

## Editorials

# "Step-down" therapy for asthma: Why, when, and how?

**Key words:** Asthma therapy, "step down"

The ultimate goal of asthma therapy is to achieve complete (or near complete) disease control while minimizing the adverse effects of the therapies used. International guidelines for asthma care all share a common message: *Control asthma with the lowest effective dose of medication*—this generally referring to the dose of inhaled corticosteroid (ICS). Furthermore, guidelines recommend reducing the amount of asthma therapy once disease control has been achieved. Unfortunately, though "step-up" therapy has been extensively studied, there is no clearly defined or validated superior algorithm that aids the clinician in "stepping down" therapy. In this issue of the Journal, Fowler et al<sup>1</sup> report the first comparative study of the efficacy of 2 "step-down" approaches: (1) decreasing ICS dosing and (2) decreasing ICS dosing in the presence of a long-acting  $\beta$ -agonist (LABA).

### Why "step down" therapy?

Current asthma guidelines suggest an approach to therapy aimed at rapidly achieving asthma control. Once control is achieved, the amount of controller therapy should be reduced to the minimal level required to maintain disease control. The strongest motivation for "stepping down" therapy is to minimize adverse effects of medications. An additional benefit of "stepping down" therapy might be to better define a patient's disease severity. The treatment recommendations in the guidelines do not account for individual differences in drug response. For example, one patient with moderate persistent asthma (based on symptom frequency) might respond favorably to a low-dose ICS, whereas another patient with asthma of comparable severity might require a higher dose of ICS or the addition of other classes of medication to achieve asthma control. By "stepping down" asthma care, one can gain valuable insight into each patient's response pattern to a given therapeutic regimen.

#### Abbreviations used

|       |                              |
|-------|------------------------------|
| AHR:  | Airways hyperresponsiveness  |
| BDP:  | Beclomethasone dipropionate  |
| DPI:  | Dry powder inhaler           |
| ECP:  | Eosinophil cationic protein  |
| FP:   | Fluticasone propionate       |
| HFA:  | Hydrofluoroalkane 134a       |
| ICS:  | Inhaled corticosteroid       |
| LABA: | Long-acting $\beta$ -agonist |
| LTM:  | Leukotriene modifier         |

ICSs remain the cornerstone of the management of persistent asthma. Numerous studies have demonstrated that ICS therapy improves asthma control and reduces airways inflammation. However, concern about the long-term safety of these agents, including dose- and duration-dependent toxicities, has led to the widespread use of adjunctive therapies in persistent asthma in an attempt to minimize ICS exposure. Evidence strongly supports the addition of agents with differing and complementary mechanisms of action, including LABAs,<sup>2-4</sup> leukotriene modifiers (LTMs),<sup>5</sup> and theophylline,<sup>6</sup> to a low-to-moderate dose of ICS rather than an escalation of doses of ICS in patients suboptimally controlled on ICS alone.

Although approaches for escalating, or "stepping up," therapy have been extensively investigated, much less attention has been paid to the patient who is doing well on a given therapeutic regimen. Guidelines recommend reducing the ICS dose by approximately 25% every 2 to 3 months as long as asthma control is appropriate.<sup>7</sup> However, this approach is applied inconsistently in clinical care and probably leads to over-treatment with ICS in a substantial proportion of well-controlled patients. Furthermore, in contrast to the evidence supporting the superiority of combination therapy in "stepping up" asthma care, there is no clear consensus to guide clinicians in "stepping down" asthma care.

### When to "step down" asthma therapy?

Patients who meet the goals of asthma treatment (Table I) are candidates for "step-down" therapy. However, these goals largely reflect clinical measures of asthma control, such as symptom frequency, nocturnal awakenings, and health care utilization. To optimize the likelihood of successful "step-down" therapy, a combination of clinical and laboratory indicators might be helpful in identifying patients likely to tolerate a "step-down" in therapy. Markers that warrant further study in their

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ability to predict successful “step-down” include changes in lung function and/or airways hyperresponsiveness (AHR) and changes in markers of inflammation, such as exhaled nitric oxide, exhaled condensates, and eosinophils and/or eosinophil cationic protein (ECP) in blood<sup>8</sup> or induced sputum.

## How to “step down” asthma therapy?

Several potential approaches exist for “step-down” therapy. Guideline recommendations suggest reducing or eliminating the last medication added<sup>7</sup> or reducing the dose of ICS in patients on combination therapy.<sup>9</sup> Although simply reducing the dose of ICS seems to be the most straightforward approach, lessons learned from “step-up” therapy—specifically, the use of adjunctive therapies—might allow for more effective reduction in ICS dosing. Several potential approaches to “step-down” care have been studied, including (1) a simple reduction in the dose of ICS, (2) addition of a LABA followed by a reduction of ICS dosing, (3) addition of an LTM followed by ICS reduction, and (4) the addition of anti-IgE therapy; however, comparative trials involving these approaches have not yet been reported.

