

The Risks, Benefits, and Uncertainties of Stepping Down Asthma Medications

Matthew A. Rank, MD^a, and Stephen P. Peters, MD, PhD^b *Scottsdale, Ariz, and Winston-Salem, NC*

INFORMATION FOR CATEGORY 1 CME CREDIT

Credit can now be obtained, free for a limited time, by reading the review articles in this issue. Please note the following instructions.

Method of Physician Participation in Learning Process: The core material for these activities can be read in this issue of the Journal or online at the *JACI: In Practice* Web site: www.jaci-inpractice.org/. The accompanying tests may only be submitted online at www.jaci-inpractice.org/. Fax or other copies will not be accepted.

Date of Original Release: September 2014. Credit may be obtained for these courses until October 31, 2015.

Copyright Statement: Copyright 2014-2016. All rights reserved.

Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

Accreditation/Provider Statements and Credit Designation: The American Academy of Allergy, Asthma & Immunology (AAAAI) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The AAAAI designates these educational activities for a maximum of 1 AMA PRA Category 1 Credit. Physicians should only claim credit commensurate with the extent of their participation in the activity.

List of Design Committee Members: Matthew A. Rank, MD, and Stephen P. Peters, MD, PhD

Activity Objectives

1. Understand the risks associated with stepping down asthma medications in ways that lead to a more informed decision with patients.
2. Incorporate specific patient characteristics into decisions about stepping down asthma medications.
3. Consider the multiple options regarding how to practically accomplish the step down of asthma medications.

Recognition of Commercial Support: This CME has not received external commercial support.

Disclosure of Significant Relationships with Relevant Commercial Companies/Organizations: S. P. Peters has received consultancy fees from AstraZeneca, Aerocrine, Airsonett, AB, Boehringer Ingelheim, GlaxoSmithKline, Merck, Ono Pharmaceuticals, Pfizer, PP Development, Quintiles, Sunovion, Targacept, and Teva; has received research support from the National Heart, Lung and Blood Institute (AsthmaNet, SARP, SPIROMICS), and the American Lung Association (Asthma Clinical Research Centers); has received lecture fees from Integrity CE and Merck; and receives royalties from UpToDate. M. A. Rank declares he has no relevant conflicts of interest.

Stepwise adjustments have been suggested as a framework to manage chronic asthma over time. In this framework, individuals with good asthma control and a low risk for future

asthma exacerbations may be considered for a reduction or “step down” of their chronic asthma medications. In this article, we discuss how patients may benefit or be harmed by stepping down asthma medications. Based on the literature presented in this article, we recommend that clinicians discuss the option of stepping down with patients when symptoms are stable, lung function is near normal, and biomarkers (if measured) are near normal. Other factors that should be considered in the decision to step down include the length of asthma stability, age of the patient, time of year, and patient preferences. Reducing the dose of inhaled corticosteroid by 25% to 50% appears to be the safest method of stepping down. A clear plan of care and follow-up is needed when stepping down asthma medications because many patients are likely to have recurrent exacerbations. © 2014 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2014;2:503-9)

Key words: Asthma; Anti-asthmatic agents; Step down; Withdraw; Discontinue; Decrease; Wean; Cessation

Asthma is a chronic airways disease with variable clinical expression related to complex interactions between genetic and environmental factors.¹ A stepwise approach to treatment has

^aDivision of Allergy, Asthma, and Clinical Immunology, Mayo Clinic, Scottsdale, Ariz

^bCenter for Genomics and Personalized Medicine Research, Wake Forest School of Medicine, Winston-Salem, NC

No funding was received for this work.

Conflicts of interest: S. P. Peters has received consultancy fees from AstraZeneca, Aerocrine, Airsonett, AB, Boehringer Ingelheim, GlaxoSmithKline, Merck, Ono Pharmaceuticals, Pfizer, PP Development, Quintiles, Sunovion, Targacept, and Teva; has received research support from the National Heart, Lung and Blood Institute (AsthmaNet, SARP, SPIROMICS), and the American Lung Association (Asthma Clinical Research Centers); has received lecture fees from Integrity CE and Merck; and receives royalties from UpToDate. M. A. Rank declares he has no relevant conflicts of interest.

Received for publication February 4, 2014; revised March 20, 2014; accepted for publication March 21, 2014.

Available online May 1, 2014.

Corresponding author: Matthew A. Rank, MD, Mayo Clinic Division of Allergy, Asthma, and Clinical Immunology, 13400 E Shea Blvd, Scottsdale, AZ 85259. E-mail: rank.matthew@mayo.edu.

