ORIGINAL RESEARCH LETTER

Suppression of F_{ENO} with observed inhaled corticosteroid therapy in severe asthma: is it a useful test in clinical practice?

To the Editor:

Biologic therapies are used in atopic and/or eosinophilic asthma that remains uncontrolled on optimised conventional therapy [1–4]. Nonadherence with prescribed therapy is common in severe asthma [5] and National Health Service England's commissioning guideline [6] advises adherence assessment prior to commencing biologic therapy.

Exhaled nitric oxide fraction (F_{ENO}) is a surrogate marker of eosinophilic airway inflammation that, when elevated, supports a diagnosis of asthma [7–9]. McNicholl *et al.* [10] studied F_{ENO} suppression during directly observed inhaled corticosteroid (DOICS) therapy in asthma patients and demonstrated that a 42% fall in F_{ENO} over 5 days indicated suboptimal ICS adherence. On this basis, F_{ENO} suppression testing has been suggested as a way to assess adherence.

We present the outcome of F_{ENO} suppression testing using DOICS in severe asthma as part of routine practice during assessment for biologic therapy.

We conducted a prospective study of F_{ENO} suppression testing during routine care in two UK severe asthma centres. Eligible patients attended between March 2017 and January 2018, and had F_{ENO} >45 ppb on two occasions, were adherent to therapy based on clinical history and met National Institute for Health and Care Excellence criteria for biologics. Patients were converted to once-daily fluticasone furoate/vilanterol 184/22 µg (Relvar Ellipta; GlaxoSmithKline, London, UK) and taught inhaler technique by a specialist nurse prior to DOICS. Daily ICS inhalation was observed in person or *via* live video link using secure, widely available videoconferencing applications for 8 days. F_{ENO}, seven-item Asthma Control Questionnaire (ACQ-7), blood eosinophils and spirometry were measured on day 0 and day 8 of DOICS. Day 4 F_{ENO} was also measured in one participating centre. Follow-up data on asthma management and exacerbations were collected in June 2018, and exacerbation rates annualised for the purpose of data analysis.

SPSS software (IBM, Armonk, NY, USA) was used to perform the following statistical analyses: paired t-test or Wilcoxon sign rank test for paired data; Mann–Whitney U- or independent t-test for independent data; and Fisher's exact for categorical data.

47 patients were eligible with 44 included in the analysis (two exclusions due to loss to follow-up/missing data and one excluded as they were on maintenance oral steroids).

Median (interquartile range) F_{ENO} decreased from 86 (55.5–116.5) ppb on day 0 to 56 (31.5–80.5) ppb on day 8 ($p<0.01$). 19 (43.2%) participants had significant F_{ENO} suppression by day 8, defined as a reduction of >42% [10]. Of the 25 patients with F_{ENO} measured on days 1, 4 and 8, 11 reached >42% F_{ENO} suppression by day 8. Significant F_{ENO} suppression was seen by day 4 in five (45%) of these patients.

@ERSpublications
F_{ENO} suppression testing is practical and feasible during assessment for biologics in severe asthma. Patients with significant F_{ENO} suppression were less likely to be recommended biologics but saw similar reductions in exacerbation frequency. http://bit.ly/35oSoxP

Cite this article as: Faruqi S, Zhou S, Thompson J, *et al.* Suppression of F_{ENO} with observed inhaled corticosteroid therapy in severe asthma: is it a useful test in clinical practice? *ERJ Open Res* 2019; 5: 00123-2019 [https://doi.org/10.1183/23120541.00123-2019].

No significant change was observed in ACQ-7, blood eosinophils or forced expiratory volume in 1 s between days 0 and 8.

Primary care prescription pick-up data was available for 35 participants. 26 (74.3%) had a >80% pick-up rate. There was no relationship between prescription pick-up rate and F_{ENO} suppression (p=0.24).

Table 1 presents the change in outcomes after DOICS depending on F_{ENO} suppression status. Patients were followed-up for median 10 months (range 6–14 months). 22 patients were recommended for treatment with biologics (mepolizumab; n=16; omalizumab, n=6) with 17 patients taking biologics at the time of follow-up (mepolizumab, n=11; omalizumab, n=6). The median time to biologic initiation following DOICS was 2 months (range 0–8 months). For those receiving biologics, the median treatment duration during follow-up was 10 months (range 5–17 months).

