

Clinical Commentary Review

The Potential Role of Allergen Immunotherapy in Stepping Down Asthma Treatment

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For patients whose asthma is controlled and who have a low risk for future exacerbations, current guidelines recommend gradually stepping down pharmacotherapy to identify the lowest dose needed to maintain control. This review article will discuss the benefits and risks of step down in asthma management and the different strategies of achieving step down with particular focus on allergen immunotherapy (AIT). A literature search was conducted to identify studies that assessed the effect of AIT on asthma step down and evaluated this and asthma control as one of the outcomes. Six studies were identified: 2 subcutaneous and 4 sublingual AIT studies. Five studies assessed house dust mite-induced asthma, whereas 1 study focused on birch-induced seasonal asthma. Regarding house dust mite-induced asthma, the AIT studies reviewed suggest that individuals with moderate rather than mild asthma are the patients who are more likely to benefit from the addition of AIT for their asthma condition. The potential value of AIT is likely to be in enabling successful step down of the inhaled corticosteroid dose in Global Initiative for Asthma step 3 or 4. It is important to further explore this effect so that affected individuals can benefit from this treatment. © 2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2016;■:■-■)

Key words: Allergen immunotherapy; Asthma control; Step down; House dust mite; Inhaled corticosteroids

“Asthma control” is now recognized as the main goal of asthma therapy. This includes 2 major domains: maximum

control of symptoms and minimizing future risk of adverse outcomes.¹ A stepwise management approach has been proposed by well-recognized groups such as British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN), Global Initiative for Asthma (GINA), National Asthma Education and Prevention Program, and the National Institute for Health and Care Excellence. This is a dynamic approach that involves continuous assessment, adjustment of treatment, and review of response on the basis of asthma control.¹ Individuals with uncontrolled asthma and/or at high risk for future exacerbations are considered for increased medicine doses or addition of other asthma medications, that is, step-up approach. For patients whose asthma is controlled and who have a low risk for future exacerbations, gradually stepping down therapy to identify the lowest dose needed to maintain control is recommended.

Different step-down options exist. Currently, it is recommended that patients should be maintained at the lowest possible dose of inhaled corticosteroids (ICSs). Step down should be considered every 3 months, decreasing the ICS dose by approximately 25% to 50% each time.¹ Stopping ICS is not recommended in adults with chronic persistent asthma. Furthermore, ICS withdrawal is not indicated if patients are on a long-acting beta-2 agonist because this must be used along with another asthma-control medicine, typically ICS. The dose decrease should be an individual clinical decision based on history of stability with respect to the patient's day-to-day symptoms, frequency of exacerbations, previous step-down attempts, and patient preference.^{1,2}

Many unanswered questions remain regarding how to best achieve step down and what the ultimate “lowest” dose should be. In addition, current recommendations for step down do not account for the heterogeneity of asthma phenotypes and do not sufficiently incorporate consideration of disease risk.

In this research review, we will initially discuss the benefits and risks of step down in asthma management followed by the different strategies of achieving step down with particular focus on the use of allergen immunotherapy (AIT) for the allergic asthma phenotype.

BENEFITS AND RISKS OF STEP DOWN

Stepping down to reduce side effects and improve adherence to treatment

There are many reasons why stepping down asthma medications can be beneficial from the patient's perspective (Figure 1). Despite asthma medications being generally well tolerated, they can have several adverse effects. These include ICS-induced oral candidiasis or hoarseness having an impact on quality of life in the short-term whereas others are long-term effects.³

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Abbreviations used

ACQ- Asthma Control Questionnaire
 AIT- Allergen immunotherapy
 FP- Fluticasone propionate
 GINA- Global Initiative for Asthma
 ICS- Inhaled corticosteroid
 RCT- Randomized controlled trial
 RDBPCT- Randomized double-blind placebo-controlled trial
 SCIT- Subcutaneous immunotherapy
 SLIT- Sublingual immunotherapy
 SQ- Standardized quality

One of the concerns is the potential growth-suppressive effect of long-term ICS in children. Evidence from systematic reviews has been conflicting, which further adds to the general public's fears of ICS use.^{4,5} Another concern is the potential risk of pneumonia.^{6,7} However, a meta-analysis of clinical randomized trials reported that patients with asthma using ICS did not have an increased risk of pneumonia, even at higher doses.⁸

Corticophobia and worries about long-term ICS use, uncertainty about the need for ICS as preventive treatment, and experiences of side effects can lead to nonadherence and loss of asthma control.⁹ It is anticipated that stepping down ICS may facilitate better adherence and maintain or even improve treatment outcomes.¹⁰ In a large pragmatic trial of patients with asthma, better adherence rates were observed with a once-daily mometasone furoate rather than twice-daily regime.¹¹

In addition, most patients prefer to be involved in management decisions and take the minimum medication necessary to control symptoms.¹² A large observational study showed that a significant reduction in ICS dose can be achieved in a community setting without any worsening of airways inflammation or lung function. This was associated with a quality-of-life improvement in most patients.¹³

Stepping down to reduce the cost of treatment without increasing exacerbation rate

Asthma is associated with significant health care expense that includes direct and indirect costs. Reducing the amount of medications while maintaining asthma control can be cost saving.¹⁴⁻¹⁶

One of the main risks of step down is the possibility of asthma exacerbation, a significant event for an individual with asthma with considerable associated cost. Exacerbation risk varies depending on individual patient characteristics and severity of asthma as well as the duration of stable asthma before attempts to reduce medications.^{2,17} Patients with well-controlled asthma who stop regular use of low-dose ICS have an increased risk of an exacerbation.¹⁸ However, in those who reduced and did not stop ICS, asthma exacerbations were no more likely compared with those who remained on the same ICS dose, thus supporting current guidelines.¹⁹