2213-2198/\$36.00

© 2014 American Academy of Allergy, Asthma & Immunology

<http://dx.doi.org/10.1016/j.jaip.2014.03.004>

*Abbreviations used**ICS- Inhaled corticosteroid**LABA- Long-acting β -agonist**LTRA- Leukotriene receptor antagonist**RCT- Randomized controlled trial*

been suggested as a framework to manage chronic asthma over time (National Asthma Education and Prevention Program, Global Initiative for Asthma). In this framework, individuals who have poor asthma control and/or a high risk for future exacerbations are considered for increased asthma medicine doses or alternative asthma medications. Conversely, individuals with good asthma control and a low risk for future exacerbations are considered for decreased asthma medication, or “step down.” The most recent asthma guidelines suggest that step down of asthma medications be considered when asthma has been stable for 3 months,^{1,2} and a reduction of inhaled corticosteroid (ICS) dose of 25% to 50% as a preferred means of accomplishing step down.² These recommendations are supported by low levels of evidence, which result in uncertainty about the risks and benefits of stepping down asthma medications. In this article, we discuss how patients can benefit from stepping down asthma medications, how they could be harmed by stepping down, when to step down asthma medications, and how to practically accomplish this in the context of the patient-clinician interaction. Next, we will identify key gaps in our understanding of asthma step down and suggest how these gaps can be filled by future research studies. Finally, we provide management recommendations for stepping down asthma medications based on the currently available evidence.

REASONS TO STEP DOWN FROM A PATIENT'S PERSPECTIVE

Why consider stepping down asthma medications at all? After all, if a patient is not having problems with asthma and is taking an asthma medication that appears to be tolerated, why not simply continue the medication? First, adverse effects of asthma medications may not be immediately apparent. Although asthma medications are generally well tolerated and safe, several risks have been reported, including risks of long-term growth suppression,³ pneumonia,⁴ and “black box” warnings of potentially life-threatening asthma exacerbations.⁵ In addition, readily apparent adverse effects, such as oral candidiasis and hoarseness, may impact quality of life in the short term.⁶ Second, patients and their families may have preferences to avoid medications, and incorporating patient preferences into decisions about their health care is an obligation of the clinician.⁷ Taking medications is associated with a burden of treatment, which may include taking time to take medications properly and to ensure that the medication is available to take (eg, interactions with pharmacy and insurance). In one community-based study of patients with stable asthma who underwent progressive step down of asthma medication, asthma-specific quality of life significantly improved after step down across all domains (symptoms, activity limitations, emotional function, and environmental stimuli).⁸ We speculate that this increased quality of life is related to a lower treatment burden for patients after asthma medication is stepped down. Third, asthma medications can be costly, and the costs can be a source of stress for patients.⁹ Cost trends in asthma

management suggest that asthma medication costs are the primary driver for increasing overall costs of managing asthma.¹⁰ Patients who can be successfully managed with less asthma medication have additional money available for other things, some of which may contribute to their overall health (eg, education, gym membership, healthier eating, managing other medical problems). The financial benefits of stepping down asthma medications remain theoretical at this point because a formal study design that accounts for the costs associated with the possibility of increasing symptoms (and potential missed work and/or school, emergency department costs, etc) is needed. Fourth, stepping down asthma medications may simplify the treatment program such that it facilitates better adherence.

Examples of simplification would be changing from administering an inhaler multiple times per day to once per day, changing an inhaler to an oral medication (“pill”), or changing from a fixed dosing schedule to an on-demand, patient-driven timing of inhaler administration. Long-term adherence and outcomes with step down strategies are poorly understood because many of the step down studies have been performed in the context of a clinical study in which adherence may be inflated due to study participation. A case-control study of a general practice database in the United Kingdom selected individuals who were stepping down asthma medications and going from twice daily to daily dosing, found no difference in adherence rates during the subsequent year.¹¹ Taken together, many benefits may exist for those who step down asthma medications. However, these benefits are not well studied and must be balanced by risks (Figure 1).

REASONS NOT TO STEP DOWN FROM A PATIENT'S PERSPECTIVE

Stepping down asthma medication may lead to an increased risk of having an asthma exacerbation or loss of asthma control. Defining this risk as precisely as possible so patients and clinicians can have an informed discussion is limited by the number of studies designed to define these risks. Next, we consider studies that provide estimates for the risks of stepping down asthma medications.

RANDOMIZED CONTROLLED TRIALS OF STEPPING DOWN ASTHMA THERAPY

ICS—long-acting β -agonist to ICS alone

Four studies measured the risk when stable asthmatics step-off from ICS long-acting β -agonist (LABA) to ICS alone.¹²⁻¹⁵ An additional unpublished study was identified by Brozek et al¹⁶ during a systematic review. These studies included mostly adults (none enrolled children younger than 15 years old) and had individuals with 4- to 8-week periods of asthma stability. In a meta-analysis of 5 trials, a relative risk of 2.24 (95% CI, 0.79-6.35) was found for an emergency department visit or unscheduled consultation for asthma and 1.68 (95% CI, 0.84-3.38) for any use of systemic corticosteroids for asthma (there were no deaths, intensive care unit admission, mechanical ventilation, or hospitalization events in any of the included studies).¹⁶ Due to few events that define asthma exacerbations in the included studies, the risk of stepping down from ICS-LABA to ICS is not well defined (CIs for risk estimates are wide); a small worsening of asthma control and quality of life were noted of the group stepping down to ICS alone, based on 3 studies^{12,14,15} and 2

