The role of FeNO in cough management: a randomised controlled trial

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BACKGROUND & AIM

Inhaled corticosteroids (ICS) often prescribed for presentation of cough in primary care, but response to ICS varies widely.

Although some evidence exists in a previous study, in which elevated FeNO was predictive of ICS response in patients with previously undiagnosed respiratory symptoms,[1] larger studies are needed to investigate this association further.

We previously showed FeNO to be associated with response to ICS in terms of asthma control measured by asthma control questionnaire (ACQ7).[2] The current poster presents a priori defined sub-analysis from the same study

Aim: To evaluate the association between baseline FeNO and response to ICS in terms of improvement in cough, in patients with non-specific respiratory symptoms.

METHODS

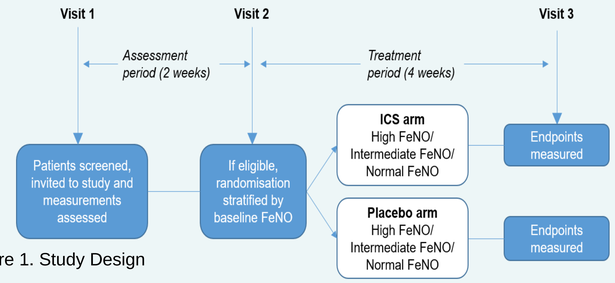


Figure 1. Study Design

Randomised, multi-centre, double-blind, placebo-controlled study, at primary care centres and hospital sites in the UK and Singapore (Fig 1).

Treatment: extrafine ICS - QVAR 80 mcg Inhalation Aerosol, two puffs 2x/ day, 400 mcg beclomethasone dipropionate equivalent.

Endpoint: change in cough symptoms, as measured on a visual analogue scale (VAS), range: 0 (no cough) - 100 (worst cough ever)

Inclusion criteria:

1. 18-80 years,
2. Presented with non-specific, persistent respiratory symptoms (cough and/or wheeze and/or chronic dyspnoea for ≥ 6 weeks),
3. No previous diagnosis of asthma,
4. Showed a reversibility to short-acting beta-agonist (SABA) of < 20% if FEV1 predicted <90% during or within one-year prior screening.

Exclusion criteria:

1. Diagnoses of asthma or any other significant chronic respiratory disease;
2. Treated with oral, inhaled or systemic corticosteroids, a leukotriene modifier or long-acting beta agonist within four weeks prior to first visit.

DATA ANALYSIS

- Generalised Linear Models (GLM) to compute the interaction effect between baseline FeNO and treatment arm. The interaction effect was interpreted as the change in treatment effect on the outcome when baseline FeNO increases
- Logistic regression was used to estimate odds of an improvement in VAS cough of more than 20 mm, for a range of potential predictors

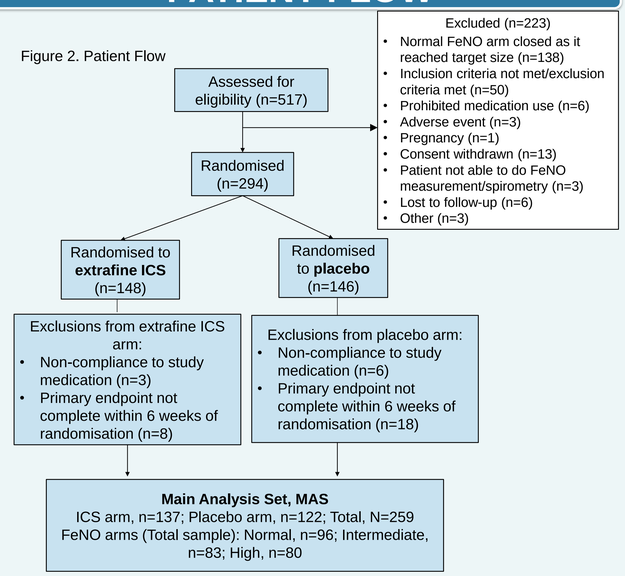
ETHICS

Approved by the National Research Ethics Service Committee Yorkshire & the Humber – South Yorkshire (14/YH/0129) for UK sites, and Parkway Independent Ethics Committee (PIEC/2014/028) and SingHealth Centralised Institutional Review Board (CIRB/2014/2052) for Singapore sites

Conducted in full accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Consolidated Guideline (E6) requirements of the ICH E2D guideline (Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting), the principles of the Declaration of Helsinki and the EU Clinical Trials Directive (2001/20/EC) as well as with any other applicable national and local laws and regulations.