OPTIONS FOR STEPPING DOWN

There are different options for stepping down ICS doses (Figure 1).²⁰⁻²⁴ Analysis of randomized controlled trials (RCTs) that examined step down, when taken together, suggested that each of these methods of stepping down from higher ICS dose to reduced ICS dose by scheduled or on-demand ICS, or substitution of leukotriene receptor antagonist, may be safe options for many patients with well-controlled asthma.⁵

Another way of achieving a reduced ICS dose is by the addition of biologicals such as omalizumab (anti-IgE). Omalizumab is recommended for moderate to severe allergic asthma that is uncontrolled on step 4 treatment.¹ As an adjunctive therapy to ICS, it has been found beneficial in reducing exacerbations and hospitalizations. It is also more effective than placebo in increasing the number of study participants who are able to reduce or withdraw their ICS.^{25,26}

Furthermore, the latest GINA report states that adjusting treatment (up or down) includes not only medications but also nonpharmacological strategies and treatment of modifiable risk factors.¹¹ One such option for achieving step down in allergic (T_H2-mediated) asthma included in some guidelines is treatment with AIT.¹

AIT AND STEP DOWN

AIT to treat allergic asthma

Asthma is a complex disease with multiple phenotypes representing several heterogeneous underlying immunological endotypes.²⁷ Allergic asthma is the target phenotype of AIT. AIT is the only treatment that can potentially change the course of the allergic disease by preventing in allergic rhinitis sufferers the development of asthma and new allergen sensitizations and by inducing allergen-specific immune tolerance.²⁸ This immunomodulation has been documented to be sustained 7 to 12 years after the end of treatment, thus suggesting a capability for preventing disease progression.^{29,30}

House dust mite (HDM) allergy is a major cause of respiratory allergic disease and a potential target for AIT.^{31,32} Interestingly, exposure to HDM allergens in adults with asthma not previously sensitized to HDM increases asthma morbidity^{33,34} while those already sensitized have an increased asthma severity.³⁵⁻³⁷ Sensitization to HDM is also a risk factor for recurrent exacerbations³⁸ and for asthma development in 20- to 44-year-old patients with allergic rhinitis.³⁹

According to the updated GINA report,¹ exacerbation risk can be reduced by identifying and treating any modifiable risk factors such as allergen exposure in sensitized individuals. AIT is mentioned as a potential option although it is stated that efficacy is limited. It is further mentioned as a possible intervention to achieve step down. Potential AIT (subcutaneous immunotherapy [SCIT] or sublingual immunotherapy [SLIT]) benefits should be weighed against the risk of adverse effects, inconvenience, and cost of the prolonged therapy course (Evidence rating D).¹ The Allergic Rhinitis and its Impact on Asthma guidelines give both SCIT and SLIT a conditional recommendation in allergic asthma because of moderate- or low-quality evidence.⁴⁰

Efficacy of AIT in asthma is supported by several RCTs and meta-analyses. A Cochrane review evaluated 88 randomized, double-blind, placebo-controlled SCIT trials including 3459 patients with allergic asthma to HDM, pollen, animal dander, and other allergens.⁴¹ Although there was significant heterogeneity, overall there was a significant reduction in asthma symptoms and medication use and improvement in bronchial hyperreactivity after AIT. However, caution is required with SCIT because 1 in 9 AIT-treated patients experienced systemic reactions.

A meta-analysis studying the efficacy and safety of SCIT in 796 HDM-sensitized subjects with asthma from 19 RCTs found that SCIT significantly reduced asthma symptom ($P = .004$) and medication scores ($P = .001$) compared with controls.⁴²

Why? Benefits & risks	
(i)	Stepping down to reduce side-effects and improve adherence to treatment because of:
	- Patients' concerns about long-term use of inhaled corticosteroids (ICS), uncertainty about needing ICS as preventive treatment, experiences of side effects can lead to non-adherence to controllers [9] - Importance to involve patients in treatment decisions, to avoid patient decision to discontinue their treatment inappropriately
(ii)	Stepping down to reduce treatment cost without increasing exacerbation rate:
	- Reducing the amount of medications while maintaining asthma control is cost saving - Asthma exacerbations are no more likely among individuals who reduce (but do not stop) ICS compared to those who maintain their ICS dose [19]
How?	
(i)	Reducing ICS dose
(ii)	Stopping ICS altogether with no substitute medication
(iii)	Stopping ICS and substituting with a leukotriene receptor antagonist (LTRA)
(iv)	Reducing ICS while adding another controller (e.g. LTRA or long-acting beta2-agonist (LABA))
(v)	Using ICS on demand based on symptoms or other agreed parameters
(vi)	Omalizumab
(vii)	Non-pharmacological strategies and treatment of modifiable risk factors, including allergen immunotherapy (AIT)
When?	
(i)	Generalised asthma care: when asthma symptoms have been well-controlled and lung function stable for three months (GINA 2016) [1]
(ii)	Individualised asthma care: stepping down is an individual clinical decision based on history of stability with respect to the patient's day-to-day symptoms, frequency of exacerbations, previous step down attempts and patient preference (GINA 2016) [1]

FIGURE 1. Benefits, risks, and ways of stepping down asthma medication.

Most SLIT efficacy studies have been performed in patients with allergic rhinoconjunctivitis with or without allergic asthma. A Cochrane review, 52 studies, found a general trend suggesting a SLIT benefit over placebo, but variation in scales used to assess outcomes meant that results were difficult to interpret.⁴³

AIT to step down asthma medications

Most efficacy analyses have been based on symptom scores, rescue medication use, peak expiratory flow, or bronchial hyperresponsiveness rather than the asthma control parameters recommended in GINA.