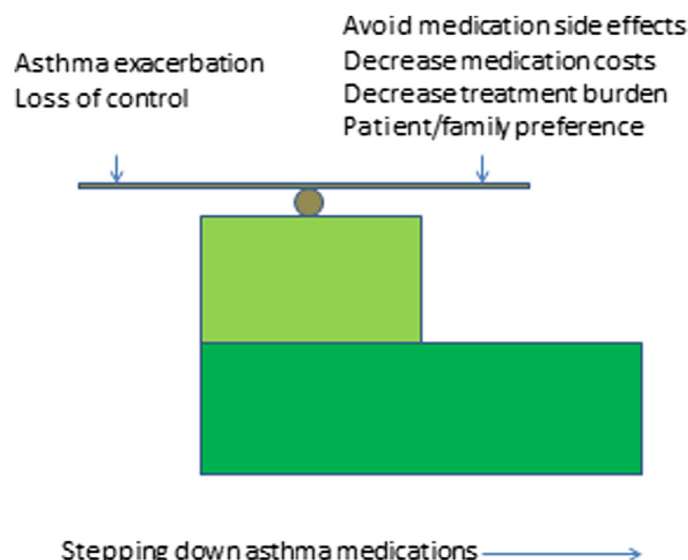


FIGURE 1. Theoretical risks and benefits of stepping down asthma medications.

studies,^{14,15} respectively.¹⁶ In summary, the risk of stepping down from ICS-LABA to ICS alone is not well characterized. Additional studies are needed, especially to clarify the risks of asthma exacerbations after ICS-LABA is stepped down to ICS alone.

ICS to reduced ICS

Four randomized controlled trials (RCT) describe the outcomes of stepping down from ICS to a lower dose of ICS.¹⁷⁻²⁰ These studies include both children^{18,19} and adults,^{17,20} and have stability periods of between 4 and 52 weeks before the step down attempt. Two RCTs describe the outcomes of reducing ICS dose by going from a fixed schedule of ICS dosing to on-demand ICS dosing.^{21,22} One of these trials found an increased risk of asthma exacerbation (35%) in the ICS on-demand group compared with the group that continued ICS by using scheduled doses (28%) but a decreased risk compared with those who stopped ICS altogether (49%); this study had a trial period of 44 weeks and included only children ages 6 to 18 years old.²¹

In another trial, which included a study arm of on-demand ICS, adults with stable asthma and ages 18 to 65 years old assessed for 24 weeks had similar per patient exacerbation rates if they continued ICS (0.71) or if they used ICS on-demand (0.74).²² A meta-analysis that included these 6 RCTs found a relative risk of only 1.25 (95% CI, 0.96-1.62; $P = .10$) of asthma exacerbation in those who reduced the ICS dose by 50% or more compared with those who maintained a stable dose, which supported the notion of a lower risk with lesser reduction of ICS.²³ A sensitivity analysis excluding the 2 RCTs that involved on-demand ICS in the intervention arm came to a similar relative risk of 1.28 (95% CI, 0.93-1.76; $P = .14$). Results of this meta-analysis suggest that the risk of asthma exacerbations in individuals who reduce the ICS dose is similar (not statistically different) to those who continue ICS. Measuring the outcomes after longer-term follow-up and after smaller reductions in ICS dose (25%-50% reduction compared with 50%-85% in the meta-analysis) are future questions that merit additional study.

Reducing the ICS dose also may be an opportunity to reduce the frequency of ICS administration from multiple times daily to once daily, potentially improving adherence and improving quality of life.¹¹ In a retrospective study of a large database, reducing ICS to daily use was associated with improved adherence and no significant change in asthma control.²⁴ Therefore, the frequency of ICS administration should be a factor that is considered when reducing ICS.

ICS to nonsteroid medication

One trial estimated the risk in substituting leukotriene receptor antagonists (LTRA) for ICS and found an increased risk of treatment failure for the LTRA group (30%) compared with the group that continued ICS (20%).²⁵ This multicenter trial included 168 individuals who continued ICS and 165 who substituted LTRA with a run-in period to ensure stability of 4 to 6 weeks and a 16-week trial period. Results of previous studies suggest that superior adherence to oral medications when compared with ICS may be another advantage of stepping down for an ICS to a nonsteroid medication.²⁶⁻²⁸ Additional studies that consider this strategy or alternative strategies are needed.

ICS to no ICS

To estimate the risk of stopping low-dose ICS compared with continuing low-dose ICS in RCTs that included at least 4 weeks of monitored stability and 12 weeks of follow-up, 7 studies were identified and together found a relative risk of 2.35 (95% CI, 1.88-2.92; $P < .001$) of having an asthma exacerbation for those who stopped low-dose ICS in studies with a mean follow-up period of 27 weeks.^{14,21,22,29-33} Put another way, individuals with stable asthma on low-dose ICS have a 16% risk of having an asthma exacerbation over the next 6 months if they continue the low-dose ICS compared with a 38% risk if the low-dose ICS is discontinued. The studies included in the meta-analysis were generally considered to be at low or unclear risk of bias,³⁴ and the inconsistency of the outcomes, as measured by the I^2 value, was low (0%). Both children and adults were included in most of the included studies; prespecified subgroup analysis found no