PATIENT FLOW

Figure 2. Patient Flow



BASELINE DEMOGRAPHICS

Table 1. Baseline demographics of patients in main analysis set

	ICS Arm (n=137)	Placebo (n=122)	p-value[2]
Age in Years, mean (SD)	49.9 (15.4)	47.1 (16.7)	0.893
Male, n (%)	67 (48.9%)	48 (39.3%)	0.122
VAS cough, mean (SD)	41.2 (28.3)	41.2 (26.2)	0.893
Clinical judgement of asthma,[1] yes (%)	73 (53.3%)	72 (59.0%)	0.347
FeNO, mean (SD)	36.2 (27.9)	38.3 (30.7)	0.707
FEV_1 % predicted, mean (SD)	91.7 (16.4)	92.2 (14.7)	0.787
Dyspnea symptoms reported, yes (%)	82 (59.9%)	86 (70.5%)	0.073
Eosinophil count, ($x10^9$/L) mean (SD)	0.24 (0.25)	0.22 (0.15)	0.722

[1]Answer to question: "Do you believe patient is asthmatic?" [2]Mann-Whitney U for continuous and chi-square test for categorical variables.

RESULTS

Table 2: Estimated change in VAS Cough every 10 ppb higher baseline FeNO

Extrafine ICS arm	1.526 (-0.300, 3.351)
Placebo arm	-1.589 (-3.342, 0.164)
Interaction effect: Difference in above estimates	3.115 (0.579, 5.651)
Adjusted by baseline FeNO and smoking status.	

Table 2:

Difference in change in VAS Cough between ICS and placebo arm was 3.115 greater (95% CI, 0.579-5.561) for every 10 ppb increase in baseline FeNO ($p_{interaction}$=0.016).

Table 3. Baseline predictors of clinical improvement in VAS Cough (decrease ≥20mm) in the extrafine ICS arm

	Improvement (n =60)	Maintenance/ Deterioration (n= 77)	Odds ratio (95%CI)	p-value
Univariate analysis				
FeNO, mean (SD)	42.1 (30.6)	31.6 (24.8)	**1.15 (1.01, 1.32)**	**0.035**
FEV_1 %predicted, mean (SD)	3.0 (0.8)	3.2 (0.9)	0.75 (0.51, 1.13)	0.167
FeNO >40ppb, n (%)	19 (31.7)	21 (27.3)	1.24 (0.59, 2.59)	0.575
FeNO >50ppn, n (%)	17 (28.3)	11 (14.3)	**2.37 (1.01, 5.55)**	**0.046**
Eosinophil count >400/µl	11 (18.3)	5 (6.5)	**3.42 (1.10, 10.60)**	**0.034**
No additional treatment at enrolment	38 (44.7%)	47 (55.3%)	1.10 (0.55, 2.22)	0.816
No dyspnoea symptoms reported	30 (54.5%)	25 (45.5%)	2.08 (1.04, 4.17)	0.039
Clinical judgment of asthma diagnosis	31 (51.7)	42 (54.5)	0.92 (0.47, 1.82)	0.816
Final multivariate model				
FeNO, mean (SD)			1.17 (1.02, 1.34)	0.026
No dyspnoea symptoms reported			2.22 (1.09, 4.53)	0.028

- FeNO > 50 ppb was associated with greater odds of improvement in cough (decrease in VAS > 20 mm); odds ratio of 2.37 (1.01-5.55)
- Neither FEV_1 %predicted nor clinical opinion of asthma were associated.
- No significant interaction between FeNO (≤50 or >50ppn) and eosinophil count ($p_{interaction}$=0.869). Both were independent predictors of VAS cough improvement

- In best adjusted model, only FeNO and dyspnoea remained significant predictors for VAS improvement.
- For every 10 ppb increase in FeNO, odds for VAS cough improvement were 1.17 (1.02 – 1.34) greater

CONCLUSION

FeNO was associated with response to inhaled corticosteroids in terms of cough, in patients with non-specific respiratory symptoms. FeNO measurement could provide a simple non-invasive diagnostic tool to support treatment decisions for these patients. Further research is needed to establish cut-points for recommendation.

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References:

1. Smith AD, Cowan JO, Brassett KP, et al. Exhaled nitric oxide: a predictor of steroid response. *Am J Respir Crit Care Med.* 2005;172(4):453-459.
2. Price DB, Buhl R, Chan A, et al. Fractional exhaled nitric oxide as a predictor of response to inhaled corticosteroids in patients with non-specific respiratory symptoms and insignificant bronchodilator reversibility: a randomised controlled trial. The Lancet Respiratory medicine. 2018;6(1):29-39.

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