A literature search was conducted to identify published, unpublished, and ongoing studies that assessed the effect of AIT on asthma step down and evaluated this and asthma control as one of the outcomes. The databases searched included PubMed, EMBASE, the Cochrane Central Register of Controlled Trials

(CENTRAL), EBSCO, ScienceDirect, Web of Science, and [ClinicalTrials.Gov](#). The terms used in different combined searches were “asthma,” “step down,” “allergen immunotherapy,” “asthma control,” “asthma treatment,” “inhaled corticosteroids,” “house dust mite,” “allergic asthma,” “sublingual immunotherapy,” and “subcutaneous immunotherapy.” The search was concluded in October 2016. Following review of all relevant abstracts, 6 studies were identified: 2 SCIT^{44,45} and 4 SLIT studies.⁴⁶⁻⁴⁹ Five studies assessed HDM asthma, whereas 1 studied silver birch allergen-induced seasonal asthma (Table I).

A randomized double-blind placebo-controlled trial (RDBPCT) evaluated the effects of a SLIT birch pollen allergen extract (Stallergenes, Antony, France) on 24 participants with severe birch-induced rhinitis and mild-to-moderate asthma.⁴⁶ A pre-coseasonal protocol was used, repeated for 2 years. The asthma severity assessed by GINA criteria stepped down in 77%

TABLE I. AIT randomized control trials to step down other asthma medications

Lead author, publication year	Study design	Population age Treatment groups	Inclusion criteria	Product name and manufacturer, type of extract	Treatment length	AIT protocol	Clinical outcomes
Voltolini ⁴⁶ (2010)	RDBPCT Single center	Adults Total n = 24 Active (n = 14): 43.8 ± 9.4 y Placebo (n = 10): 39.9 ± 6.6 y	Monosensitized to <i>Betulaceae</i> pollen & Moderate/severe persistent rhinitis (ARIA criteria) & slight-intermittent to moderate persistent asthma (levels I to III, GINA criteria)	SLIT with allergen extract of birch at 10 Index of Reactivity (IR)/mL and 300 IR/mL (Stallergenes, Antony, France)	2 y	Pre-coseasonal protocol repeated for 2 y Updosing over 11 d starting with 10 IR and culminating at 300 IR Maintenance: daily administration for 4 mo	Decrease ($P < .05$) in rhinorrhea and nasal obstruction Asthma severity (GINA criteria) stepped down in 77% of active compared with 0 of 9 placebo patients ($P = .05$)
Blumberga ⁴⁴ (2006)	RDBPCT	Adults 18-60 y Total n = 54 SCIT n = 26 Placebo n = 28	Allergy to HDM Perennial asthma with regular symptoms requiring long-term treatment with ICS (fluticasone propionate equivalent to 500-2000 µg daily)	SCIT with Alutard SQ <i>D pteronyssinus</i> (ALK-Abelló)	3 y	Stepwise reduction of ICS dose repeated (September-December) after 1, 2, and 3 y of SCIT The updosing was performed during an 8-wk period with 2-3 injections at each visit followed by maintenance treatment for 3 y. In the maintenance phase, patients received the individual maximum tolerated dose up to a maximum dose of 100,000 SQ-U (corresponding to 9.8 µg major allergen Der p1/mL) Updosing during 8-wk period with 2-3 injections/visit Maintenance: injections every 6 ± 2 wk. Individual maximum tolerated dose up to a maximum dose of 100,000 SQ-U (corresponding to 9.8 µg major allergen Der p1/mL)	In moderate and severe asthma, reduction in ICS significant after 2 y of SCIT ($P = .03$) but not after 3 y. Median reductions after third year: active 82%, placebo 42% In moderate persistent asthma, median reductions after 3 y 90% for SCIT and 42% for placebo ($P = .04$)
Zielen ⁴⁵ (2010)	RCT	Children 6-17 y Total n = 65 Active (SCIT + ICS) n = 33 Control (ICS only) n = 32	Mild-to-moderate HDM-allergic asthma (GINA treatment levels II and III)	Acaroid HDM (<i>D pteronyssinus</i>) allergoid SCIT (Allergopharma Joachim Ganzer KG)	2 y	Updosing: weekly injections with increasing doses of 1000 therapeutic units (TUs/mL) (0.1, 0.2, 0.4, and 0.6 mL) followed by 10,000 TUs/mL (0.1, 0.2, 0.4, and 0.6 mL) Maintenance: maximum individually tolerated dose, injections gradually extended to 6 ± 2 wk	After 2 y: children on SCIT plus ICS significantly reduced the ICS dose by more steps ($P < .05$), compared with controls on ICS alone Mean daily ICS dose in the SCIT group decreased from 330.3 µg at baseline to 151.5 µg after 2 treatment years, whereas in the control group, it decreased from 290.6 µg to 206.3 µg