TABLE I. Summary of key RCTs of asthma step down by types

Step down method	Population studied, age (y)	Outcomes
ICS-LABA to ICS alone		
Koenig et al, ¹³ 2008	>15	Decreased asthma control (composite measure) in the ICS-alone group
Godard et al, ¹² 2008	>18	Decreased peak flow and asthma control in the ICS alone group
Reddel et al, ¹⁵ 2010	18-80	No significant differences between groups
Berger et al, ¹⁴ 2010	>16	Decreased asthma control and quality of life in the ICS alone group
ICS to reduced ICS		
Juniper et al, ¹⁷ 1991	>18	Decline in FEV ₁ in reduced ICS group
ZuWallack et al, ¹⁸ 1997	6-70	Decline in PEF in reduced ICS group
Visser et al, ¹⁹ 2001	6-10	No significant differences between groups
Hawkins et al, ²⁰ 2003	18-86	No significant differences between groups
ICS to on-demand ICS		
Papi et al, ²² 2007	18-65	No significant differences between groups
Martinez et al, ²¹ 2011	6-18	No significant differences between groups
ICS to LTRA		
American Lung Association Asthma Clinical Research Network, ²⁵ 2007	>6	Increased risk of treatment failure in the LTRA group
ICS to no controller		
Waalkens et al, ³⁰ 1993	7-16	No significant differences between groups
Haahela et al, ³¹ 1994	>15	Decline in FEV ₁ in the no controller group
Condemi et al, ³² 1997	>12	Increased risk of asthma exacerbation, decline in FEV ₁ , decline in PEF, and increased symptoms in the no controller group
Lazarus et al, ³³ 2001	12-65	Increased risk of asthma exacerbation, decline in PEF, and increased symptoms in the no controller group
Papi et al, ²² 2007	18-65	Increased risk of asthma exacerbation, decline in PEF, and increased symptoms in the no controller group
Berger et al, ¹⁴ 2010	>16	Increased risk of asthma exacerbation in the no controller group
Martinez et al, ²¹ 2011	6-18	Increased risk of asthma exacerbation in the no controller group

PEF, peak expiratory flow.

differences in outcomes for pediatric studies or for studies with longer follow-up periods. Of note, the mean of the follow-up period to assess for asthma exacerbation after step down was 27 weeks (range, 12-52 weeks), which makes conclusions about long-term safety of asthma step down less certain. The information from this meta-analysis provides a risk estimate that can be used for discussions between clinicians and patients when deciding about asthma step down.

Summary of RCTs that examined step down of asthma medications

Analysis of these studies when taken together suggests that each of these methods of stepping down from ICS-reduced ICS dose scheduled, on-demand ICS, or substitution of LTRA may be safe options for many patients with stable asthma. However, each of these reductions in asthma medication likely confers an additional risk of exacerbation compared with continuing the current asthma medication type and dose (summarized in Tables I and II).

NONCONTROLLED TRIALS OF STEPPING DOWN ASTHMA THERAPY

Several noncontrolled studies describe rates of step down failure and are summarized in Table III.³⁵⁻⁴⁴ In general, the results from these nonrandomized studies suggest similar failure rates to those measured in trials, which ranged from 13% to

TABLE II. Summary of systematic review and meta-analyses of asthma step down types

Step down type	Relative risk of asthma exacerbation (95% CI)
ICS-LABA to ICS alone*	1.68 (0.84-3.38)
ICS to reduced ICS†	1.25 (0.96-1.62)
ICS to no ICS‡	2.35 (1.88-2.92)

*From Ref 16.

†From Ref 23.

‡From Ref 29.

78%, a range that likely varies based on the type of step down and the length of the study.

WHEN TO STEP DOWN ASTHMA MEDICATION

Many step down decisions occur outside of a typical clinician-patient interaction and are often decisions made by patients alone.⁴⁵ In a community study of asthma visits, very few visits were found to be opportunities to discuss step down.⁴⁶ Systems that facilitate communication between clinicians and patients such that these decisions can be decided on together are likely needed. Therefore, when assessing patients with asthma, it is important to keep in mind that step down of asthma medications may have already occurred, which makes an assessment of adherence to medications and detailed information about how

TABLE III. Summary of noncontrolled studies of asthma step down

Study	Participants	Step down type	% Step down failure
Tsurikisawa et al, ³⁵ 2012	90 Adults	Decrease ICS by half	44
Tonelli et al, ³⁶ 2006	71 Adults	Stop ICS	55
Leuppi et al, ³⁷ 2001	50 Adults	Decrease ICS by half every 8 wk	78
Belda et al, ³⁸ 2006	17 Adults	Decrease ICS by half every 8 wk	53
Baba et al, ³⁹ 2002	35 Adults	Decrease ICS by half	51
Zacharasiewicz et al, ⁴⁰ 2005	40 Children	Decrease ICS by half every 8 wk	38
Kwong et al, ⁴¹ 2009	84 Children	Decreased every 3 mo	60
Ciolkowski et al, ⁴³ 2013	84 Children	Substitute LTRA for ICS	13
Rank et al, ⁴⁴ 2013	166 Children	Step down of any type defined by guidelines	28

TABLE IV. Key research questions for stepping down asthma medications

Defining the benefits of stepping down asthma medication
Improved and individualized risk prediction for stepping down medication
Identifying the most-effective care models for implementation of step down
Deeper understanding of patient's decision making about step down, including nonadherence

long it has been since the last time they filled their controller medication a crucial part of any visit.

