Stepping down asthma treatment: how and when

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Purpose of review
Guidelines suggest that asthma medication should be reduced once asthma control is sustained. Moderate-dose inhaled corticosteroids (ICS) can typically be reduced, but questions remain about the lowest effective ICS dose and the role of non-ICS controllers in treatment reduction. Long-acting beta agonist (LABA) safety concerns have created controversy about how to step down patients on ICS/LABA therapy. This review will focus on the current status of these issues.

Recent findings
Intermittent ICS treatment, often in fixed combination with short-acting beta agonist, is an emerging strategy for control of mild asthma. Addition of leukotriene modifiers, LABAs, and omalizumab to ICS can allow for reduced ICS dosing. Doses of ICS that control symptoms may be inadequate to control exacerbations. Reducing ICS dose before discontinuing LABAs may be the more effective approach for patients on combination therapy.

Summary
Use of non-ICS controllers allows for ICS dose reduction with superior outcomes. Tapering of ICS prior to LABA discontinuation may be the favored approach for patients on ICS/LABA therapy, but an understanding of long-term outcomes and further safety data are required. The lowest ICS dose that adequately controls both asthma impairment and risk remains to be determined.

Keywords
asthma, inhaled corticosteroids, long-acting beta agonists, step-down

INTRODUCTION

Asthma guidelines focus on achieving and maintaining asthma control and balancing the risk of medications with control of disease [1,2]. They suggest that once symptoms are controlled for at least 3 months, therapy can be reduced to the lowest dose that maintains control. Despite these recommendations, questions remain about when and how to reduce asthma therapy. Benefits of inhaled corticosteroids (ICS) are well established, and adverse effects are uncommon at low and moderate doses [3]. However, concerns about adverse effects remain, particularly with sustained high doses, and include osteoporosis, adrenal axis suppression, cataracts, hoarseness, dysphonia, oral candidiasis, and dermal thinning and bruising. Recent links of ICS to diabetes and pneumonia are cause for concern and require further investigation [4▪▪,5,6]. HIV patients on antiretroviral therapy and ICS can have significant systemic absorption and adverse effects [7]. Ongoing concerns in children include continued evidence of reduced growth velocity without an ultimate impact on adult height [8,9▪▪]. Apart from concerns about adverse effects of higher doses of ICS, safety concerns about long-acting beta agonists (LABAs) create questions about the optimal way to reduce combination ICS/LABA therapy [10]. Carefully monitored therapy reduction trials can clarify disease severity and reduce over-treatment. This review will discuss the current state of knowledge of how one should reduce therapy when asthma control is sustained.

CAN DAILY LOW-DOSE INHALED CORTICOSTEROIDS BE REDUCED OR STOPPED IN MILD-TO-MODERATE PERSISTENT ASTHMA?

Once on low-dose therapy, the risk of adverse effects of ICS is low [3,4▪▪,11,12]. However, patients and some providers still have doubts about ICS safety, leading to the desire to reduce or stop these

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KEY POINTS

- Although step-down of asthma therapy is recommended once asthma control is sustained for at least 3 months, questions remain about when and how to reduce treatment.
- In milder patients, ICS can often be reduced by 50%, and intermittent ICS treatment, often in fixed combination with short-acting beta agonist, is an emerging strategy for control of mild asthma.
- A large body of data now support omalizumab as a treatment that can allow for reduction of ICS dosing, but its use is limited by expense and logistics of administration.
- Although data are mixed, biomarkers including FeNO are not clearly helpful at determining which patients can have therapy reduced and are often not available in many practice settings.
- In patients on fixed-dose combination ICS/LABA, data currently suggests that reducing ICS dose before discontinuing LABA may be the more effective approach for patients on combination therapy, but more data are needed.

medications [13,14]. When mild asthma is controlled, ICS can often be reduced by 50%, but reducing therapy is less successful with rapid medication tapering and in moderate-to-severe disease [15–18]. Roughly 50% of children and adults will redevelop symptoms within 1–12 months if ICS are stopped [16–19]. Seasonal effects are noted, with greater success weaning in spring and summer, and more failure in the fall [20]. In adults with persistent asthma, the ability to achieve sustained discontinuation of ICS with good control is rare [21].

More recently, the utility of biomarkers such as sputum eosinophilia [22,23], exhaled nitric oxide [24,25], and suppression of bronchial hyperreactivity (BHR) [26,27] have been considered as tools to guide step-down of asthma therapy. Results are inconclusive, and even the best studied of these approaches, the fraction of exhaled nitric oxide (FeNO), cannot consistently predict which patients tolerate reduced therapy [28▪▪]. Sputum eosinophilia has fared the best as a biomarker of loss of control, but access to biomarker monitoring is not widely available in primary care settings where most mild-to-moderate asthmatics receive their care [28▪▪].