Numerous studies have confirmed that ongoing therapy with ICS is necessary to maintain asthma control; patients in whom ICSs were completely withdrawn have experienced prompt return of symptoms and AHR.<sup>10,11</sup> Fortunately, several trials have demonstrated that ICS reduction is achievable without loss of asthma control.<sup>12,13</sup> Haahela et al<sup>12</sup> reported that patients treated with high-dose ICS (budesonide 1200 µg/d) for 2 years were able to reduce their ICS dose by 66% and maintain similar levels of AHR, whereas patients who discontinued ICS after 2 years experienced worsening AHR. Juniper et al<sup>13</sup> examined the effect of ICS reduction on AHR after 1 year of ICS therapy (budesonide 400-800 µg/d) and found that a 50% reduction in ICS dose was not associated with a change in AHR over a 3-month period. The patients who had greater improvements in AHR while receiving the higher doses of ICS were more likely to tolerate ICS reduction. Two recent studies have compared the approach of starting ICS therapy with a higher dose of ICS and then reducing ICS therapy with the approach of starting therapy at a lower dose of ICS; the investigators were unable to demonstrate a difference in the 2 strategies at the end of the study periods (18 weeks<sup>14</sup> and 1 year<sup>15</sup>). It thus appears that ICS reduction is possible in many patients, though ICS elimination is probably unlikely to be achievable in most.

The ability of LABAs to improve asthma control when added to ICS has led to the study of these agents as adjuncts to ICS in facilitating “step-down” therapy. Several studies have demonstrated that the addition of salmeterol in patients already receiving ICS facilitated reduction of ICS doses.<sup>16-20</sup> Lemanske et al<sup>17</sup> used salmeterol as an adjunct to moderate-dose ICS therapy in patients suboptimally controlled on ICS and demonstrated that the addition of salmeterol allowed for a 50%

**TABLE I.** Goals of asthma treatment

|                                                                                |
|--------------------------------------------------------------------------------|
| Prevent chronic and troublesome symptoms                                       |
| Maintain (near) “normal” lung function                                         |
| Maintain normal activity levels (including exercise)                           |
| Prevent recurrent exacerbations of asthma                                      |
| Minimize (or eliminate) emergency department visits and hospitalizations       |
| Provide optimal pharmacotherapy with minimal or no adverse effects             |
| Meet patients’ and families’ expectations of and satisfaction with asthma care |

Adapted from National Asthma Education and Prevention Program. Expert panel report II: guidelines for the diagnosis and management of asthma. Publication no. 97-4051A. Bethesda (MD): US Department of Health and Human Services; 1997.

reduction in ICS dose without deterioration in asthma symptoms scores or AHR. However, total elimination of ICS resulted in a significant decline in asthma control even with continued salmeterol therapy. The addition of an LABA thus facilitates ICS reduction but does not permit ICS elimination.

A third approach toward facilitating reduction in ICS dosing is the addition of an LTM. Patients receiving high-dose ICS (mean, >1500 µg/d) were able to significantly reduce their ICS dose with no decline in asthma control when montelukast was added to ICS therapy (47% reduction in ICS) in comparison with patients who received placebo in addition to ICS (30% reduction).<sup>21</sup> Similarly, the addition of pranlukast in patients maintained on high-dose ICS (>1500 µg/d) allowed for a 50% reduction in ICS dose without changing lung function, symptoms scores, or rescue bronchodilator use over a 6-week period.<sup>22</sup> Although the role of LTMs as facilitators of “step-down” therapy in patients receiving high-dose ICS therapy is suggested in these trials, data are not yet available as to the efficacy of this approach in patients on low-to-moderate-dose ICS.

Given the strong association of atopy and asthma, treatment directed against IgE has been examined for its ability to permit ICS reduction. Treatment with humanized monoclonal anti-IgE antibodies over a 20-week period was associated with statistically significant reductions in ICS and oral corticosteroid dose,<sup>23</sup> making this approach a potential future adjunct in “step-down” therapy.