For patients who make decisions with clinicians, a decision to step down may potentially be tailored to the individual. Several studies report possible predictors for failing step down attempts and can be categorized as clinical and/or demographic, biologic, physiologic, and pharmacogenetic. Clinical or demographic characteristics associated with step down failure include age >40 years old,^{36,37} disease duration >5 years,³⁸ length of time with no clinical symptoms before ICS reduction,³⁵ and time of year.⁴⁴ Biologic markers that have been associated with step down failure include sputum eosinophils,^{37,38,40} fractional excretion of nitric oxide,^{35,40} serum eotaxin (CCL-11),⁴⁷ serum eosinophil count,³⁸ and serum eosinophil cationic protein.³⁹ Sputum for eosinophils was predictive in 3 studies, including serial measurements, although it is not widely performed outside of select specialty clinics and may not be easily implemented. Physiologic markers associated with step down failure include bronchial hyper-responsiveness^{35,37} and FEV₁.³⁵ The pharmacogenetics of asthma controller medications is another promising method for predicting response to specific asthma medications and may be helpful for deciding which asthma medications to reduce or stop if multiple controllers are currently being used.⁴⁸ Several single nucleotide polymorphisms have been associated with responsiveness to ICS, LTRA, and LABA. Studies that specifically test pharmacogenetic markers for predicting step down failure were not identified.

One study combined clinical and/or demographic and physiologic predictors to derive a failure index for substituting a LTRA (montelukast) with ICS.⁴⁹ When assigning points for age <10 years old, FEV₁% predicted in 10% intervals, and systemic steroid burst within the past year, the researchers constructed risk estimates for failure with step down to montelukast, which ranged from 4% to 76%, depending on the number of total points from the failure index. Additional testing of this index and derivation of additional indices may provide valuable information to point-of-care decisions about stepping down asthma medications.

HOW TO STEP DOWN ASTHMA MEDICATIONS

Patients and clinicians have choices when stepping down, both in types of medication and degree of dose reductions. The decision on how to step down depends on the starting point from which the step down is occurring. The current guidelines suggest a 25% to 50% reduction in the ICS dose for stepping down asthma medication, which is supported by recent systematic review and meta-analysis findings.^{2,21} However, guidelines about non-ICS chronic asthma medications are less clear. For example, for patients who may be taking ICS and another controller medication such as LTRA or LABA, how many times should the ICS be reduced 25% to 50% until the LTRA or LABA is discontinued? There are no studies that have addressed this question. One approach that may be considered is to discontinue (or reduce) the last asthma controller medication that was added. However, we identified no studies that assessed whether this is a safe way to approach asthma step down. One could imagine how this approach may be ineffective when the most recent medication added has promoted a period of prolonged stability that leads to the consideration for step down; differential response to asthma medications must be taken into account. Despite the uncertainty we have described in how to best step down asthma medications, we believe that the studies support an approach to gradually reduce ICS dose (by 25%-50%) until a low or medium dose of ICS is reached, at which time discontinuation of non-ICS such as LTRA or LABA should be considered when assuming that the asthma has remained stable. Reduction of ICS dosing to daily also should be considered when reducing the dose by 25% to 50% because this may be preferred by patients and lead to improved adherence.

Another approach to step down that requires additional study is patient-directed step down of asthma medications. We have noted that this approach has been successful in children²¹ and adults.²² In addition, on-demand use of ICS has been studied in another adult population and compared with physician-adjusted treatment and biomarker (fractional excretion of exhaled nitric oxide) adjusted treatment with similar asthma outcomes reported.⁵⁰ On-demand use of ICS in adults was studied in mild persistent asthma (not necessarily in a step down study) and found to have similar outcomes as scheduled ICS.⁵¹ Additional studies focused on patient-directed step down by using asthma controller medications intermittently are needed to better define the risks of this approach.

Given the risks associated with stepping down asthma medication, an adequate plan for assessing response is needed. Guidelines suggest a 2- to 6-week follow-up to assess for response

to management changes in patients with poorly controlled asthma. A similar approach for patients who step down asthma medication could be considered, although the timing of follow-up assessments has not been formally studied. Having a written asthma action plan is associated with patients who have stepped down,⁴⁵ which suggests that having an adequate plan that addresses symptom recurrence makes patients and clinicians more comfortable when stepping down. In patients with severe asthma dependant on oral corticosteroid, many were effectively stepped down by using a Web-based model with frequent patient contact and follow-up.⁵² Although data that support the use of written asthma action plans when stepping down asthma medication is limited, we recommend having a clear plan for patients if symptoms recur.

AVOIDING STEPPING UP WHEN INITIATING THERAPY (AVOIDING THE NEED FOR FUTURE STEP DOWN)

Stepping down asthma medications may not be needed as frequently if patients were initiated on lower steps of asthma care. A systematic review and meta-analysis of starting ICS doses suggest that the small benefits of starting at high-dose ICS provide insufficient benefit when compared with starting with moderate or low doses of ICS.⁵³ Furthermore, when stepping up asthma medications in patients already on controller medications, a careful assessment of adherence is needed to avoid unnecessarily stepping up.