The use of ICS on an 'as needed' basis either alone or paired in the same inhaler with a short-acting beta agonist may minimize ICS exposure. Step-down from daily ICS to symptom-driven use of fixed-dose combination ICS (beclomethasone) and short-acting beta agonist (SABA) was as effective with a lower ICS dose over 6 months compared to daily ICS [29]. Questions remain: will this strategy remain effective over time? In the Treating Children to Prevent Exacerbations (TREXA) study, 288 children aged 5–18 stabilized on 80 μg beclomethasone daily were stepped down to either daily ICS plus additional rescue ICS as needed, daily ICS alone, rescue ICS alone, or placebo in a 44-week study. Exacerbations were lower in the daily ICS (28%, 18–40, $P = 0.03$), combined (31%, 21–43, $P = 0.07$), and rescue (35%, 24–47, $P = 0.07$) groups compared to placebo (49%) [9▪▪]. Treatment failure occurred in 23% (95% CI 14–43) of the placebo group, compared with 5.6% (1.6–14) in the combined ($P = 0.012$), 2.8% (0–10) in the daily ($P = 0.009$), and 8.5% (2–15) in the rescue ($P = 0.024$) groups. Overall daily therapy had the best outcomes, but rescue therapy was better than placebo and may reflect real-world patient behavior [30].

In summary, reduction of ICS dose is often successful in well controlled mild asthma. Long-term cessation of ICS can be achieved at times in children, but is rarely successful in adults. Few biomarkers accurately determine which patients can have therapy reduced and these techniques are often not available in many practice settings. Approaches using low-dose ICS plus additional as-needed ICS or as-needed ICS/SABA combination require further study.

STEPPING DOWN INHALED CORTICOSTEROIDS WITH THE USE OF NON-INHALED CORTICOSTEROIDS ANTI-INFLAMMATORY CONTROLLERS

When escalating therapy in uncontrolled asthma, addition of nonsteroid agents is favored over increasing to high-dose ICS for most patients [1,2]. Less data are available to suggest that this approach 'works in reverse' – that lowering ICS prior to removing nonsteroid drugs is effective at sustaining asthma control. Recent systematic reviews reinforce that LABAs are effective at controlling asthma with lower ICS doses [31]. Leukotriene modifiers (LTMs) are effective as add-on therapy in asthma not controlled on low-dose ICS, but not as effective as LABAs in adults and possibly children [32,33]. LTM may allow treatment reduction, but complete cessation of ICS with step-down to LTM or LABA alone is associated with a significant loss of asthma control compared to maintenance of ICS [34–36].

There are ample data documenting that omalizumab (anti-IgE) allows reduced ICS dosing. A 2011 systematic review including eight trials and

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3429 patients found that omalizumab-treated patients were able to reduce their ICS by 50% or discontinue it entirely [37▪]. In the Inner-City Anti-IgE Therapy for Asthma (ICATA) Study, inner-city children with moderate-to-severe asthma treated with omalizumab plus guidelines-based treatment experienced a 30–48% reduction in exacerbations, including elimination of seasonal peaks, and better control on less ICS and LABA use [38▪▪]. Although perhaps justified in moderate-to-severe disease, enthusiasm for this approach must by tempered by the fact that omalizumab has an average wholesale price of $4000–$20 000 per year [39]. Given that risk of clinically significant long-term side-effects of low-to-moderate dose ICS are low, and the modest median ICS dose reduction observed in pooled omalizumab data (median reduced ICS = 141 μg budesonide), use of an expensive, resource intensive medication to taper ICS beyond low-to-moderate dose may not be warranted.

STEPPING DOWN FIXED-DOSE COMBINATION THERAPY: REDUCE INHALED CORTICOSTEROIDS OR STOP LONG-ACTING BETA AGONIST?

One of the most common dilemmas currently faced by practicing physicians is how to reduce ICS/LABA once asthma is controlled. Guidelines recommend a two-step approach: reducing the ICS by 50% and maintaining the LABA, and stopping the LABA if control is sustained with low-dose ICS [2]. In February 2010, in the context of ongoing debates about LABA safety, the US Food and Drug Administration recommended that LABAs be used for the shortest duration of time required to control asthma and that LABA therapy should be discontinued if possible once asthma control is achieved [40]. Regulatory agencies worldwide have not issued a similar recommendation [41]. This recommendation has been interpreted to suggest that LABA should preferentially be discontinued prior to lowering ICS, which is in conflict with at least some guidelines [2]. To date, some limited data are available comparing these two methods of reducing fixed-dose combination therapy, and published studies on this issue are outlined in Table 1.

