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Inhaled corticosteroid dose response in asthma
Should we measure inflammation?

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ABSTRACT

Background: Inhaled corticosteroid (ICS) titration in asthma is primarily based on symptoms and pulmonary function. ICSs may not be increased on this basis despite residual airway inflammation.
Objective: To compare the dose-response relationships of ICSs on measures of pulmonary function, symptoms, and inflammation in patients with persistent asthma.
Methods: We performed a pooled post hoc analysis of 121 patients with mild to moderate asthma from 4 randomized clinical trials that incorporated an ICS dose ramp. Dose ramps were 0 to 200, 0 to 800, and 200 to 800 μg/d (beclomethasone equivalents). Outcome measures included spirometry, fractional exhaled nitric oxide, airway hyperresponsiveness (AHR), symptoms, serum eosinophilic cationic protein, and blood eosinophils.
Results: We found a plateau beyond a small improvement at 0 to 200 μg for forced expiratory volume in 1 second: 3.3% (95% confidence interval [CI], 2.0%–4.7%) at 0 to 200 μg vs 0.3% (95% CI, −0.8% to 1.4%) 200 to 800 μg ($P = .001$). A similar plateau was seen for symptom improvement beyond 0 to 200 μg. Inflammatory and AHR outcomes revealed further room for improvement beyond low-dose ICSs. There was dose-related suppression ($P < .001$) for fractional exhaled nitric oxide: 40.4 ppb (95% CI, 34.7–46.9 ppb) for ICS free, 26.8 ppb (95% CI, 23.4–30.2 ppb) for 200 μg, and 20.8 ppb (95% CI, 18.8–23.1 ppb) for 800 μg. Eosinophilic cationic protein concentration was significantly reduced with both higher dose ramps. Eosinophil counts also improved across all 3 dose ramps, with dose separation of 370/μL (95% CI, 280–450/μL) for ICS free vs 250/μL (95% CI, 200–300/μL) 800 μg ($P = .03$). AHR improved with all 3 dose ramps, with greater improvement at lower doses for indirect vs direct challenges.
Conclusion: ICS dose response may extend beyond low dose for inflammation and AHR but not symptoms or spirometry. Further study is required to identify whether this correlates with suboptimal longitudinal asthma control.
Trial Registration: ClinicalTrials.gov Identifiers: NCT00667992, NCT00995657, NCT01216579, NCT01544634.

Introduction

Asthma is a heterogeneous chronic inflammatory disease of global importance[1] that places a significant burden on individual patients and health care services, where many patients remain inadequately treated[2,3] with an ongoing attendant mortality.[4] The concept of achieving total asthma control[5] is important for reducing the future risk of exacerbations.[6–8] It is therefore imperative that we have robust procedures for accurate diagnosis, measurement of severity, prediction of future risk, and appropriate personalized treatments to achieve this goal. Nevertheless, current guidelines for the identification and treatment of asthma merely include symptoms and lung function measurements.[5,9] The Royal College of Physicians' recent National Review of Asthma Deaths report[4] found that only 39% of patients who died were actually diagnosed as having severe asthma according to current guidelines, with the remainder therefore diagnosed as having mild or moderate asthma, suggesting we may not be accurately identifying those at greatest risk.

Measurement of inflammatory outcomes has improved our understanding of asthma and improved personalized treatment. Studies have found that titrating steroid therapy against inflammation may improve outcomes, such as exacerbation rates.[10–12] For example, one primary care–based study that titrated inhaled corticosteroid (ICS) dose against mannitol challenge vs a reference strategy resulted in a 27% significant reduction in mild exacerbations but no difference in severe exacerbations.[11] Similar findings were observed in another study using methacholine challenge.[13] Green

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et al[10] found this by titrating steroid treatment against sputum eosinophil counts, resulting in significantly fewer severe exacerbations compared with standard guideline-driven treatment. It is interesting that this was achieved with no difference in overall mean dosage of ICSs between the 2 groups, suggesting that for the individual, any steroid titration was performed at the right time for them when their levels of inflammation were greater. However, other studies have suggested a more muted response to inflammatory steroid titration in unselected patients with asthma.[14,15]

Price et al[16] found retrospectively, in a primary care cohort, that patients with asthma with higher blood eosinophil counts fared worse in terms of experiencing more severe exacerbations and poorer asthma control. Moreover, eosinophilic inflammation may be masked when using a long-acting β_2-agonist as a steroid-sparing agent.[17,18] Sputum and blood eosinophilia in asthma have both been separately found to predict loss of asthma control and increased exacerbation rates.[6,19,20] This is also true of fractional exhaled nitric oxide (FeNO) levels[21] and airway hyperresponsiveness (AHR),[6] the latter being largely driven by airway inflammation.[22] It is therefore logical that one might wish to control inflammation over and above simply controlling symptoms and lung function—much like controlling asymptomatic hypertension to prevent subsequent cardiovascular sequelae. This is relevant given that lung function and lack of symptoms may be deemed normal despite the possibility of an ongoing underlying inflammatory process.[23]

We performed a post hoc pooled analysis of data from 4 previously published randomized clinical trials in which ICS dose titration was used in a prospective manner. Outcome measurements included symptoms, lung function, inflammation, and AHR. We then analyzed the dose-response relationship to ICSs for these outcomes to identify where incremental ICS dosing provides the greatest effect and thus is likely to be most informative when titrating a given individual's treatment to achieve optimal or total asthma control.