Wang ⁴⁷ (2014)	RDBPCT parallel-group, Multicenter	16-50 y Total n = 484 Active n = 322 Placebo n = 162	Mild or moderate, persistent, HDM-induced asthma for at least previous 12 mo	STALORAL SLIT solution containing equal proportions of <i>D pteronyssinus</i> and <i>D farinae</i> extracts (Stallergenes)	12 mo	12-wk baseline phase and 12-mo treatment phase with daily 300 IR maintenance dose (equivalent to 28 µg Der p 1 and 50 µg Der f 1) or placebo After 24 wk of treatment, a second, 16-wk budesonide step-down phase was initiated to identify any steroid-sparing effect of AIT	Significant active vs placebo difference in both well- controlled asthma ($P = .021$) and totally controlled asthma ($P = .008$) in patients with moderate (but not mild) persistent asthma ICS dose reduction in patients with moderate asthma in the active group was greater (218.5 µg and 126.2 µg, respectively; $P = .004$) than in the placebo group
Mosbech ⁵⁰ (2014) de Blay ⁴⁸ (2014)	RDBPCT parallel-group Multicenter	14 y or older Active n = 461 Placebo n = 143	Mild-to-moderate, HDM-allergic asthma requiring ICS use (100-800 micrograms/d) and mild-to-severe HDM-allergic rhinitis	1:1 mix <i>D</i> <i>pteronysinus</i> and <i>D farinae</i> SLIT tablet (ALK)	12 mo	Daily treatment with 1 of 3 active doses (1, 3, or 6 SQ-HDM) Primary end point: reduction in ICS dose from the individual's baseline dose until end of 1-y treatment (with ICS dose at both time points being the lowest dose providing symptom control). Secondary end points: ICS dose, ACQ score, FEV ₁ , peak expiratory flow, AQLQ score, number of asthma exacerbations	Significant mean difference between 6 SQ-HDM and placebo in the reduction in daily ICS dose ($P = .004$). Mean and median values for the relative reduction from baseline in ICS dose were 42% and 50% for 6 SQ-HDM compared with 15% and 25% for placebo In subgroup (daily ICS use of 400-800 µg), difference between placebo and 6 SQ- HDM in change from baseline in daily ICS use was 327 µg ($P < .0001$), whereas it was 0.52 ($P = .010$) for AQLQ
Virchow ⁴⁹ 2016	RDBPCT Multicenter	Total n = 834 12 SQ-HDM n = 282 6 SQ-HDM n = 275 Placebo n = 277	>1-y history of HDM-allergic asthma, not well controlled by ICS (400-1200 µg budesonide or equivalent) at enrolment and with positive tests of HDM sensitization	1:1 mix <i>D pteronyssinus</i> and <i>D</i> <i>farinae</i> SLIT tablet (ALK)	18 mo	Once-daily treatment 6 SQ-HDM or 12 SQ-HDM Participants received concomitant ICS for 7-12 mo, whereafter ICS was reduced by 50% for 3 mo and then by 100% for 3 mo	6 SQ-HDM and 12 SQ-HDM tablets significantly reduced the risk of a moderate or severe asthma exacerbation compared with placebo (HR, 0.72 [95% CI, 0.52-0.99]) for the 6 SQ-HDM group, $P = .045$, and 0.69 (95% CI, 0.50-0.96) for the 12 SQ-HDM group ($P = .03$)

ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; AQLQ, Asthma Quality of Life Questionnaire; ARIA- Allergic Rhinitis and its Impact on Asthma; HR, hazard ratio.

of participants treated with SLIT compared with 0 of the 9 individuals treated with placebo ($P = .05$). Although this pilot study suggested that SLIT may be able to induce a step down of seasonal asthma treatment, it was limited by the low number of participants.

An RDBPCT evaluating the steroid-sparing effect of SCIT (Alutard, ALK-Abelló, Hørsholm, Denmark) in moderate and severe HDM-allergic adults with asthma found a statistically significant reduction in ICS after 2 years of SCIT ($P = .03$) but not after 3 years. The reduction was larger in patients with moderate persistent asthma after years 2 and 3. After 3 years of treatment, the median reduction for SCIT was 90% ($P = .04$). However, there was no difference in asthma assessments between the 2 groups despite the significant steroid reduction in the SCIT group. No serious reactions to SCIT injections were observed.⁴⁴

An RCT assessed the efficacy of a high-dose *D pteronyssinus* SCIT preparation (allergoid) (Acaroid, Allergopharma Joachim Ganzer KG, Reinbek, Germany) as a steroid-sparing agent in 65 children with allergic asthma (GINA levels II and III). Following a 5-month baseline ICS control period, participants were randomized to SCIT together with fluticasone propionate (FP) or FP alone for 2 years. The primary end point was the change in ICS dose steps required to achieve asthma control (according to GINA). Participants receiving SCIT together with FP were able to significantly reduce the FP dose by more steps after 2 years ($P < .05$) compared with controls. The mean daily dose in the SCIT group decreased from 330.3 µg in the baseline period to 151.5 µg after 2 treatment years. It was concluded that adding this allergoid SCIT to pharmacological treatment is effective and a safe way to reduce ICS doses while maintaining asthma control.⁴⁵

Wang et al⁴⁷ performed a randomized double-blind placebo-controlled parallel-group study of HDM SLIT (300 Index of Reactivity mixture of *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* extract, Staloral, Stallergenes) in 484 adults with asthma using a primary efficacy outcome of well-controlled asthma and a well-defined ICS dose step-down phase and secondary outcome of totally controlled asthma. According to the authors, “the primary efficacy criterion was not met because of a higher than expected well-controlled asthma rate at randomization in both groups.” *Post hoc* analysis by asthma severity identified a significant difference between active and placebo groups in both well-controlled asthma and totally controlled asthma in individuals with moderate persistent asthma but not those with mild asthma. A significant active versus placebo difference was observed for the percentage of patients with moderate asthma with an Asthma Control Questionnaire score of less than 0.75. For individuals with moderate asthma, the ICS dose reduction in the active group was greater (218.5 µg and 126.2 µg, respectively; $P = .004$) than in the placebo group. The product was well tolerated with only mild, local, transient adverse events.⁴⁷