Reducing ICS dose prior to discontinuing LABA is supported by several early studies in which the addition of LABA to ICS allowed a reduction in ICS dose without loss of asthma control [18,35,42]. Steroid naïve patients with moderate persistent asthma controlled on fluticasone/salmeterol (FSC) 250/50 twice daily were randomized to a 12-week step-down comparing fluticasone 250 twice daily vs. FSC 100/50 twice daily [43]. Peak expiratory flow

Table 1. Step-down from fixed-dose combination ICS/LABA

Study/reference	Design	*n*	Duration	Population	Intervention	Primary outcome	Results	Comment
Koenig *et al.* [36]	RDBPG	647	16 weeks	Uncontrolled on low–moderate ICS but controlled on FSC 100/50	Step-down to FP100, SAL 50 or montelukast	PEF	Control deteriorated in all step-down groups	
Fowler *et al.* [42]	RDBPG	39	12 weeks	Moderate–severe asthma	1000 BDP b.i.d. × 4 weeks then BDP 200 2× daily or FSC 100/50 2× daily	PC20	Doubling dose improvement in MCT with FSC greater than either BDP dose	Lung function and QOL better on FSC vs. BDP step-down
Bateman *et al.* [43]	RDBPG	484	24 weeks	Moderate asthma, well controlled	FSC 250/50 stepped down to FSC 100/50 vs. FP 250	PEF	PEF lower in FP vs. FSC	Symptoms, rescue albuterol and control better on FSC than FP
Godard *et al.* [44]	RDBPG	473	6 months	Well controlled on FSC 250/50	Decrease to FSC 100/50 vs. FP 250	PEF	FSC 100/50 similar to 250/50 but better than FP 250	
Reddel *et al.* [45▪]	RDBPG	82	13 months	FSC 500/50	500/50 vs. FP 500 and down titrated every 8 weeks	Mean daily FP dose	No difference in mean daily dose FP but final dose lower in FSC	Question if patients were over treated

BDP, beclomethasone dipropionate; BHR, bronchial hyperreactivity; CS, corticosteroids; FP, fluticasone; FSC, fluticasone/salmeterol; ICS, inhaled corticosteroid; MCT, methacholine challenge test; PEF, peak expiratory flow; QOL, quality of life; RDBPG, randomized double-blinded parallel group; SAL, salmeterol.

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(PEF), the primary endpoint, was maintained in the FSC100/50 group, but decreased slightly in fluticasone group. The proportion of patients with well controlled asthma, a secondary endpoint, was reduced in both groups compared to 250/50, but remained higher in FSC vs. fluticasone. In a study by Koenig *et al*. [36], patients uncontrolled on low-dose ICS but controlled on FSC 100/50 for 4 weeks were either continued on FSC or stepped down to either same dose fluticasone alone (100 μg), salmeterol alone (50 μg), or montelukast alone. FSC was superior for all endpoints [morning PEF, forced exhaled volume in 1 s (FEV_1), symptom scores, and likelihood of remaining in the study]. Similarly, in a 6-month trial of patients well controlled on FSC 250/50 twice daily who were stepped down to FSC 100/50 or fluticasone 250 twice daily, FSC 100/50 was better than fluticasone at maintaining lung function and symptom control [44]. FSC 100/50 was noninferior to continuing FSC 250. The withdrawal rate in the fluticasone group (20%) was double that of either FSC 250 (11%) or FSC 100 (9%). Recently, Reddel *et al.* [45▪] stepped down patients from FSC 500 twice daily to either fluticasone 500 twice daily or progressively lower dose FSC at 8-week intervals. No difference was found in the primary endpoint (mean fluticasone dose), but the FSC group achieved a lower final ICS dose than the fluticasone group. Finally, in a complex retrospective study of a large managed care claims database, patients stepped down from higher to lower dose FSC compared to fluticasone alone had less SABA use (30%, 1.72 vs. 2.48, $P = 0.001$), 26% lower risk of systemic corticosteroid use (24 vs. 32%, $P = 0.006$), 48% lower risk of an asthma-related hospitalization or ED visit (3.8 vs. 7.4%, $P = 0.01$), and higher refill persistence rates compared with fluticasone [46▪]. Although data so far suggest improved outcomes maintaining LABA during step-down, given the short step-down phases in most studies (12–24 weeks) and use of primary outcomes such as PEF rather than composite measures of control or exacerbation rates, a definitive answer awaits further study. Efficacy studies such as these are always underpowered to address the issue of LABA safety, a critical issue in weighing risks vs. benefits of asthma therapies. A best estimate of the risk of adverse effects of LABA is important, and is an area of significant controversy that may or may not be clarified with the upcoming US FDA mandated LABA safety mega-trial [47].