Exacerbation rate significantly reduced following DOICS compared to the year before (average decrease of 3.76 exacerbations per year, p<0.01). There was no difference in exacerbation rate reduction in those that went onto biologics compared with those that did not (p=0.14).

This is the first prospective study of F_{ENO} suppression testing during routine assessment for biologic therapy in asthma. Overall, F_{ENO} significantly reduced during DOICS. Individuals with significant F_{ENO} suppression were younger on average and were significantly less likely to be recommended biologics. Despite this, they experienced a similar reduction in exacerbations to those that did not suppress and were more likely to be recommended for biologics. Although this real-world study is not designed or powered to detect small differences in exacerbation rate, our findings suggest that the majority of patients that achieve F_{ENO} suppression during DOICS can improve their asthma control without the need for biologic therapy.

A number of patients recommended for biologic treatment did not receive a biologic during follow-up. This was either due to patient choice or failure to attend their appointment for biologic initiation. As a result, although the proportion of patients receiving a biologic was higher in the non-F_{ENO} suppressor group, this did not reach statistical significance.

All participants received inhaler technique training and adherence advice during routine care. However, despite participants self-reporting good adherence, nearly half had significant F_{ENO} suppression. Sustained improvement in adherence is likely responsible for the reduction in exacerbations in those not commencing biologics. This may be due to positive behavioural feedback provided by F_{ENO} suppression. A proportion of patients opted to remain on once-daily Relvar Ellipta following DOICS, which may also have impacted adherence.

TABLE 1 Change in outcomes after directly observed inhaled corticosteroid (DOICS) therapy depending on exhaled nitric oxide fraction (F_{ENO}) suppression status

	All patients	F_{ENO} suppressors (>42%)	Non-F_{ENO} suppressors (<42%)	p-value
Patients	44	19	25	
Age years	49.61 (44.36–55.03)	42.4 (33.42–51.38)	55.5 (49.84–61.16)	0.03
Male/female	22/22	7/12	15/10	0.21
Baseline FEV_1 mL	2.14 (1.88–2.40)	2.24 (1.76–2.73)	2.07 (1.76–2.37)	0.70
Baseline eosinophil count %	0.59 (0.46–0.72)	0.68 (0.44–0.92)	0.52 (0.38–0.66)	0.40
Patients recommended for biologics post-DOICS	52.3%	21.1%	72%	<0.01
Patients taking a biologic at follow-up	38.6%	21.1%	52%	0.06
Patients' (n=35) prescription pick-up rate >80%	74.3%	80%	62.5%	0.24
Baseline exacerbation rates 1 year prior to DOICS	6.37 (5.03–7.7)	6.7 (4.6–8.8)	6.05 (4.18–7.91)	0.58
Change in annual number of exacerbations after DOICS, adjusted to 1 year	−3.69 (−5.13– −2.24)	−4.0 (−6.56– −1.44)	−3.48 (−5.23– −1.73)	0.67
ACQ-7 score change	−0.24 (−0.48–0.01)	−0.4 (−0.88–0.08)	−0.12 (−0.38–0.150	0.08
FEV_1 change mL	0.1 (−0.08–0.37)	0.2 (−0.11–0.51)	−0.1 (−0.2–0.05)	0.05
FEV_1 change %	3.77 (−2.22–9.76)	8.7 (−1.12–18.52)	−3.1 (−7.40–1.24)	0.01

Data are presented as n or mean (95% CI) unless otherwise stated. FEV_1: forced expiratory volume in 1 s; ACQ-7: seven-item Asthma Control Questionnaire.

There was no significant relationship between prescription pick-up rate assessed by reviewing primary care records and F_{ENO} suppression response. This suggests that in our cohort, having a high prescription pick-up rate does not indicate adherence as defined by F_{ENO} suppression testing. Although F_{ENO} suppression identified a cohort of patients that experienced clinical improvement without biologics, one fifth of F_{ENO} suppressors did require biologic therapy due to continued exacerbations. Adherence assessment is complex and we feel that F_{ENO} suppression alone should not preclude treatment with biologics [11]. Newer technologies, including digital inhaler devices [12], may enhance adherence assessment and enable F_{ENO} suppression testing to be undertaken remotely.

