixed dose ICS/LABA [13]. Similarly, ICS therapy guided by symptoms in mild asthma and by albuterol use in moderate asthma has been shown to be as effective as maintenance controller therapy[14, 15]. While the question of whether to adjust ICS or LABA may still be an issue with our current treatment paradigm, approaches that educate patients to "auto-adjust" controller therapy may obviate our need to consider whether to taper ICS or LABA. Perhaps in many cases it is best for the patient to do it for us.

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