A multiple-dose, parallel-group RDBPCT performed in 8 European countries investigated the efficacy and safety of a standardized quality (SQ)-HDM SLIT tablet (1:1 mix *D pteronyssinus* and *D farinae*) (ALK) in 604 subjects (≥ 14 years) with mild-moderate HDM-allergic asthma.⁵⁰ Participants were randomized to 1, 3, or 6 SQ-HDM or placebo. The study end points are presented in Table I. Primary analysis found a mean difference between 6 SQ-HDM and placebo in the reduction of 81 µg in daily ICS dose ($P = .004$). The mean and median values for the relative reduction from baseline in ICS dose were

42% and 50% for 6 SQ-HDM compared with 15% and 25% for placebo. The most common adverse events were local oral reactions. A limitation of this study according to the investigators was that “accepting an ICS dose as low as 100 µg/d at inclusion left little room for improvement in terms of ICS reduction.”⁵⁰ A *post hoc* analysis in a subgroup with daily ICS use of 400 to 800 µg and Asthma Control Questionnaire score of 1 to 1.5 corresponding to partly controlled asthma ($n = 108$) was performed. The difference between placebo and 6 SQ-HDM in change from baseline in daily ICS use was 327 µg ($P < .0001$), while it was 0.52 ($P = .010$) for Asthma Quality of Life Questionnaire. Sixty-nine percent members of the 6 SQ-HDM group were able to reduce the ICS dose by 50% or more without impairment of asthma control versus 19% of the placebo group. The treatment effect on ICS reduction and Asthma Quality of Life Questionnaire was increased for the subgroup compared with the residual population (ICS reduction: $P < .001$ Asthma Quality of Life Questionnaire: $P = .044$).⁴⁸

Following on from this study, an RDBPCT included participants from 13 European countries with HDM asthma, not well controlled by ICS (400-1200 µg budesonide). A total of 834 participants were randomized into placebo, 6 SQ-HDM, 12 SQ-HDM SLIT tablet (ALK) once-daily for up to 18 months. Subjects received concomitant ICS for 7 to 12 months, after which ICS was reduced by 50% for 3 months and then by 100% for 3 months. The primary end point was reduction in the risk of moderate or severe asthma exacerbation during ICS reduction as measured by the time to the first exacerbation. The 6 and 12 SQ-HDM doses both significantly reduced the risk of a moderate or severe asthma exacerbation compared with placebo (hazard ratio, 0.72, $P = .045$ for the 6 SQ-HDM group and 0.69 for the 12 SQ-HDM group, $P = .03$). The absolute risk differences based on the observed data (full analysis set) in the active versus the placebo group were 0.09 for the 6 SQ-HDM group and 0.10 for the 12 SQ-HDM group. Compared with placebo, there was a reduced risk of an exacerbation (hazard ratio, 0.72; $P = .11$) for the 6 SQ-HDM group and 0.64 ($P = .03$) for the 12 SQ-HDM group.⁴⁹ These data confirm an effect on both current asthma control and future risk.

The treatment was well tolerated with a favorable safety profile⁵¹ including in a subset of subjects (28% of total population) with uncontrolled asthma based on GINA criteria. This finding may be of high clinical significance because uncontrolled asthma is considered a contraindication to presently available allergy SCIT and SLIT immunotherapy products.

Data from this trial have resulted in the 12 HDM-SQ dose (ACARIZAX, Hørsholm, Denmark) recently being authorized for treatment of HDM-allergic asthma in adults (18-65 years) by 11 European countries. The indications include HDM-allergic asthma not well controlled by ICS and associated with mild-to-severe HDM-allergic rhinitis.

DISCUSSION

One of the main issues when evaluating the results of AIT studies in asthma has been the significant heterogeneity in terms of allergen doses and schedules, use of different outcome measures, definitions of asthma control and exacerbations, and time periods selected. In view of the widespread uptake of the GINA guidelines and the value of “asthma control” as a tool for assessing drug efficacy, this appears to be an appropriate outcome

measure for assessing AIT efficacy in asthma and should be more widely included in future studies. Robust evidence needed to support treatment recommendations for HDM-allergic asthma is now starting to emerge.³² Well-designed studies assessing step down as an outcome have strengthened the evidence base for the efficacy and safety of AIT in allergic asthma with and without allergic rhinitis and are an important step toward inclusion of this treatment option in the next round of guideline updates.

The HDM AIT studies assessing step down of asthma medications reviewed in this article suggest that individuals with moderate rather than mild asthma are the patients who are more likely to benefit from the addition of AIT for their asthma condition. This is likely due to patients with mild asthma only being on low ICS doses to start with for AIT to cause a significant reduction. Thus, the potential value of AIT is likely to be in enabling successful step down of the ICS dose in GINA 3 or 4.

Achievement of step down with the addition of AIT is beneficial not only as a reduction in medication use with potentially less side effects but also provides a demonstration of the efficacy of the protection brought by AIT to the patient. Protection in this context means prevention of exacerbation but potentially also capacity to somehow reverse part of the pathophysiologic process. This can be of benefit in patients with any asthma severity, from mild to severe.

Current AIT guidelines recommend that patients with severe or uncontrolled asthma be excluded from consideration for the use of AIT. The major reason for this being that most fatal reactions to SCIT in the past occurred in patients with uncontrolled asthma at the time of the injection.^{52,53} No fatal reactions have been reported to SLIT but the indication to start the treatment only in patients with well-controlled asthma remains valid in principle.⁵⁴ However, SLIT-tablet preparations were well tolerated in patients with asthma not well controlled by ICS (400–1200 µg budesonide or equivalent).^{49,51} SLIT-tablet preparations have been found to have a good safety profile and given the clinical benefit it appears to be a clinically relevant option.