More recent trials of adjustable and maintenance dosing of combination budesonide and formoterol (Bud/Form) suggest that adjustable vs. fixed therapy may be associated with equal symptom control at lower ICS doses [48]. In a complex study that simultaneously compared the effects of lowering ICS, removing LABA, and once vs. twice daily ICS dosing, twice-daily Bud/Form generally fared better than once daily ICS or ICS/LABA. Combination therapy once or twice daily fared better than ICS alone [49▪]. Enthusiasm for this approach has been somewhat hampered by LABA safety concerns, although a recent meta-analysis did not show an increased risk of adverse events compared with fixed dosing of ICS/LABA [50]. Further studies of adjustable and maintenance dosing of Bud/Form as a means of reducing medication once asthma is controlled seem warranted.

IS STEPPING DOWN BEYOND MODERATE-DOSE INHALED CORTICOSTEROIDS IN ADULTS AND LOW-DOSE INHALED CORTICOSTEROIDS IN CHILDREN NECESSARY?

Once asthma control is achieved and sustained, how low should the ICS dose be reduced? Low and moderate dose ICS do not differ in terms of symptom control, but moderate-dose ICS may have a slight advantage in terms of lung function (FEV_1 in adults but not children) and at reducing exacerbations [51]. Good data suggest that the long-term safety profile of low-to-moderate dose ICS is favorable [3,12,52]. In adults with persistent asthma, continuation of moderate dose (FSC 250) ICS/LABA resulted in marginally better symptom control and lung function compared to adjustable and maintenance Bud/Form, but a striking 50% lower exacerbation rate [53]. At the end of 1 year, both groups ended up on just under 500 μg daily of either fluticasone or budesonde, respectively. This study suggests that patient-dictated adjustment of medication according to symptoms slightly lowers ICS exposure, but possibly at the cost of a higher exacerbation rate. It also suggests that there is a minimum daily ICS dose needed to prevent exacerbations, at least in adults. The suggestion has been made to use low-dose ICS and then increase ICS at the first signs of an exacerbation. Data evaluating this approach show that doubling ICS does not prevent exacerbations [54]. It seems that once control is lost, it may not be easily regained. These findings highlight the critical need for long-term, step-down studies in both children and adults. If the tradeoff of reduced ICS results in additional exacerbations per year, any benefit gained by ICS reduction may be offset by greater exposure to systemic steroids. In adults, where asthma remission is uncommon, and comorbid conditions abound, the addition of even one extra course of oral steroids per year over many years may carry more risk of adverse events than

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maintenance of moderate-dose ICS. In terms of risk of accelerated decline of lung function, prevention by ICS is currently not supported by data and further study is needed [11,55]. A key study would be a long-term study along the lines of the Childhood Asthma Management Program study, including both children and adults and comparing reducing ICS vs. maintaining stable dosing and evaluating long-term outcomes and adverse effects [11].

CONCLUSION

Although step-down of controller medication to the lowest dose which controls asthma is an appropriate goal, many unanswered questions remain regarding how to best accomplish this, and what the ultimate 'lowest' dose should be. Current recommendations for step-down of therapy do not account for the heterogeneity of asthma, do not make clear distinctions based on disease severity, and do not sufficiently incorporate consideration of disease risk. Current data is overrepresented with short-term studies that may underestimate the risk of exacerbations on lower medication dosing and may overstate the benefits of lower dosing compared to risks. More data are needed regarding the ideal duration of control prior to tapering, and the best approach to stepping down patients with severe asthma, particularly those on moderate-to-high dose ICS/LABA. It is unclear whether the outcomes of clinical trials, in which patients undergo careful monitoring, is representative of outcomes that can be achieved in general practice settings. Pragmatic clinical trials that recreate typical practice may be needed for better answers.

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Conflicts of interest

J.R. and L.R. are investigators for the American Lung Association Asthma Clinical Research Centers (ALAACRC). The ALAACRC is currently funded for a study looking at the best approach to stepping down asthma therapy for patients on fixed dose combination inhaled corticosteroids and long acting beta agonists. The study is funded by the American Lung Association through a grant from Glaxo Smith Kline (GSK). Neither of the authors receive salary for their roles as ACRC investigators, nor do they receive any form of compensation from GSK.

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