Methods

Patients

Nonsmoking men and women (age range, 18–65 years) with mild-moderate, persistent asthma receiving 1,000 μg/d of ICSs or less (ie, expressed as a reference dose of large particle beclomethasone dipropionate equivalent dose) were recruited to each of 4 RCTs.[11,24–26] For example, large-particle hydrofluoroalkane-fluticasone (200 μg) or small-particle hydrofluoroalkane-beclomethasone (200 μg) would be equivalent to large-particle hydrofluoroalkane-beclomethasone dipropionate (400 μg). Their post–run-in baseline measurements are presented in Table 1. Further detailed inclusion and exclusion criteria can be found in each of the reported trials.

Study Design

We performed a post hoc analysis using data from 4 RCTs,[11,24–26] each comprising a component where the effects of ICS dose ramp

Table 1
Baseline Values After Run-in at the Given Beclomethasone Dipropionate Equivalent Doses for Large-Particle Hydrofluoroalkane–Fluticasone Propionate, Large-Particle Hydrofluoroalkane-Budesonide, Small-Particle Hydrofluoroalkane-Beclomethasone, and Small-Particle Hydrofluoroalkane-Ciclesonide[a]

Variable	All (N = 121)	Fluticasone propionate (ICS free) (n = 21)	Budesonide (ICS free) (n = 72)	Hydrofluoroalkane-beclomethasone dipropionate (200 μg of beclomethasone dipropionate) (n = 16)	Ciclesonide (200 μg of beclomethasone dipropionate) (n = 12)
Age, mean (95% CI), y	39.8 (37.2–42.4)	36.8	39.6	37.8	48.7
Sex, M:F	44:77	6:15	29:43	6:10	3:9
SPT allergens, median (IQR)	3 (2–4)	3 (1–4)	3 (2–3.25)	2.5 (1–4)	1.5 (0–3.25)
SPT positivity, % patients	89	81	94	88	63
FEV_1, mean (95% CI), % predicted	85.1 (82.9–87.3)	88.5	82	90.3	89
$FEF_{25\%–75\%}$, mean (95% CI), % predicted	65.7 (61.5,69.8)	53.5	70.4	60.3	-
FEV_1/FVC ratio, mean (95% CI), %	75.2 (73.7–76.7)	71.2	75.6	74.6	80.5
FeNO, geometric mean (95% CI), ppb	37.3 (32.3–42.6)	72.4	34.7	29.1	25.4 (n = 10)
AHR, geometric mean (95% CI)		102 mg (57–183 mg) mannitol PD_{15}	0.72 mg/mL (0.58–0.90 mg/mL) methacholine PC_{20}	1.31 mg/mL (0.64–2.69 mg/mL) histamine PC_{20}	59 mg (15–233 mg) mannitol PD_{10}
ECP, geometric mean (95% CI), μg/L (n = 47)	20.5 (15.9,26.3)	18.6	-	22.4	21.9
Eos, mean (95% CI), /μL (n = 37)	330 (280,390)	370	-	290	-
Symptom score, mean (95% CI)[b]		5.8 (5.4–6.2)	0.96[c] (0.79–1.12)	6.2 (5.9–6.5)	6.1 (5.6–6.5)
Screening ICS (beclomethasone dipropionate equivalent, mean (95% CI), μg/d	420 (361–479)	440	414	406	436

Abbreviations: AHR, airway hyperresponsiveness; CI, confidence interval; ECP, eosinophilic cationic protein; $FEF_{25\%–75\%}$, forced expiratory flow between 25% and 75%; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroid; IQR, interquartile range; PC_{10}, provocation concentration causing a 10% decrease in FEV_1; PC_{20}, provocation concentration causing a 20% decrease in FEV_1; PD_{15}, provocation dose causing a 10% decrease in FEV_1; SPT, skin prick test to common allergens.

[a]Overall means (95% CIs) are presented in the leftmost column. All other data are expressed as arithmetic means (95% CIs) unless otherwise stated.

[b]Symptom scores are the symptom component of the Mini Asthma Quality of Life Questionnaire, except for budesonide.

[c]Total symptom score was scored as follows: 0, no symptoms; 1, mild; 2, moderate; and 3, severe.