Another aspect to consider is the possibility of using AIT even in severe asthma. Omalizumab has been found to serve as an effective combination therapy with AIT and data confirm that by pretreating children and young adults with severe asthma with omalizumab, AIT can be more safely performed.^{55–57} Pre-administration followed by concomitant treatment of AIT and omalizumab can thus allow its use in patients with more severe or uncontrolled asthma. This is already current practice in some centers but further evaluation is required.

Furthermore, most patients with allergic asthma and HDM sensitization also have allergic rhinitis, and approximately half of the patients with allergic rhinitis and HDM sensitization also have asthma.^{32,58} Two recent large RDBPCT studies in adults found 2 different SLIT-tablet preparations to be effective in treating HDM-allergic rhinitis.^{59,60} Moreover, recent data suggest that AIT can be an effective therapy for asthma allowing the reduction of ICSs.^{44–50} The comorbidity of allergic rhinitis and allergic asthma is likely to worsen each condition⁶¹; thus, using AIT to target both these conditions according to the one airway one disease concept is more likely to lead to better asthma control. The importance of also treating rhinitis is further supported by a recent study of 126 adults with controlled asthma. This study found that comorbidity with

rhinitis or rhinosinusitis was an independent predictor of failed stepping down of ICS.⁶²

Another aspect to consider when assessing AIT as a potential treatment to achieve step down is cost-effectiveness because this is a treatment requiring prolonged administration. The cost-effectiveness findings of AIT in asthma depend on the duration of the clinical benefit after treatment suspension and the balance between the direct costs of AIT during its maintenance phase and the drug cost savings afforded by the introduction of AIT.⁶³ There is evidence suggesting that AIT is cost-effective for allergic rhinoconjunctivitis associated with asthma. A systematic review of AIT health economics found that 23 comparative cost studies provided compelling evidence for the cost savings of AIT (whether SCIT or SLIT) over symptomatic drug treatments.⁶⁴ A study assessing SCIT with a high-dose HDM allergoid (Acaroid) preparation in children and adolescents with HDM-induced allergic asthma found it to be cost-effective on analyzing the drug cost savings 4 years after treatment suspension versus children who had continued with conventional therapy only.⁶⁵ A recent cost analysis study indicated that the SQ®HDM SLIT tablet (Acarizax) plus pharmacotherapy is cost-effective compared with placebo plus pharmacotherapy for HDM-allergic asthma patients in Germany.⁶⁶

Thus, there is currently promising evidence that AIT can assist in stepping down asthma controller treatment and it is important to further explore this effect so that affected individuals can benefit from this.

REFERENCES

1. Global Initiative for Asthma: Global strategy for asthma management and prevention. Updated April 2015. Available from: <http://www.ginasthma.org/documents/4>. Accessed May 10, 2016.
2. Hagan JB, Rank MA. Assessing the risks and benefits of step-down asthma care: a case-based approach. *Curr Allergy Asthma Rep* 2015;15:503.
3. Rank MA, Peters SP. The risks, benefits, and uncertainties of stepping down asthma medications. *Allergy Clin Immunol Pract* 2014;2:503-9.
4. Pruteanu AI, Chauhan BF, Zhang L, Prietsch SO, Ducharme FM. Inhaled corticosteroids in children with persistent asthma: dose-response effects on growth. *Cochrane Database Syst Rev* 2014;7:CD009878.
5. Loke YK, Bianco P, Thavarajah M, Wilson AM. Impact of inhaled corticosteroids on growth in children with asthma: systematic review and meta-analysis. *PLoS One* 2015;10:e0133428.
6. Sibila O, Soto-Gomez N, Restrepo MI. The risk and outcomes of pneumonia in patients on inhaled corticosteroids. *Pulm Pharmacol Ther* 2015;32:130-6.
7. 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.
8. O'Byrne PM, Pedersen S, Carlsson LG, Radner F, Thorén A, Peterson S, et al. Risks of pneumonia in patients with asthma taking inhaled corticosteroids. *Am J Respir Crit Care Med* 2011;183:589-95.
9. Cooper V, Metcalf L, Versnel J, Upton J, Walker S, Horne R. Patient-reported side effects, concerns and adherence to corticosteroid treatment for asthma, and comparison with physician estimates of side-effect prevalence: a UK-wide, cross-sectional study. *NPJ Prim Care Respir Med* 2015;25:15026.
10. 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.
11. Price D, Robertson A, Bullen K, Rand C, Horne R, Staudinger H. Improved adherence with once-daily versus twice-daily dosing of mometasone furoate administered via a dry powder inhaler: a randomized open-label study. *BMC Pulm Med* 2010;10:1.
12. Reddel HK, Bateman ED, Becker A, Boulet LP, Cruz AA, Drazen JM, et al. A summary of the new GINA strategy: a roadmap to asthma control. *Eur Respir J* 2015;46:622-39.
13. 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.

