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Predictors of inhaled corticosteroid taper failure in adults with asthma

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TO THE EDITOR:

Guidelines recommend considering stepping down asthma controller therapy when symptoms are controlled for at least 3 months.[1] When an inhaled corticosteroid (ICS) dose taper is chosen as the step-down method, these guidelines recommend 25% to 50% dose reductions. Other than these recommendations, there is little guidance on which patients will taper successfully, mostly based on small ($n \leq 50$ participants)[2,3] or retrospective studies.[4]

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A preliminary version of these analyses was presented as an abstract at the 2016 annual American Thoracic Society meeting: Cardet JC, King TS, Bacharier LB, Carr TF, Chinchilli VM, Codispoti CD, et al. Predictors of inhaled corticosteroid reduction failure in adult asthmatics. Am J Respir Crit Care Med 2016;193:A1310.

Other studies have investigated the effects of either discontinuing or reducing the ICS dose by more than the recommended maximum.[3,5] The Vitamin D Add-on Therapy Enhances Corticosteroid Responsiveness in Asthma (VIDA) trial used a guideline-driven, ICS dose-reduction approach (2 sequential 50% dose-reduction phases) to determine whether vitamin D supplementation reduces treatment failures.[6] We performed an exploratory analysis of the VIDA trial to identify clinical features associated with ICS reduction failure.

The VIDA trial was a multicenter, randomized, double-blind, parallel-arm, placebo-controlled trial that included adults 18 years or older with symptomatic asthma and vitamin D insufficiency (<30 ng/mL).[6] Asthma diagnosis required (1) physician-diagnosed disease and (2) evidence of either bronchodilator reversibility (postbronchodilator FEV_1 increase ≥12% following 180 μg [4 puffs] of levalbuterol) or airway hyperresponsiveness ($PC_{20} \leq 8$ mg/mL). The outcome of this exploratory analysis was ICS reduction failure in the second 50% ICS reduction phase, algorithmically defined as either an increase in rescue inhaler use or peak flow variability, or experiencing a VIDA protocol–defined treatment failure[6] (see the Methods section in this article's Online Repository at www.jaci-inpractice.org). Potential predictors were chosen on the basis of availability and group consensus, and appear in Table I and Table E1 in this article's Online Repository at www.jaci-inpractice.org. Hip and waist circumference, smoking history, asthma duration, methacholine PC_{20}, and sputum inflammatory cells were defined as continuous variables, others categorically. Categorical cutoff point thresholds were based on a validation analysis during the trial's first 50% ICS reduction phase, except for the Asthma Control Test (ACT) threshold for uncontrolled asthma (<20). Clinical covariates were collected at baseline before the run-in. ACT data were collected before randomization and 12 weeks after the initial ICS dose (before tapering). We used bivariate logistic regression to evaluate independent factors associated with failed ICS reduction. The most predictive factors ($P < .10$) were included in subsequent multivariable logistic regression models, and remained in these models if P was less than .05 with adjustment for other factors. Two multivariable logistic regression models were developed, with and without sputum eosinophil data, which affected sample size for analyses. All analyses were performed using SAS v9.3 (SAS Institute Inc., Cary, NC).

Three hundred of the 408 randomized participants started on ciclesonide 320 μg/d completed both 50% ICS reduction phases, had outcome data available, and were included in this exploratory analysis (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). Baseline characteristics of included participants appear in Table E1 and entered regression analyses. Twenty-two percent experienced a failed ICS reduction. The following variables predicted ICS reduction failures at a $P = .10$ significance level in bivariate regression analyses: older age, obesity, greater hip and waist circumference, nasal polyposis, baseline ACT score of less than 20; previous exacerbations, emergency department and unscheduled office visits, hospitalizations, asthma controller therapy with either ICS alone or combination ICS + long-acting beta-agonists (LABAs), systemic corticosteroid use in the year before enrollment, and baseline sputum eosinophils of more than 2% (Table I). We then identified in a multivariable model that having high baseline sputum eosinophils (>2%) (odds ratio [OR], 2.11; 95% CI, 1.02-4.36; $P = .04$), older age (for every 10-year increase, OR, 1.33; 95% CI, 1.04-1.70; $P = .02$), and ICS + LABA use in the year before enrollment (OR, 2.62; 95% CI, 1.31-5.22; $P = .01$) were the only variables

remaining associated with ICS reduction failure (Table II). Because sputum eosinophils are usually unavailable in clinical practice, we built an additional multivariable model excluding sputum eosinophil data, and found that nasal polyposis (OR, 2.74; 95% CI, 1.11-6.78; $P = .03$), greater waist circumference (for every 10-cm increase, OR, 1.19; 95% CI, 1.03-1.38; $P = .02$), and ICS + LABA use in the year before enrollment (OR, 2.07; 95% CI, 1.09-3.93; $P = .03$) were associated with ICS reduction failure (Table II).

