FeNO Predicts Response to Inhaled Corticosteroids in Patients with Non-specific Respiratory Symptoms and Insignificant Bronchodilator Reversibility

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BACKGROUND

- NICE[1] recommends fractional exhaled nitric oxide (FeNO) to guide the management of asthma, while GINA has not yet recommended the use of FeNO for asthma management.[2]
- While this inconsistency in guidance exists for FeNO use in management of patients with asthma, there is even less guidance for patients without clear asthma diagnosis.

AIM

To evaluate the association between baseline FeNO and symptomatic response to ICS in patients with non-specific respiratory symptoms (NSRS) and no asthma diagnosis.

DESIGN & METHODOLOGY

- A 6-week multicentre, randomised, double-blind, placebo-controlled trial, at 29 primary care centres and hospitals in the UK and Singapore.
- Eligible patients were randomised to either: extrafine ICS QVAR 80 µg inhalation aerosol, two puffs twice daily (equivalent to standard 400 µg beclomethasone dipropionate) or placebo inhaler with inactive ingredient on the same dosage regimen.
- Primary endpoint: change in Asthma Control Questionnaire-7 questions (ACQ7) from baseline (Visit 2) to follow-up (Visit 3).
- Generalised Linear Models (GLM) were used to estimate the treatment effects in change of ACQ7 (ICS versus placebo) in three baseline FeNO categories.
- Interaction effect between baseline FeNO and treatment was analysed using GLM. 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 ACQ7 of more than 0.5, for a range of potential predictors.

Visit 1
(n=517 screened)

Inclusion:

- 18-80 years old
- NSRS (cough and/or wheeze and/or chronic dyspnoea for ≥ 6 weeks before Visit1)
- FEV_1 < 90% predicted, with <20% reversibility within previous year

Exclusion:

- Previous diagnosis of asthma or any other significant chronic respiratory disease
- Oral, inhaled or systemic corticosteroids or leukotriene modifier or long-acting beta-agonist within 4 weeks prior to study

Visit 2
(n=214 randomised, PP)

If patient still eligible after 2 weeks assessment period (between Visit 1 and 2) at Visit 2, patient is randomised to a 4-week treatment period with either:

ICS (n=114) or **Placebo** (n=100)

Baseline categorisation:

- High FeNO (>40 ppb, n=69)
- Intermediate FeNO (25-40 ppb, n=68)
- Low FeNO (<25 ppb, n=77)

Visit 3
(follow-up visit)

Primary endpoint:

Change in ACQ7 from baseline to follow-up after 4 weeks of treatment (Visit 3)

Additional endpoints:

- Change in cough VAS from baseline to follow-up after 4 weeks of treatment (Visit 3)
- Testing of various baseline measurements in prediction models

PP=per protocol
VAS=visual analogue scale

RESULTS

Table 1: Change in ACQ7 by treatment arm and baseline FeNO

Model Estimate	PP (n=214)
Adjusted treatment effect* (extrafine ICS minus placebo) for change in ACQ7	
Normal FeNO (< 25 ppb)	0.10 (-0.24, 0.44) p=0.56
Intermediate FeNO (25-40 ppb)	0.25 (-0.10, 0.61) p=0.16
High FeNO (> 40 ppb)	0.49 (0.14, 0.84) p=0.0068
Interaction effect: Difference (95% CI) in treatment effect† for every 10 ppb increase in baseline FeNO	0.071 (0.002, 0.139) p=0.044

*All models adjusted for baseline FeNO and smoking status. †Difference in treatment effect is interpreted as the additional change in ACQ7 in the extrafine ICS versus placebo arm when baseline FeNO is 10 ppb higher. CI=confidence interval. PP=per protocol.