KNOWLEDGE GAPS TO ADDRESS WITH FUTURE RESEARCH

First, the benefits of stepping down asthma medication are not clearly defined. Without clarifying the benefits, many patients and clinicians may decide that “fixing what does not appear to be broken” is not the best approach. Second, patients and clinicians would benefit from more confident risk estimates for asthma step down decisions. We have outlined the currently available risk estimates and their limitations in this article; many providers and patients who make these decisions continue to operate with limited information. Specifically, additional studies that measure risks with step down approaches that involve patient-guided therapies appear to be warranted. Developing and validating predictors of long-term success by using clinical or biologic markers may help to individualize risk estimates. A leading-edge example of an individualized risk assessment was published for substitution of LTRA for ICS.⁴⁹ However, there are many potential predictors to consider, including clinical characteristics and/or demographics, pulmonary function tests, biomarkers, and pharmacogenetics. The markers of highest interest will be those that can easily be obtained in multiple care settings (eg, primary care practices, perhaps measured at home and reported remotely to clinicians). Third, it is unclear which care models will be most effective for implementation of step down. Care models, such as with care managers,⁴⁴ Web based,⁵² or that include point-of-care shared decision making,⁵⁴ that include more contact with patients may be more effective than our current model, which provides limited opportunities for asthma step down.⁴⁶ However, these models need to be compared before widespread implementation. Finally, to help identify which care models will be most effective, we need a better understanding of how step down decisions are made from a patient’s perspective. The role of adherence (intentional and nonintentional) likely plays a pivotal role in

which patients step down asthma medications. A summary of the key knowledge gaps for stepping down asthma medications is provided in Table IV.

MANAGEMENT RECOMMENDATIONS

By using a growing evidence base for making decisions about stepping down asthma medication, we have several management recommendations for clinicians. Before stepping up, assess for factors that may be interfering with treatment response (eg, adherence, inhaler technique, environmental triggers). Careful step up will obviate the need for step down in some patients. We recommend that clinicians discuss the option of stepping down asthma medication when symptoms are stable, lung function is normal or near normal, and biomarker assays (if measured) are normal or near normal. The length of asthma stability, age of the patient, and the time of year should be taken into account as well when deciding on when to step down. Patient and/or family preferences should be considered when making decisions about step down. Reducing the dose of ICS by 25% to 50% appears to be the safest method of stepping down, although many methods have not been subject to study. We recommend that a clear plan of care and follow-up is presented when stepping down asthma medications because many patients will likely have recurrent symptoms.

REFERENCES

1. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention 2011 update. Available from: http://www.ginasthma.org/uploads/users/files/GINA_Report_2011.pdf. Accessed December 29, 2013.
2. National Heart Lung and Blood Institute. National Asthma Education and Prevention Program. Available from: <http://www.nhlbi.nih.gov/about/naepp/>. Accessed December 29, 2013.
3. Kelly HW, Sternberg AL, Lescher R, Fuhlbrigge AL, Williams P, Zeiger RS, et al. Effect of inhaled glucocorticoids in childhood on adult height. *N Engl J Med* 2012;367:904-12.
4. McKeever T, Harrison TW, Hubbard R, Shaw D. Inhaled corticosteroids and the risk of pneumonia in people with asthma: a case-control study. *Chest* 2013;144:1788-94.
5. Chowdhury BA, Dal Pan G. The FDA and safe use of long-acting beta-agonists in the treatment of asthma. *N Engl J Med* 2010;362:1169-71.
6. Fanta CH. Asthma. *N Engl J Med* 2009;360:1002-14.
7. Montori VM, Brito JP, Murad MH. The optimal practice of evidence-based medicine: incorporating patient preferences in practice guidelines. *JAMA* 2013;310:2503-4.
8. Cleary KL, Jackson CM, Fardon TC, Williamson PA, Vaidyanathan S, Burns P, et al. Supervised step-down of inhaled corticosteroids in the community: an observational study. *Respir Med* 2011;105:558-65.
9. Ubel PA, Abernethy AP, Zafar SY. Full disclosure: out-of-pocket costs as side effects. *N Engl J Med* 2013;369:1484-6.
10. Rank MA, Liesinger JT, Ziegenfuss JY, Branda ME, Lim KG, Yawn BP, et al. Asthma expenditures in the United States comparing 2004 to 2006 and 1996 to 1998. *Am J Manag Care* 2012;18:499-504.
11. Guest JF, Davie AM, Ruiz FJ, Greener MJ. Switching asthma patients to a once-daily inhaled steroid improves compliance and reduces healthcare costs. *Prim Care Respir J* 2005;14:88-98.
12. Godard P, Greillier P, Pigearias B, Nachbaur G, Desfougères JL, Attali V. Maintaining asthma control in persistent asthma: comparison of three strategies in a 6-month double-blind randomized study. *Respir Med* 2008;102:1124-31.
13. Koenig SM, Ostrom N, Pearlman D, Waitkus-Edwards K, Yancey S, Prilaman BA, et al. Deterioration in asthma control when subjects receiving fluticasone propionate/salmeterol 100/50 mcg Diskus are “stepped-down.” *J Asthma* 2008;45:681-7.
14. Berger WE, Bleeker ER, O’Dowd L, Miller CJ, Mezzanotte W. Efficacy and safety of budesonide/formoterol pressured metered-dose inhaler: randomized controlled trial comparing once-and twice-daily dosing in patients with asthma. *Allergy Asthma Proc* 2010;31:49-59.
15. Reddel HK, Gibson PG, Peters MJ, Wark PA, Sand IB, Hoyos CM, et al. Down-titration from high-dose combination therapy in asthma: removal of long-acting beta(2)-agonist. *Respir Med* 2010;104:1110-20.