In summary, we have found that baseline clinical characteristics help predict which participants are more likely to fail ICS reduction in the setting of a randomized controlled trial. Because sputum eosinophils are not universally available to clinicians or investigators, we built 2 different multivariable models based on their availability. The models indicate that when sputum eosinophils are available, features that predict failure of ICS tapering are older age, use of ICS + LABA in the year before enrollment, and high sputum eosinophil levels; when sputum eosinophils are not available, features that predict failure of ICS tapering are nasal polyps, larger waist circumference, and use of ICS + LABA in the year before enrollment. Previous studies have identified sputum eosinophils as associated with taper failures, but these have been limited by retrospective design or small sample size.[5]

It is perhaps unsurprising that “nasal polyposis” appeared as a significant variable when data on sputum eosinophils were unavailable considering the observed correlation between nasal polyposis and sputum eosinophils.[7] We also identified “older age” and “waist circumference” as features associated with ICS reduction failure, which are 2 recognized markers of corticosteroid resistance.[8,9] It may seem counterintuitive for markers of corticosteroid resistance to predict reduction failure. However, by study design, all participants required having *well-controlled* symptoms to qualify for tapering. Our results identify these populations as more susceptible to relapsing during ICS reductions. “ICS + LABA use” in the year before enrollment may signify individuals with more severe asthma, therefore more liable to ICS reduction failures (indeed, participants who used ICS + LABA in the year before enrollment had a lower %predicted FEV_1 [80%] compared with those who did not [85%]; $P < .001$).

A potential limitation is that the predictors identified were restricted to those available in the parent VIDA study and may not reflect all important contributors. Although retrospective in nature, our results may be useful to clinicians and investigators: clinicians may wish to prescribe *slower* ICS tapers in patients with any of these characteristics (obesity, old age, high sputum eosinophil levels, nasal polyposis, or ICS + LABA use in the past year) to reduce the risk of asthma symptom relapse; investigators may optimize their recruitment strategies by considering these characteristics in trials with ICS monotherapy and dose reductions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Conflicts of interest:

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Clinical Implications

- Baseline characteristics predict which participants are more likely to fail inhaled corticosteroid (ICS) reduction, including obesity, old age, high sputum eosinophil levels, nasal polyposis, or use of ICS + long-acting beta-agonist in the past year. A slower ICS taper may be necessary in these patients.

TABLE I.

Bivariate associations between participant characteristics and failed ICS tapers (n = 300, with 65 taper failures)*

Predictors	Taper failure, Mean ± SD or n (%)†	Taper success, Mean ± SD or n (%)†	Unadjusted OR (95% CI; *P*)
Demographic characteristics			
Age (y)‡	42.3 ± 11.7	39.0 ± 12.8	1.23 (0.99-1.54; **.06**)
Sex: male	21 (32)	83 (35)	1.14 (0.64-2.05; .65)
Race/ethnicity			
Black	24 (36.9)	69 (29.4)	1.38 (0.76-2.52; .29)
Hispanic	6 (9.2)	22 (9.4)	1.08 (0.41-2.89; .87)
Other	2 (3.1)	13 (5.5)	0.61 (0.13-2.84; .53)
White	33 (50.8)	131 (55.7)	Reference
Household income (<$50,000/y)	35 (58.3)	110 (50.5)	1.38 (0.77-2.45; .28)
Clinical characteristics			
Obesity (BMI > 30)	38 (58.5)	106 (45.1)	1.71 (0.98-2.99; **.06**)
Hip circumference§	116.2 ± 17.58	111.9 ± 17.8	1.01 (0.998-1.03; **.08**)
Waist circumference§	103.5 ± 20.77	97.5 ± 18.73	1.02 (1.00-1.03; **.03**)
GERD	13 (22.0)	55 (23.8)	0.90 (0.46-1.80; .77)
Nasal polyposis	9 (14.5)	15 (6.7)	2.38 (0.99-5.73; **.05**)
Sleep apnea	5 (7.7)	14 (6.0)	1.32 (0.46-3.80; *P* = .61)
Smoking history (pack-years)	0.88 ± 2.09	0.56 ± 1.77	1.09 (0.95-1.24; *P* = .22)
Age of asthma onset	Median = 10-19 y	Median = <10 y	1.13 (0.93-1.37; *P* = .23)
Duration of asthma (y)	4.7 ± 0.73	4.6 ± 0.80	1.13 (0.78-1.65; *P* = .52)
Clinical asthma history in the year before enrollment			
ACT score < 20‖	28 (43.1)	72 (30.8)	1.70 (0.97-2.99; ***P* = .06**)
ED/unscheduled office visit	28 (43.1)	69 (29.4)	1.82 (1.03-3.21; ***P* = .04**)
Hospitalizations	5 (7.7)	5 (2.1)	3.83 (1.08-13.67; ***P* = .04**)
Corticosteroid use			
Systemic corticosteroids (oral, IV, or IM)	24 (36.9)	60 (25.5)	1.71 (0.95-3.06; ***P* = .07**)