McNicholl *et al.* [10] demonstrated that a F_{ENO} reduction of >42% on day 5 was consistent with suboptimal ICS adherence. The F_{ENO} suppression testing protocol used in the severe asthma centres in this study undertook DOICS over 8 days with a subgroup undergoing F_{ENO} measurement on day 4. This method appears useful for identifying a cohort of patients in whom biologic therapy is likely to be required (nonsuppressors) and those where it may not (suppressors). It is noteworthy that almost half of patients that achieved significant F_{ENO} suppression by day 8 had suppressed by day 4. In these patients, DOICS could be stopped early, reducing the burden on the clinical team. Those that fail to suppress by day 4 should continue with DOICS for 8 days. It is unclear if longer periods of DOICS would cause F_{ENO} suppression in additional patients.

This is a real-world, study and the relatively small sample size and observational nature limit its generalisability. However, it is currently the largest prospective patient cohort in which the relationship between F_{ENO} suppression testing with DOICS and subsequent asthma management is examined in asthmatics otherwise meeting criteria for biologic therapy.

F_{ENO} suppression testing using DOICS is practical and feasible during assessment for biologic therapy in severe asthmatics. There is a clear relationship between F_{ENO} suppression and subsequent recommendation for biologic treatment. This supports a role for F_{ENO} suppression testing in clinical practice, with potential to prevent the need for biologics in a cohort of otherwise eligible patients.

Shoaib Faruqi[1], Sean Zhou[1], Joanne Thompson[1], Terry Robinson[2], Karen Watkins[1], Helena Cummings[1], Nicola Jackson[1], Anoop Prakash[1] and Michael Crooks[1]
[1]Castle Hill Hospital, Respiratory Medicine, Cottingham, UK. [2]Harrogate and District NHS Foundation Trust, Respiratory, Harrogate, UK.

Correspondence: Sean Zhou, Hull Royal Infirmary, Hull, HU3 2JZ, UK. E-mail: sean.zhou@doctors.org.uk

Received: 19 May 2019 | Accepted after revision: 3 Oct 2019

Conflict of interest: None declared.

References

1 Ortega HG, Liu MC, Pavord ID, *et al.* Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med* 2014; 371: 1198–1207.
2 Normansell R, Walker S, Milan SJ, *et al.* Omalizumab for asthma in adults and children. *Cochrane Database Syst Rev* 2014; 1: CD003559.
3 Bleecker ER, FitzGerald JM, Chanez P, *et al.* Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet* 2016; 388: 2115–2127.
4 Bjermer L, Lemiere C, Maspero J, *et al.* Reslizumab for inadequately controlled asthma with elevated blood eosinophil levels: a randomized phase 3 study. *Chest* 2016; 150: 789–798.
5 Makela MJ, Backer V, Hedegaard M, *et al.* Adherence to inhaled therapies, health outcomes and costs in patients with asthma and COPD. *Respir Med* 2013; 107: 1481–1490.
6 NHS England. Specialised Respiratory Services (adult) – Severe Asthma. www.england.nhs.uk/publication/specialised-respiratory-services-adult-severe-asthma/. Date last updated: 2017. Date last accessed: 29 May 2018.
7 British Thoracic Society, Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma. www.brit-thoracic.org.uk/standards-of-care/guidelines/btssign-british-guideline-on-the-management-of-asthma/. Date last updated: 2016. Date last accessed: 29 May 2018.
8 National Institute of Health and Care Excellence. Asthma: diagnosis, monitoring and chronic asthma management. www.nice.org.uk/guidance/ng80. Date last updated: 2017.
9 Coumou H, Bel EH. Improving the diagnosis of eosinophilic asthma. *Expert Rev Respir Med* 2016; 10: 1093–1103.
10 McNicholl DM, Stevenson M, McGarvey LP, *et al.* The utility of fractional exhaled nitric oxide suppression in the identification of nonadherence in difficult asthma. *Am J Respir Crit Care Med* 2012; 186: 1102–1108.
11 Green RH, Shaw D. Strict adherence rules to obtain monoclonal therapy might cost lives. *Lancet Respir Med* 2017; 5: 678–679.
12 Gaga M, Samitas K, Zervas E. Inhaler adherence in severe asthma: is there an electronic solution? *Eur Respir J* 2018; 51: 1702219.