16. Brozek JL, Kraft M, Krishnan JA, Cloutier MM, Lazarus SC, Li JT, et al. Long-acting β_2 -agonist step-off in patients with controlled asthma. *Arch Intern Med* 2012;172:1365-75.
17. Juniper EF, Kline PA, Vanzielegheem MA, Hargreave FE. Reduction of budesonide after a year of increased use: a randomized controlled trial to evaluate whether improvements in airway responsiveness and clinical asthma are maintained. *J Allergy Clin Immunol* 1991;87:483-9.
18. ZuWallack RL, Rosen JP, Cohen L, Rachelefsky GS, Gong H Jr, Goldsobel AB, et al. The effectiveness of once-daily dosing of inhaled fluticasone in maintaining asthma control. *J Allergy Clin Immunol* 1997;99:278-85.
19. Visser ML, Postma DS, Arends LR, de Vries TW, Duiverman EJ, Brand PL. One-year treatment with different dosing schedules of fluticasone propionate in childhood asthma. *Am J Respir Crit Care Med* 2001;164:2073-7.
20. Hawkins G, McMahon AD, Twaddle S, Wood SF, Ford I, Thomson NC. Stepping down inhaled corticosteroids in asthma: a randomized controlled trial. *BMJ* 2003;326:1115.
21. Martinez FD, Chinchilli VM, Morgan WJ, Boehmer SJ, Lemanske RF Jr, Mauger DT, et al. Use of beclomethasone dipropionate as rescue treatment for children with mild persistent asthma (TREXA): a randomized, double-blind, placebo-controlled trial. *Lancet* 2011;377:650-7.
22. Papi A, Canonica GW, Maestrelli P, Paggiaro P, Olivieri D, Pozzi E, et al. Rescue use of beclomethasone and albuterol in a single inhaler for mild asthma. *N Engl J Med* 2007;356:2040-52.
23. Hagan JB, Samant SA, Volcheck GV, Li JT, Hagan CR, Erwin PJ, et al. The risk of asthma exacerbation after reducing inhaled corticosteroids: a systematic review and meta-analysis of randomized controlled trials. *Allergy* 2014;69:510-6.
24. Price D, Chisholm A, Hillyer EV, Burden A, von Ziegenweid J, Svedater H, et al. Effect of inhaled corticosteroid therapy step-down and dosing regimen on measures of asthma control. *J Allergy Ther* 2013;4:1-8.
25. American Lung Association Asthma Clinical Research Network. Randomized comparison of strategies for reducing treatment in mild persistent asthma. *N Engl J Med* 2007;356:2027-39.
26. Kelloway JS, Wyatt RA, Adlis SA. Comparison of patients' compliance with prescribed oral and inhaled asthma medications. *Arch Intern Med* 1994;154:1349-52.
27. Sherman J, Patel P, Hutson A, Chesrown S, Hendeles L. Adherence to oral montelukast and inhaled fluticasone in children with persistent asthma. *Pharmacotherapy* 2001;21:1464-7.
28. Tan H, Sarawate C, Singer J, Elward K, Cohen RI, Smart BA, et al. Impact of asthma controller medications on clinical, economic, and patient-reported outcomes. *Mayo Clin Proc* 2009;84:675-84.
29. Rank MA, Hagan JB, Park MA, Podjasek JC, Samant SA, Volcheck GW, et al. The risk of asthma exacerbation after stopping low-dose inhaled corticosteroids: a systemic review and meta-analysis of randomized controlled trials. *J Allergy Clin Immunol* 2013;131:724-9.
30. Waalkens HJ, Van Essen-Zandvliet EE, Hughes MD, Gerritsen J, Duiverman EF, Knol K, et al. Cessation of long-term treatment with inhaled corticosteroid (budesonide) in children with asthma results in deterioration. *Am Rev Respir Dis* 1993;148:1252-7.
31. Haahtela T, Jarvinen M, Kava T, Kiviranta K, Koskinen S, Lehtonen K, et al. Effects of reducing or discontinuing inhaled budesonide in patients with mild asthma. *N Engl J Med* 1994;331:700-5.
32. Condemi JJ, Chervinsky P, Goldstein MF, Ford LB, Berger WE, Ayars GH, et al. Fluticasone propionate powder administered through Diskhaler versus triamcinolone acetonide aerosol administered through metered-dose inhaler in patients with persistent asthma. *J Allergy Clin Immunol* 1997;100:467-74.
33. Lazarus SC, Boushey HA, Fahy JV, Chinchilli VM, Lemanske RF Jr, Sorkness CA, et al. Long-acting β_2 -agonist monotherapy vs continued therapy with inhaled corticosteroids in patients with persistent asthma: a randomized controlled trial. *JAMA* 2001;285:2583-93.
34. Higgins JPT, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from: www.cochrane-handbook.org. Accessed December 18, 2013.