14. Bahadori K, Doyle-Waters MM, Marra C, Lynd L, Alasaly K, Swiston J, et al. Economic burden of asthma: a systematic review. *BMC Pulm Med* 2009;9:24.
15. Ubel PA, Abernethy AP, Zafar SY. Full disclosure: out-of-pocket costs as side effects. *N Engl J Med* 2013;369:1484-6.
16. 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.
17. Rank MA, Johnson R, Branda M, Herrin J, van Houten H, Gionfriddo MR, et al. Long term outcomes after stepping down asthma controller medications: a claims-based, time-to-event analysis. *Chest* 2015;148:630-9.
18. 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 systematic review and meta-analysis of randomized controlled trials. *J Allergy Clin Immunol* 2013;131:724-9.
19. Hagan JB, Samant SA, Volcheck GW, 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.
20. Bacharier LB. Step-down therapy in asthma: a focus on treatment options for patients receiving inhaled corticosteroids and long-acting beta-agonist combination therapy. *Allergy Asthma Proc* 2012;33:13-8.
21. Brozek JL, Kraft M, Krishnan JA, Cloutier MM, Lazarus SC, Li JT, et al. Long-acting beta agonist step-off in patients with controlled asthma—systematic review with meta-analysis. *Arch Internal Med* 2012;27:1-11.
22. Ahmad S, Kew KM, Normansell R. Stopping long-acting beta2-agonists (LABA) for adults with asthma well controlled by LABA and inhaled corticosteroids. *Cochrane Database Syst Rev* 2015;6:CD011306.
23. Kew KM, Beggs S, Ahmad S. Stopping long-acting beta2-agonists (LABA) for children with asthma well controlled on LABA and inhaled corticosteroids. *Cochrane Database Syst Rev* 2015;5:CD011316.
24. Gionfriddo MR, Hagan JB, Hagan CR, Volcheck GW, Castaneda-Guarderas A, Rank MA. Stepping down inhaled corticosteroids from scheduled to as needed in stable asthma: systematic review and meta-analysis. *Allergy Asthma Proc* 2015;36:262-7.
25. Normansell R, Walker S, Milan SJ, Walters EH, Nair P. Omalizumab for asthma in adults and children. *Cochrane Database Syst Rev* 2014;1:CD003559.
26. Thomson NC. Omalizumab decreases exacerbations and allows a step down in daily inhaled corticosteroid dose in adults and children with moderate-to-severe asthma. *Evid Based Med* 2014;19:135.
27. Anderson WC III, Szefer SJ. New and future strategies to improve asthma control in children. *J Allergy Clin Immunol* 2015;136:848-59.
28. Schmitt J, Schwarz K, Stadler E, Wüstenberg EG. Allergy immunotherapy for allergic rhinitis effectively prevents asthma: results from a large retrospective cohort study. *J Allergy Clin Immunol* 2015;136:1511-6.
29. Burks AW, Calderon MA, Casale T, Cox L, Demoly P, Jutel M, et al. Update on allergy immunotherapy: American Academy of Allergy, Asthma & Immunology/European Academy of Allergy and Clinical Immunology/PRACTALL consensus report. *J Allergy Clin Immunol* 2013;131:1288-96.
30. Canonica GW, Cox L, Pawankar R, Baena-Cagnani CE, Blaiss M, Bonini S, et al. Sublingual immunotherapy: World Allergy Organization position paper 2013 update. *World Allergy Organ J* 2014;7:6.
31. Calderon MA, Casale TB, Nelson HS, Demoly P. An evidence-based analysis of house dust mite allergen immunotherapy: a call for more rigorous clinical studies. *J Allergy Clin Immunol* 2013;132:1322-36.
32. Calderón MA, Kleine-Tebbe J, Linneberg A, De Blay F, Hernandez Fernandez de Rojas D, Virchow JC, et al. House dust mite respiratory allergy: an overview of current therapeutic strategies. *J Allergy Clin Immunol Pract* 2015;3:843-55.
33. Langley SJ, Goldthorpe S, Craven M, Woodcock A, Custovic A. Relationship between exposure to domestic allergens and bronchial hyperresponsiveness in non-sensitized, atopic asthmatic subjects. *Thorax* 2005;60:17-21.
34. Kanchongkittiphon W, Mendell MJ, Gaffin JM, Wang G, Phipatanakul W. Indoor environmental exposures and exacerbation of asthma: an update to the 2000 review by the Institute of Medicine. *Environ Health Perspect* 2015;123:6-20.
35. Gent JF, Belanger K, Triche EW, Bracken MB, Beckette WS, Leaderer BP. Association of pediatric asthma severity with exposure to common household dust allergens. *Environ Res* 2009;109:768-74.
36. Kovac K, Dodig S, Tjesic-Drinkovic D, Raos M. Correlation between asthma severity and serum IgE in asthmatic children sensitized to *Dermatophagoides pteronyssinus*. *Arch Med Res* 2007;38:99-105.
37. Zureik M, Neukirch C, Bene Leynaert B, Liard R, Bousquet J, Neukirch F. European Community Respiratory Health Survey. Sensitization to airborne moulds and severity of asthma: cross sectional study from European Community Respiratory Health Survey. *BMJ* 2002;325:411-4.
38. ten Brinke A, Sterk PJ, Masclee AA, Spinoven P, Schmidt JT, Zwiderman AH, et al. Risk factors of frequent exacerbations in difficult-to-treat asthma. *Eur Respir J* 2005;26:812-8.
39. Shaaban R, Zureik M, Soussan D, Neukirch C, Heinrich J, Sunyer J, et al. Rhinitis and onset of asthma: a longitudinal population-based study. *Lancet* 2008;372:1049-57.
40. Brozek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB, et al. Global Allergy and Asthma European Network; Grading of Recommendations Assessment, Development and Evaluation Working Group. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol* 2010;126:466-76.
41. Abramson MJ, Puy RM, Weiner JM. Injection allergen immunotherapy for asthma. *Cochrane Database Syst Rev* 2010;(8):CD001186.
42. Lu Y, Xu L, Xia M, Li Y, Cao L. The efficacy and safety of subcutaneous immunotherapy in mite-sensitized subjects with asthma: a meta-analysis. *Respir Care* 2015;60:269-78.
43. Normansell R, Kew KM, Bridgman AL. Sublingual immunotherapy for asthma. *Cochrane Database Syst Rev* 2015;8:CD011293.
44. Blumberg G, Groes L, Haugaard L, Dahl R. Steroid-sparing effect of subcutaneous SQ-standardised specific immunotherapy in moderate and severe house dust mite allergic asthmatics. *Allergy* 2006;61:843-8.
45. Zielen S, Kardos P, Madonini E. Steroid-sparing effects with allergen-specific immunotherapy in children with asthma: a randomized controlled trial. *J Allergy Clin Immunol* 2010;126:942-9.
46. Voltolini S, Troise C, Incorvaia C, Bignardi D, Di Cara G, Marcucci F, et al. Effectiveness of high dose sublingual immunotherapy to induce a stepdown of seasonal asthma: a pilot study. *Curr Med Res Opin* 2010;26:37-40.
47. Wang L, Yin J, Fadel R, Montagut A, de Beaumont O, Devillier P. House dust mite sublingual immunotherapy is safe and appears to be effective in moderate, persistent asthma. *Allergy* 2014;69:1181-8.
48. de Blay F, Kuna P, Prieto L, Ginko T, Seitzberg D, Riis B, et al. SQ HDM SLIT-tablet (ALK) in treatment of asthma—post hoc results from a randomised trial. *Respir Med* 2014;108:1430-7.
49. Virchow JC, Backer V, Kuna P, Prieto L, Nolte H, Hedegaard Villesen H, et al. Efficacy of a house dust mite sublingual allergen immunotherapy tablet in adults with allergic asthma—a randomized clinical trial. *JAMA* 2016;315:1715-25.
50. Mosbech H, Deckelmann R, de Blay F, Pastorello EA, Trebas-Pietras E, Andres LP, et al. Standardized quality (SQ) house dust mite sublingual immunotherapy tablet (ALK) reduces inhaled corticosteroid use while maintaining asthma control: a randomized, double-blind, placebo-controlled trial. *J Allergy Clin Immunol* 2014;134:568-75.
51. Emminger W, Smeenk F, Guzik T, Dyczek A, Fejerskov P, Brodersen R, et al. The SQ HDM SLIT-tablet is well-tolerated in respiratory allergic disease: results from 2 DBPC phase III trials (MERIT and MITRA). *Allergy* 2014;69:184.
52. Jutel M, Agache I, Bonini S, Burks AW, Calderon M, Canonica W, et al. International consensus on allergy immunotherapy. *J Allergy Clin Immunol* 2015;136:556-68.
53. Epstein TG, Liss GM, Murphy-Berendts K, Bernstein DI. AAAAI/ACAAI surveillance study of subcutaneous immunotherapy, years 2008-2012: an update on fatal and nonfatal systemic allergic reactions. *J Allergy Clin Immunol Pract* 2014;2:161-7.
54. Incorvaia C, Ridolo E. In the strategies to prevent asthma exacerbations, allergic asthma needs specific treatment. *Curr Med Res Opin* 2015;31:821-3.
55. Massanari M, Nelson H, Casale T, Busse W, Kianifard F, Geba GP, et al. Effect of pretreatment with omalizumab on the tolerability of specific immunotherapy in allergic asthma. *J Allergy Clin Immunol* 2010;125:383-9.
56. Lambert N, Guiddir T, Amat F, Just J. Pre-treatment by omalizumab allows allergen immunotherapy in children and young adults with severe allergic asthma. *Pediatr Allergy Immunol* 2014;25:829-32.
57. Braidio F, Corsico A, Rogkakou A, Ronzoni V, Baiardini I, Canonica GW. The relationship between allergen immunotherapy and omalizumab for treating asthma. *Expert Rev Respir Med* 2015;9:129-34.
58. Linneberg A, Henrik Nielsen N, Frolund L, Madsen F, Dirksen A, Jorgensen T. The link between allergic rhinitis and allergic asthma: a prospective population based study. *The Copenhagen Allergy Study*. *Allergy* 2002;57:1048-52.
59. Demoly P, Emminger W, Rehm D, Backer V, Tommerup L, Kleine-Tebbe J. Effective treatment of house dust mite-induced allergic rhinitis with 2 doses of the SQ HDM SLIT-tablet: results from a randomized double-blind, placebo-controlled phase III trial. *J Allergy Clin Immunol* 2016;137:444-51.
60. Bergmann KC, Demoly P, Worm M, Fokkens WJ, Carrillo T, Tabar AI, et al. Efficacy and safety of sublingual tablets of house dust mite allergen extracts in adults with allergic rhinitis. *J Allergy Clin Immunol* 2014;133:1608-14.

