Regarding the role of F_{ENO} in predicting failure after ICS reduction in mild-to-moderate asthma patients

To the Editor:

Although exhaled nitric oxide fraction (F_{ENO}) is one of most widely used type-2 biomarkers, there remains some controversy about its role in diagnosing asthma, assessing adherence, predicting steroid responsiveness and preventing exacerbations by adjusting medication dosage. Thus, we read with great interest the well-conducted individual patient data meta-analysis by Wang *et al.* [1]. The study showed that the use of F_{ENO} can potentially assist clinicians in deciding whether to reduce inhaled corticosteroid (ICS) dose in well-controlled asthmatics. We appreciate the authors' efforts in illuminating this important topic, but there is an essential methodological consideration that must be taken into account, which has already been outlined by Dinh-Xuan and Brusselle [2] in their editorial and by the authors themselves: the study did not evaluate the impact of other potential risk factors for exacerbations.

In a prospective, multicentre study that included 218 patients with well-controlled moderate asthma, followed-up for 12 months, with the aim of developing and externally validating a tool to predict failure when stepping down treatment, we assessed the impact of several prognostic variables (a documented history of previous bronchial obstruction, a history of severe exacerbations, forced expiratory volume in 1 s <80%, peak expiratory flow variability, the presence of a significant bronchodilator response, F_{ENO} values >50 ppb, an Asthma Control Test score <25, and adherence) on loss of control [3]. We found that, on multivariate analysis, high F_{ENO} levels were not significantly associated with loss of control, in line with the conclusions of a systematic review [4].

The discordance between the results found by Wang *et al.* [1] and those we have previously reported could have several explanations.

1) F_{ENO} primarily reflects the activity of the interleukin (IL)-4/IL-13 pathway, and an additional mechanism, related to airway eosinophilia and independent of F_{ENO}, could be responsible for some severe exacerbations [5]. Therefore, an ongoing inflammatory process may persist in asthmatics with low F_{ENO} values, leading to a "false sense of security".

2) It is well known that F_{ENO} levels can remain elevated in some asthmatics with eosinophilic chronic rhinosinusitis, even after adequate treatment [6]. Thus, if we decide not to reduce the ICS dose based only on a high F_{ENO} value, these patients would never benefit from step-down treatment despite having controlled bronchial inflammation.

3) It has been reported that absolute exhaled nitric oxide measurements may differ to a clinically relevant extent, depending on which device is used, with individual differences as great as 150 ppb in a single patient [7]. Thus, an exact cut-off point cannot be established if different analysers were used in the studies that went into the meta-analysis. Although the same device is normally employed to repeatedly quantify F_{ENO} in a given patient, clinicians must ensure the reproducibility of F_{ENO} results between multiple measurements.

In conclusion, we must be cautious in deciding whether or not to reduce the ICS dose based only on the F_{ENO} measurement. As Wang *et al.* [1] acknowledge, we need further evidence.

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We must be cautious in deciding whether or not to reduce ICS dose based only on the measurement of F_{ENO} https://bit.ly/2VAHLVu

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References

1 Wang K, Verbakel JY, Oke J, *et al.* Using fractional exhaled nitric oxide to guide step-down treatment decisions in patients with asthma: a systematic review and individual patient data meta-analysis. *Eur Respir J* 2020; 55: 1902150.
2 Dinh-Xuan AT, Brusselle G. F_{ENO} as a biomarker guide for inhaled corticosteroid step down in patients with mild-to-moderate well-controlled asthma. *Eur Respir J* 2020; 55: 2001319.
3 Pérez de Llano L, García-Rivero JL, Urrutia I, *et al.* A simple score for future risk prediction in patients with controlled asthma who undergo a guidelines-based step-down strategy. *J Allergy Clin Immunol Pract* 2019; 7: 1214–1221.
4 Lehtimäki L, Csonka P, Mäkinen E, *et al.* Predictive value of exhaled nitric oxide in the management of asthma: a systematic review. *Eur Respir J* 2016; 48: 706–714.
5 Pavord ID, Holliday M, Reddel HK, *et al.* Predictive value of blood eosinophils and exhaled nitric oxide in adults with mild asthma: a prespecified subgroup analysis of an open-label, parallel-group, randomised controlled trial. *Lancet Respir Med* 2020; 8: 671–680.
6 Kobayashi Y, Asako M, Ooka H, *et al.* Residual exhaled nitric oxide elevation in asthmatics is associated with eosinophilic chronic rhinosinusitis. *J Asthma* 2015; 52: 1060–1064.
7 Korn S, Telke I, Kornmann O, *et al.* Measurement of exhaled nitric oxide: comparison of different analysers. *Respirology* 2010; 15: 1203–1208.

Using fractional exhaled nitric oxide to guide step-down treatment decisions in asthma: practical considerations

From the authors:

We thank L. Pérez de Llano and colleagues for their comments on our study [1] and for comparing our findings with those of their prospective multicentre study describing a simple score for predicting step-down failure in adults with well-controlled asthma [2]. However, we would like to clarify that recent systematic review findings conclude that there is insufficient evidence, rather than evidence against, the ability of low fractional exhaled nitric oxide (F_{ENO}) to identify individuals in whom treatment can be safely stepped down [3].

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Using F_{ENO} to guide safe step-down treatment decisions in patients with well-controlled asthma should involve gradual, carefully monitored reductions and consider other potential risk factors for acute exacerbations https://bit.ly/2E2W679

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We fully acknowledge that F_{ENO} should be interpreted in the context of other potential risk factors and that pro-active efforts should be made to identify and treat other conditions that increase F_{ENO}, particularly in patients whose F_{ENO} is high despite satisfactory medication adherence and inhaler technique.