35. Tsurikawa N, Oshikata C, Tsuburai T, Mitsui C, Tanimoto H, Takahashi K, et al. Markers for step-down of inhaled corticosteroid therapy in adult asthmatics. *Allergol Int* 2012;61:419-29.
36. Tonelli M, Bacci E, Dente FL, Bartoli ML, Cianchetti S, Di Franco A, et al. Predictors of symptom recurrence after low-dose inhaled corticosteroid cessation in mild persistent asthma. *Respir Med* 2006;100:622-9.
37. Leuppi JD, Salome CM, Jenkins CR, Anderson SD, Xuan W, Marks GB, et al. Predictive markers of asthma exacerbation during stepwise dose reduction of inhaled corticosteroids. *Am J Respir Crit Care Med* 2001;163:406-12.
38. Belda J, Parameswaran K, Lemiere C, Kamada D, O'Byrne PM, Hargreave FE. Predictors of loss of asthma control induced by corticosteroid withdrawal. *Can Resp J* 2006;13:129-33.
39. Baba K, Sakakibara A, Yagi T, Niwa S, Wakayama H, Takagi K. Long-term observations of the clinical course after step down of corticosteroid inhalation therapy in adult chronic asthmatics: correlation with serum levels of eosinophil cationic protein. *Respirology* 2002;7:255-66.
40. Zacharasiewicz A, Wilson N, Lex C, Erin EM, Li AM, Hanse T, et al. Clinical use of noninvasive measurements of airway inflammation in steroid reduction in children. *Am J Respir Crit Care Med* 2005;171:1077-82.
41. Kwong KYC, Morpheu T, Huynh P, Scott L, Radjal N, Dale G. Loss of asthma control in inner city children with asthma after withdrawal of asthma controller medication. *J Asthma* 2009;46:1001-5.
42. Obase Y, Ikeda M, Kurose K, Abe M, Shimizu H, Ohue Y, et al. Step-down of budesonide/formoterol in early stages of asthma treatment leads to insufficient anti-inflammatory effect. *J Asthma* 2013;50:718-21.
43. Ciolkowski J, Mazurek H, Stasiowska B. Evaluation of step-down therapy from an inhaled steroid to montelukast in childhood asthma. *Allergol Immunopathol (Madr)* 2013, May 16 [Epub ahead of print].
44. Rank MA, Branda ME, McWilliams DB, Johnson SK, Samant SA, Podjasek JC, et al. Outcomes of stepping down asthma medications in a guideline-based pediatric asthma management program. *Ann Allergy Asthma Immunol* 2013;110:354-8.
45. Rank MA, Ziegenfuss JY, Shah KM, Jenkins SM, Lackore KA, Eton DT, et al. Factors associated with decisions to step down asthma medications. *J Allergy Clin Immunol Pract* 2013;1:312-4.
46. Yawn BP, Wollan PC, Bertram SL, Lowe D, Butterfield JH, Bonde D, et al. Asthma treatment in a population-based cohort: putting step-up and step-down treatment changes in context. *Mayo Clin Proc* 2007;82:414-21.
47. Hoffmann HJ, Nielsen LP, Harving H, Heinig JH, Dahl R. Asthmatics able to step down from inhaled corticosteroid treatment without loss of asthma control have low serum eotaxin/CCL11. *Clin Respir J* 2008;2:149-57.
48. Mougey EB, Chen C, Tantisira KG, Blake KV, Peters SP, Wise RA, et al. Pharmacogenetics of asthma controller treatment. *Pharmacogenomics J* 2013;13:242-50.
49. Drummond MB, Peters SP, Castro M, Holbrook JT, Irvin CG, Smith LJ, et al. Risk factors for montelukast treatment failure in step-down therapy for controlled asthma. *J Asthma* 2011;48:1051-7.
50. Calhoun WJ, Ameredes BT, King TS, Icitovic N, Bleecker ER, Castro M, et al. Comparison of physician-, biomarker-, and symptom-based strategies for adjustment of inhaled corticosteroid therapy in adults with asthma: the BASALT randomized controlled trial. *JAMA* 2012;308:987-97.
51. Boushey HA, Sorkness CA, King TS, Sullivan SD, Fahy JV, Lazarus DC, et al. Daily versus as-needed corticosteroids for mild persistent asthma. *N Engl J Med* 2005;352:1519-28.
52. Hashimoto S, Ten Brinke A, Roldaan AC, van Zeen IH, Moller GM, Sont JK, et al. Internet-based tapering of oral corticosteroids in severe asthma: a pragmatic randomised controlled trial. *Thorax* 2011;66:514-20.
53. Powell H, Gibson PG. High dose versus low dose inhaled corticosteroid as initial starting dose for asthma in adults and children. *Cochrane Database Syst Rev* 2009;4.
54. Wilson SR, Strub P, Buist AS, Knowles SB, Lavori PW, Lapidus J, et al. Shared treatment decision making improves adherence and outcomes in poorly controlled asthma. *Am J Respir Crit Care Med* 2010;181:566-77.