61. Lin J, Su N, Liu G, Yin K, Zhou X, Shen H, et al. The impact of concomitant allergic rhinitis on asthma control: a cross-sectional nationwide survey in China. *J Asthma* 2014;51:34-43.
62. Yamasaki A, Tomita K, Kato K, Fukutani K, Sano H, Tohda Y, et al. Development and validation of a predictive model of failed stepping-down of inhaled corticosteroids in adult asthmatics. *Patient Prefer Adherence* 2016;10:339-44.
63. Domínguez-Ortega J, Phillips-Anglés E, Barranco P, Quirce S. Cost-effectiveness of asthma therapy: a comprehensive review. *J Asthma* 2015;52:529-37.
64. Hankin CS, Cox L. Allergy immunotherapy: what is the evidence for cost saving? *Curr Opin Allergy Clin Immunol* 2014;14:363-70.
65. Reinhold T, Ostermann J, Thum-Oltmer S, Brüggengjürgen B. Influence of subcutaneous specific immunotherapy on drug costs in children suffering from allergic asthma. *Clin Transl Allergy* 2013;3:30.
66. Hahn-Pedersen J, Worm M, Green W, Nørgaard Andreasen J, Taylor M. Cost utility analysis of the SQ® HDM SLIT-tablet in house dust mite allergic asthma patients in a German setting. *Clin Transl Allergy* 2016;6:35.