In their study, Fowler et al<sup>1</sup> compared 2 potential approaches to “step-down” therapy. They enrolled 39 patients with asthma experiencing asthma symptoms at least 5 days per week and using rescue medications on a daily basis despite receiving at least 800 µg/d of beclomethasone dipropionate (BDP) or at least 200 µg/d of BDP with second-line therapy. If patients were controlled on their current dose of ICS, the dose of ICS was reduced until the patients developed this level of symptoms. Thus, each patient entered this trial from one of 3 possible therapeutic starting points, and the numbers of patients from the 3 potential prestudy treatment groups (those receiving BDP ≥800 µg/d; those receiving BDP ≥200 µg/d in combination with a second agent; and those

requiring ICS reduction to develop sufficient symptoms) are not specified. All patients were initially treated with high-dose ICS (BDP 2000 µg/d via dry powder inhaler [DPI]) for 4 weeks in an attempt to rapidly achieve control of their asthma. Patients were then randomized to one of the following treatment approaches: (1) changing to an alternate ICS (BDP-hydrofluoroalkane 134a [HFA]) at a dose of 400 µg/d or (2) a combination of fluticasone propionate (FP) 100 µg and salmeterol 50 µg via a DPI twice daily for 8 weeks. AHR after 8 weeks of therapy with either BDP-HFA or FP/salmeterol served as the primary outcome measure.

Initial treatment with high-dose ICS (BDP 2000 µg/d) led to statistically significant improvements in AHR (approximately 1 doubling dose of methacholine). Patients who subsequently received the combination of ICS and LABA experienced even greater improvements in AHR (an additional doubling dose) than were seen with high-dose ICS alone, whereas the patients who were switched to the lower ICS dose maintained the same level of AHR. After 4 and 8 weeks of treatment, the group receiving the combination therapy (FP/salmeterol) was statistically superior, in terms of AHR, to the group receiving moderate-dose ICS alone. However, because methacholine challenge was performed less than 12 hours after a dose of LABA, it is difficult to separate the protective effects of LABA on methacholine-induced airway narrowing from a true reduction in AHR. These results would have been more convincing if LABA had been withheld for at least 24 hours before methacholine challenge.

Somewhat surprising is the fact that though patients demonstrated an improvement in lung function during the high-dose ICS phase, patients receiving moderate-dose ICS (BDP-HFA 400 µg/d) experienced a decline in lung function measures, whereas those receiving FP/salmeterol had improved measures of pulmonary function. Symptom scores, however, did not differ between the 2 approaches. Anti-inflammatory effects, reflected by decreasing levels of ECP in serum, were demonstrable after the initial BDP-DPI treatment and were maintained with BDP-HFA, but serum ECP levels rose in patients treated with FP/salmeterol, demonstrating the lack of clinically relevant anti-inflammatory activity of LABAs.<sup>24</sup> The authors conclude that once asthma control has been achieved with high-dose ICS, "stepping down" to a combination of ICS and LABA is superior to "stepping down" to a lower dose of ICS in terms of AHR and pulmonary function, though the lack of LABA washout complicates the interpretation of these findings. Furthermore, no clinically significant differences were apparent in most secondary outcome measures, including symptom scores, and the BDP-HFA approach was superior to the combination therapy in terms of markers of allergic inflammation.

Interpretation of the results of this study is further complicated by the fact that 2 different ICS products (different molecules with differing delivery systems) were used during the treatment phase, inasmuch as the true relative potencies of the FP-DPI and BDP-HFA are not well described. The use of various doses of the same ICS mol-

ecule and delivery system (such as FP 200 µg bid versus FP 100 µg/salmeterol 50 µg bid) would have simplified the interpretation and extrapolation of these findings. Second, this study was statistically powered to detect a one-doubling-dose change in AHR and was likely underpowered to detect differences in many of the secondary outcome measures, including symptom scores, rescue medication use, and overall quality of life measures.

It is to be hoped that this study is the beginning of a series of clinical trials addressing the concept of "step-down" therapy in asthma. Future studies focusing on direct, head-to-head comparisons of a variety of "step-down" approaches will be critical in shaping the clinical approach to the patient who has achieved asthma control. Furthermore, future studies should examine additional nonspirometric indicators of asthma control, such as symptom-free days, exacerbation rates, and treatment failures, because these are the outcomes that matter most to patients.

In contrast to candidates for "step-up" therapy, who are easily identifiable from their uncontrolled asthma symptoms, candidates for "step-down" therapy are less obvious. Identification of features that might be predictive of success with a "step-down" approach would provide clinicians with practical criteria that would probably increase the likelihood of prescribing a "step-down" approach. Ideally, incorporation of noninvasive markers of airway inflammation, such as exhaled nitric oxide, could provide additional support for optimal "step-down" therapy.

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