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Predictors	Taper failure, Mean ± SD or n (%)†	Taper success, Mean ± SD or n (%)†	Unadjusted OR (95% CI; *P*)
Inhaled	21 (32.3)	116 (49.4)	0.49 (0.27-0.87; **P = .02**)
Inhaled + long-acting beta-agonist	49 (75.4)	131 (56.0)	2.41 (1.30-4.48; **P = .01**)
Previous exacerbations¶	34 (52.3)	88 (37.5)	1.83 (1.05-3.19; **P = .03**)
Asthma phenotyping and physiological tests			
Sputum eosinophils (>2%)	16 (27.6)	31 (16.1)	1.99 (0.99-3.98; **P = .05**)
Change in FEV_1 with prednisone (>5%)	8 (14.0)	37 (18.7)	0.71 (0.31-1.63; *P* = .42)
ΔFEV_1 ≥12% with 4 puffs of levalbuterol	36 (56.3)	127 (54.3)	1.08 (0.62-1.89; *P* = .78)
MCh PC_{20} (mg/mL), geometric mean (CV)	1.68 (1.73)	2.32 (1.65)	0.92 (0.82-1.04; *P* = .18)
Sputum neutrophils	41.9 (24.0)	40.3 (22.5)	1.00 (0.99-1.02; *P* = .64)
Sputum macrophages	35.0 (19.8)	37.3 (20.0)	0.99 (0.98-1.01; *P* = .45)
Sputum lymphocytes	0.75 (0.92)	0.98 (1.29)	00.84 (0.63-1.11; *P* = .22)

ACT, Asthma Control Test; *BMI*, body mass index; *CV*, coefficient of variation; *ED*, emergency department; *GERD*, gastroesophageal reflux disease; *IM*, intramuscular; *IV*, intravenous; *MCh*, methacholine challenge.

*Predictors were selected for inclusion in our multivariable models if bivariate analysis *P* < .10, and appear bolded.

†Percentages shown are within column percentages (eg, the percent of all participants who experienced a taper failure and who were male was 32%; the percent of all participants who experienced a taper success and who were male was 35%).

‡Per 10-y increase in age.

§Per 10-cm increase in circumference.

‖An ACT score of <20 signifies uncontrolled asthma symptoms.

¶*Previous exacerbations* was defined as having experienced an ED visit, *or* an hospitalization, *or* having received a systemic corticosteroid burst for the treatment of asthma in the year before enrollment.

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TABLE II.

Predictors of failed ICS tapers

Predictors	Adjusted OR (95% CI; *P*)
Model *including* sputum eosinophils at baseline (n = 250)	
Sputum eosinophils (>2%)	2.11 (1.02-4.36; **.04**)
Age[*]	1.33 (1.04-1.70; **.02**)
ICS + LABA[†]	2.62 (1.31-5.22; **.01**)
Model *not including* sputum eosinophils at baseline (n = 286)	
Nasal polyposis[‡]	2.74 (1.11-6.78; **.03**)
Waist circumferenc[‡§]	1.19 (1.03-1.38; **.02**)
ICS + LABA[†]	2.07 (1.09-3.93; **.03**)

LABA, Long-acting beta-agonist.

Statistically significant values appear bolded.

[*]Per 10-y increase in age.

[†]ICS + LABA combination controller therapy used in the year before enrollment.

[‡]At the time of enrollment.

[§]Per 10-cm increase in waist circumference.