We also acknowledge that, although there is well-established evidence that F_{ENO} is correlated with sputum eosinophil counts in nonsmoking patients with stable asthma [4], this correlation is not strong and it is possible for eosinophilic airway inflammation to occur in the presence of low F_{ENO}. However, it is neither feasible nor acceptable to obtain induced sputum samples in primary care. Blood eosinophil counts may be an adequate surrogate but this has not been demonstrated. We therefore recommend that, in community-based healthcare settings, treatment should be stepped down gradually and patients should be monitored carefully in case any reductions subsequently unmask undetected airway inflammation.

We are aware of the practical implications of variability in F_{ENO} measurements between different devices. However, this is unlikely to have had an undue impact on the findings of our meta-analysis, as only two included studies used Sievers rather than Aerocrine analysers [5, 6] and only three participants across these two studies had one or more exacerbations.

The study by L. Pérez de Llano and colleagues also highlights other issues that should be considered when using F_{ENO} to guide step-down decisions.

1) The definition of step-down failure. The primary outcome used by L. Pérez de Llano and colleagues was "loss of control". This was defined as an Asthma Control Test score of $\leqslant$19, a decrease in forced expiratory volume in 1 s of $\geqslant$20% from baseline, or exacerbations resulting in symptom deterioration, whether or not these required treatment with systemic corticosteroids or hospitalisation. However, the primary outcome of our meta-analysis was exacerbations requiring antibiotics, systemic corticosteroids, hospitalisation or unscheduled healthcare visits. These events may relate more closely to type-2 airway inflammation than less severe events [7] and have a significant detrimental impact on health-related quality of life [8], which is in turn associated with increased asthma-related costs and healthcare resource utilisation [9]. Only ~13% of participants who experienced loss of control in the study by L. Pérez de Llano and colleagues required systemic corticosteroids (13 out of 102 participants) and no participants were hospitalised. This would suggest that, while F_{ENO} may not be a reliable predictor of mild-to-moderate deteriorations in symptom control or lung function, it could still be a useful predictor of clinically important exacerbations requiring further intervention.

2) Target population characteristics. The list of possible diagnostic criteria for asthma used by L. Pérez de Llano and colleagues included F_{ENO} >50 ppb. However, none of the studies we included in our meta-analysis selected participants based on their F_{ENO} measurement at baseline. F_{ENO} may therefore have a greater predictive value in asthma populations that do not include individuals who have been pre-selected on the basis of already having a high F_{ENO}.

3) Follow-up after stepping down treatment. Whilst our meta-analysis only analysed one step-down episode per participant, L. Pérez de Llano and colleagues analysed all step-down episodes. Each participant could undergo up to three step-down episodes over a 12-month period, with a 6-month follow-up period after the step-down episode at the third study visit. However, analysis of multiple episodes per participant is likely to result in clustering of outcomes within individuals. Additionally, extended follow-up periods may result in exacerbations or "loss of control" episodes unrelated to treatment being stepped down.

In conclusion, we agree with L. Pérez de Llano and colleagues that F_{ENO} should not be considered in isolation to guide step-down treatment decisions. However, in real life clinical practice, it is practically impossible to control for every potential source of confounding or variability. We therefore advocate using F_{ENO} as part of a gradual, safely monitored step-down approach.

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References

1 Wang K, Verbakel JY, Oke J, *et al.* Using fractional exhaled nitric oxide to guide step-down treatment decisions in patients with asthma: a systematic review and individual patient data meta-analysis. *Eur Respir J* 2020; 55: 1902150.
2 Pérez de Llano L, García-Rivero JL, Urrutia I, *et al.* A simple score for future risk prediction in patients with controlled asthma who undergo a guidelines-based step-down strategy. *J Allergy Clin Immunol Pract* 2019; 7: 1214–1221.
3 Lehtimaki L, Csonka P, Makinen E, *et al.* Predictive value of exhaled nitric oxide in the management of asthma: a systematic review. *Eur Respir J* 2016; 48: 706–714.
4 Berry MA, Shaw DE, Green RH, *et al.* The use of exhaled nitric oxide concentration to identify eosinophilic airway inflammation: an observational study in adults with asthma. *Clin Exp Allergy* 2005; 35: 1175–1179.
5 Harada S, Harada N, Itoigawa Y, *et al.* Evaluation of switching low-dose inhaled corticosteroid to pranlukast for step-down therapy in well-controlled patients with mild persistent asthma. *J Asthma* 2016; 53: 207–212.
6 Lazarus SC, Boushey HA, Fahy JV, *et al.* Long-acting beta2-agonist monotherapy *vs* continued therapy with inhaled corticosteroids in patients with persistent asthma: a randomized controlled trial. *JAMA* 2001; 285: 2583–2593.
7 Pauwels RA, Löfdahl CG, Postma DS, *et al.* Effect of inhaled formoterol and budesonide on exacerbations of asthma. Formoterol and Corticosteroids Establishing Therapy (FACET) International Study Group. *N Engl J Med* 1997; 337: 1405–1411.
8 Lloyd A, Price D, Brown R. The impact of asthma exacerbations on health-related quality of life in moderate to severe asthma patients in the UK. *Prim Care Respir J* 2007; 16: 22–27.
9 Lee LK, Obi E, Paknis B, *et al.* Asthma control and disease burden in patients with asthma and allergic comorbidities. *J Asthma* 2018; 55: 208–219.