Main Findings:

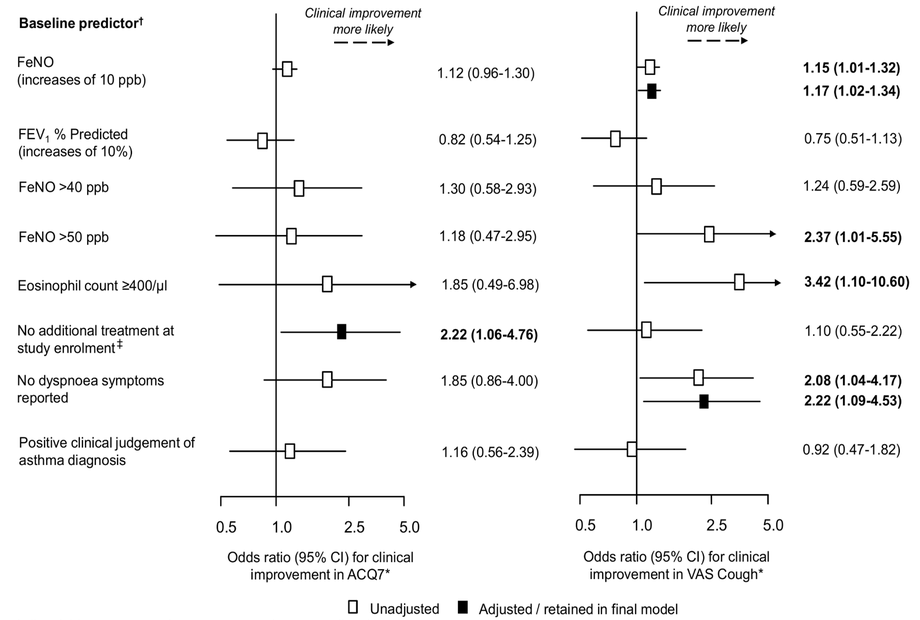
- A significant treatment effect (p=0.0068) was observed in the high FeNO group (>40 ppb), but not in the normal (<25 ppb) or intermediate (25-40 ppb) FeNO groups (Table 1).
- There was a significant interaction (p=0.044) between FeNO and ICS treatment in the PP set, showing that the difference in change in ACQ7 between ICS and placebo arm was 0.071 greater (95% CI, 0.002-0.139) for every 10 ppb increase in baseline FeNO (Table 1).

Additional Endpoints

Of the baseline measurements tested in the prediction models:

- No additional treatment taken at study enrolment was associated with clinical improvement of ACQ7 (decrease > 0.5), in the ICS group (Figure 1).
- Patients who did not have additional treatments were more than twice as likely to show clinical improvement in ACQ7 compared to those who had additional treatments (OR, 2.22; 95% CI, 1.06-4.76) (Figure 1).
- In the model for clinical improvement in cough (defined as a VAS Cough decrease > 20 mm), baseline FeNO (continuous and binary [≤ and >50 ppb]), blood eosinophil count and report of dyspnoea were significantly predictive in unadjusted models.
- In the best adjusted model, dyspnoea and FeNO were retained as significant predictors.
- For every 10 ppb increase in baseline FeNO, odds of clinical improvement in VAS cough were 1.17 times greater (95% CI; 1.02-1.34)

Figure 1: Clinical response defined as a decrease of >0.5 in ACQ7 and a decrease of >20mm on VAS Cough



†All variables except continuous FeNO and FEV_1 predicted are binary
‡Additional treatment defined as any treatment received for non-specific respiratory symptoms at study enrolment, apart from extrafine ICS or any treatment listed in the exclusion criteria. **Bold text** indicates significant association.

CONCLUSION

- This study showed an association between high FeNO and response to inhaled corticosteroids (ICS) in terms of ACQ7 in patients with non-specific respiratory symptoms (NSRS).
- ICS treatment may be beneficial in patients with cough and high FeNO.
- FeNO measurement is a simple, near patient, quantitative and non-invasive diagnostic tool that could be supportive in treatment decisions for NSRS patients and for patients with cough
- Further research is needed to establish FeNO cut-points for recommendation.

References:

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Presented at the ERS International Congress, Milan 9-13 September 2017

This study was partially funded by Circassia (formerly Aerocrine), FeNO was measured using NIOX VERO provided by Circassia.