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Asthma Step-Down Strategies

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1 **Asthma step down strategies: Perhaps the patient should decide?**

2

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

30

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

39

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

50

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

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

64

65 While these data at first sight appear to be reassuring, it is important to understand
66 that none of the groups did substantially worse than the other. This leads one to the
67 possible interpretation that the patients in this study were being over-treated prior to
68 enrollment and thus they were equally able to come off extra ICS or a possibly
69 superfluous LABA. Perhaps these patients were already on more ICS than they
70 needed? In an observational community study of ICS tapering it was possible to
71 achieve a 37 % dose reduction without any deterioration in inflammatory markers in
72 the majority of individuals in conjunction with a commensurate improvement in quality
73 of life⁹. Thus, we are still unclear as to whether patients who truly required
74 combination therapy will be better able to tolerate ICS reduction or LABA elimination.

75

76 With this caveat in mind, it might help to consider the Rogers study as more of a
77 pragmatic study. It suggests, that in the context of current prescribing patterns, when
78 faced with patients who are well controlled on moderate dose ICS/LABA, reducing
79 ICS may be a reasonable first choice. However, in settings where prescribing may be
80 more “parsimonious” these results may not hold. Further, it is important to point out
81 that carrying this line of reasoning to the next step is not advisable. Namely, it is not
82 reasonable to eliminate ICS in patients on low dose ICS/LABA. That strategy results
83 in increased exacerbations and is therefore not recommended¹⁰.

84

85 Are there patients in whom one should favor one type of reduction versus the other?
86 Adverse effects might guide the clinician. There was more hoarseness in the group
87 maintained on moderate dose ICS in the Rogers study. Are there biomarkers that
88 can assist with this decision? Several come to mind. Patients who possess one or
89 two copies of the arginine allele at the 16th amino-acid position of the beta-2 receptor
90 have been shown to develop worsening of airway hyperresponsiveness when treated
91 with ICS and formoterol¹¹. ICS naïve patients with elevated exhaled nitric oxide
92 have been shown to develop loss of bronchoprotection with regular use of salmeterol

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

95

96

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

108

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