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Exhaled nitric oxide and inhaled corticosteroid dose reduction in asthma: a cohort study

To the Editor:

Inhaled corticosteroids (ICS) reduce airway inflammation; however, guidelines recommend titrating ICS dose based on symptoms [1], which are not closely associated with airway inflammation [2]. Once symptoms are controlled for $\geqslant$3 months, ICS reduction is recommended [3] but step-down is often not implemented. Studies suggest that the majority of patients treated with ICS can have their therapy stepped down, although there is no clear evidence on how best to achieve this [4].

We assessed whether exhaled nitric oxide fraction ($F_{E}NO$) measurements could predict a loss of symptom control or exacerbation following a reduction in ICS dose in a cohort study of people with well-controlled asthma recruited from primary care.

All participants had a recorded asthma diagnosis, were aged 18–75 years, and had received at least one ICS prescription in the last year. The study was restricted to nonsmokers (<10 pack-years). Poorly compliant participants, and participants with an asthma exacerbation requiring oral steroids in the previous 12 weeks or with a Juniper five-item Asthma Control Questionnaire (ACQ-5) [5] score >1.5 at visit 1 (indicating poor control) were excluded.

Participants were seen at the same time of day on four occasions: days 0, 14, 21 and 110. At each visit, ACQ-5, $F_{E}NO$ (Flex Flow; Aerocrine, Solna, Sweden) and spirometry were performed. Symptoms were assessed using the ACQ-5 [6]. Airway inflammation was measured using $F_{E}NO$ at 50 mL·s^{-1}; participants were blinded to their measurements. Differential cell counts were performed on induced sputum. Spirometry was performed. Airway hyperresponsiveness was assessed using the concentration of methacholine required to provoke a 20% fall in forced expiratory volume in 1 s (PC_{20}). Differential blood eosinophil count and IgE measurement were performed.

Participants were re-assessed at visit 2; if their ACQ-5 score remained <1.5 and had not increased by >0.5, their ICS dose was reduced by 50%. Inhaler types were kept the same. Participants were asked to take the half dose of ICS for 7 days and then return for visit 3. At visit 3, the ACQ-5 score was re-measured.

A loss of control was defined as an increase in ACQ-5 score >0.5 (the minimal important difference in asthma control [7]). An exacerbation was defined as increasing asthma symptoms requiring a course of antibiotics or oral steroids [8]. All participants who contacted the emergency team were assessed by a physician within 24 h and their ACQ-5 recorded; decisions on treatment were based on British Thoracic Society guidelines.

We estimated that 154 subjects would provide 80% power to show that a low $F_{E}NO$ or lack of change in $F_{E}NO$ following ICS reduction could successfully predict stable control [8, 9]. Data were analysed in two ways: firstly, we assessed whether a low baseline $F_{E}NO$ predicted successful ICS dose reduction; secondly, we evaluated whether an increase in $F_{E}NO$ following dose reduction predicted deterioration. We also evaluated whether other clinical measures predicted successful dose reduction at 3 months. Measures included: spirometry; methacholine PC_{20}; IgE; blood eosinophil count; ACQ-5; and differential sputum eosinophil and neutrophil count.

191 participants had their $F_{E}NO$ level measured at before (visit 2) and 7 days after (visit 3) a 50% reduction in ICS dose (visit 3) (table 1). 128 (67%) participants completed the 3-month study period (after ICS reduction) with no loss of control or exacerbation, and 63 (33%) out of 191 experienced either a loss of control (n=32, 17%) or exacerbation (n=31, 16%). The median (interquartile range) baseline ACQ-5 was 0.6 (0.2–1.0) for the stable group and 0.8 (0.2–1.0) for the deterioration group (p=0.53). The mean$\pm$SD ICS beclomethasone dipropionate (BDP)-equivalent dose reduction across the study was 363$\pm$267 μg.

There were no significant differences in baseline $F_{E}NO$ (visit 2) between those successfully reducing ICS dose and those suffering from a loss of control or exacerbation. At 50 mL·s^{-1}, the geometric mean baseline $F_{E}NO$

TABLE 1 Baseline demographics presented for study population[#]

