

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-agonists (LABAs) 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 proinflammatory activity due to activation of beta-arrestin and extracellular signal regulated kinases via noncanonical G protein cyclic adenosine monophosphate-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 LABAs on airway smooth muscle and inflammatory cells because of downregulation and uncoupling of G protein cyclic adenosine monophosphate.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, the Global Initiative for Asthma recommends continuing LABA while reducing concomitant ICS dose, whereas the US Food and Drug Administration 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 5 trials revealed impaired asthma control and

quality of life when stepping off LABA,⁵ but did not clearly show an increase in exacerbations. The Food and Drug Administration—mandated safety studies examining adding a LABA versus 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 with 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 al⁸ 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 3 strategies. However, LABA step off was associated with a 70 mL mean decline in FEV₁ compared with reducing the ICS dose. There were 5 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 with those taking a medium dose. A responder analysis for asthma control test (ACT) scores 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.

Although 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 overtreated before 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 most 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 Rogers et al's 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 in which prescribing may be more "parsimonious," these results may not hold. Furthermore, it is important to point out that

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Conflicts of interest: B. Lipworth has received research support from Teva, Meda, Boehringer Ingelheim, AstraZeneca, Chiesi, Sanofi, Janssen, and Roche; has received consultancy fees from Boehringer, Cipla, Dr Reddys, Sandoz, Chiesi, Teva, and Meda; has received travel support from Teva, Boehringer, Napp, and GlaxoSmithKline; and has a son who is employed by Boehringer Ingelheim. E. Israel has received consultancy fees from AstraZeneca, Philips Respironics, Regeneron Pharmaceuticals, Bird Rock Bio, Novolun Pharmaceuticals, Vitaeiris, Sanofi, and Merck; has received consultancy fees from and is a member of the data and safety monitoring board for Novartis; has received travel support from Research in Real Life; has received consultancy fees and travel support from Teva Specialty Pharmaceuticals; and has received research support from Genentech, Boehringer Ingelheim, GlaxoSmithKline, Merck, Sunovion, Teva, and Sanofi.

Received for publication August 8, 2017; accepted for publication August 8, 2017.
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J Allergy Clin Immunol Pract 2018;6:644-5.
2213-2198

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<http://dx.doi.org/10.1016/j.jaip.2017.08.026>

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 Rogers et al's study. Are there biomarkers that can assist with this decision? Several come to mind. Patients who possess 1 or 2 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 et al study brings us to the issue of variable use of controller therapy. Single inhaler maintenance and reliever therapy using combinations containing formoterol and ICS has repeatedly been shown to be accompanied by improved overall control and lower overall ICS exposure compared with 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} Although 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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