Variable	Result
Age years	54.15±13.50
Sex n (%)	
Males	83 (43.5)
Females	108 (56.5)
Age when diagnosed years	
0–5	16 (8.4)
>5	175 (91.6)
BTS treatment step	
2	57 (29.84)
3	111 (58.12)
4	23 (12.04)
Smoking pack-years	0 (0–4)
Height cm	169.24±9.89
Mass kg	81.14±17.31
BMI kg·m^{-2}	28.27±5.36
BDP-equivalent[¶] daily dose μg·day^{-1}	400 (200–1000)
FEV_1 L	2.68±0.85
FEV_1 % predicted	89.85±19.15
FVC L	3.65±1.00
FVC % predicted	99.81±16.87
Airway hyperresponsiveness PC_{20} mg·mL^{-1} geometric mean (95% CI)	8.02 (6.31–10.17)
Blood IgE kIU·L^{-1}	91.5 (28.50–253.50)
Blood eosinophils ×10^9 cells·L^{-1}	0.20 (0.12–0.32)
Sputum eosinophils %	0.80 (0.25–4.75)
Sputum neutrophils %	64.75 (42.25–84.00)
ACQ-5 score	0.60 (0.20–1.00)

Data are presented as mean±SD, n (%) or median (interquartile range), unless otherwise stated. BTS: British Thoracic Society; BMI: body mass index; BDP: beclomethasone dipropionate; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; PC_{20}: provocative concentration of methacholine producing a 20% fall in FEV_1; ACQ-5: five-item Asthma Control Questionnaire. [#]: n=191; [¶]: QVAR (Teva, Castleford, UK), 2:1 BDP; Flixotide (GlaxoSmithKline, London, UK), 2:1 BDP; budesonide, 1:1 BDP.

was 18.9 ppb (95% CI 16.8–21.5 ppb) in the stable group and 19.7 ppb (95% CI 16.4–23.6 ppb) in the deterioration group (p=0.76).

There was no significant difference in the change in $F_{E}NO$ in the week following ICS reduction (visit 2 to visit 3) between the stable and deterioration groups. The mean±SD absolute change between visit 2 and 3 was 1.58±11.9 ppb for the stable group and 1.03±14.88 ppb for the deterioration group (p=0.80). There were no significant differences in any of the clinical measurements between groups.

Although guidelines recommend a 50% reduction in ICS dose after 3 months of good symptom control, there is evidence of overtreatment with ICS [10] and a reluctance to reduce treatment [11]. Consequently, using inflammometry to guide treatment decisions may be beneficial. We addressed previous criticisms by evaluating both individual baseline $F_{E}NO$ and change from baseline. Neither baseline $F_{E}NO$ measurements nor change at 7 days following ICS dose reduction could predict which participants would remain stable or lose control over the next 3 months.

Participants were not blinded to their treatment allocation and a period of 7 days was used after step-down before repeating the $F_{E}NO$ measurements. This design was chosen to reflect real-life practice and for maximum future practical benefit. A 50% reduction was chosen as it is consistent with guideline recommendations. Our study was well powered to identify any change in $F_{E}NO$ values: the relationship between sputum eosinophilia and $F_{E}NO$ levels is strongest between 100 and 800 μg ICS (BDP equivalent) [12]; previous studies have shown that ICS dose reductions less than the mean reduction in our study result in an increase in $F_{E}NO$ levels [13]; dose-dependent onset and cessation of action effects of ICS on $F_{E}NO$ levels have been demonstrated, with levels rising after one day of treatment reduction [14]; and the largest change in $F_{E}NO$ values is found at 400 μg BDP [15], the mean value in our population.

The lack of change in *F*ENO following dose reduction may reflect that: 1) *F*ENO measurements do not correlate well enough with airway inflammation in mild-to-moderate asthma; 2) ICS dose reduction was not large enough; and 3) the episodes of loss of control were not due to increased airway inflammation.

In addition to the failure to predict ICS reduction using *F*ENO, we found that none of the baseline clinical indices (induced sputum, methacholine responsiveness and spirometry) had predictive value for future stability following ICS step-down. This has important implications for ICS dose reduction and suggests better methods of identification of those at risk of a loss of control following ICS dose reduction are needed.

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Change in *F*ENO does not identify people who are at risk of losing asthma control within the next 3 months http://ow.ly/A79aQ

Emma Wilson[1], Tricia McKeever[2], Beverley Hargadon[3], Glenn Hearson[1], John Anderson[1], David Hodgson[1], Helen Bailey[1], Garry Meakin[1], Mike Thomas[4], Ian D. Pavord[5], Tim Harrison[1] and Dominick Shaw[1]
[1]Nottingham Respiratory Research Unit, University of Nottingham, Nottingham, UK. [2]Dept of Epidemiology and Public Health, University of Nottingham, Nottingham, UK. [3]Institute for Lung Health, Glenfield Hospital, Leicester, UK. [4]Dept of Primary Care, University of Southampton, Southampton, UK. [5]University of Oxford, Oxford, UK.

Correspondence: Dominick Shaw, University of Nottingham, Respiratory Research Unit, Clinical Sciences Building, Nottingham City Hospital, Hucknall Road, Nottingham, Notts, NG5 1PB, UK. E-mail: dominic.shaw@nottingham.ac.uk

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