



Fractional exhaled nitric oxide and asthma treatment adherence

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Purpose of review

Despite increased clinician awareness, nonadherence to inhaled corticosteroid treatment presents a major challenge to successful asthma management and risks inappropriate treatment escalation, particularly in severe disease. In patients with Type-2 mediated biology, fractional exhaled nitric oxide (FeNO) has a role in assessment and monitoring of adherence to inhaled corticosteroids.

Recent findings

Asthmatic patients with elevated FeNO are at an increased risk of exacerbation. High FeNO is often secondary to suboptimal adherence to inhaled corticosteroid treatment, whether intentional or nonintentional. FENO-suppression can 'unmask' underlying adherence issues and is a useful test in the presence of Type-2 biology in the 'difficult-to-control' asthma population. Identification of nonadherence can improve asthma control and prevent inappropriate commencement of costly biologic therapies.

Summary

Assessment of adherence and FeNO response to monitored inhaled corticosteroid in Type-2 biomarker high asthmatic individuals may prevent unnecessary escalation to biologic therapy. Establishing an 'optimised' FeNO may alert clinicians to the possibility of underlying nonadherence at future clinical assessments.

Keywords

adherence, asthma, fractional exhaled nitric oxide

INTRODUCTION

Asthma is a common condition worldwide affecting approximately 300 million people [1]. Current estimations suggest around 20% of patients have 'difficult-to-control' asthma and after systematic assessment and identification of 'treatable traits' approximately 4% of patients have severe or refractory asthma [2,3]. One reason for poor asthma control is nonadherence to prescribed therapies, which can be intentional (concern regarding potential side effects, secondary gain and so on), or nonintentional (poor inhalation technique, missed doses and so on) [4,5]. Poor adherence, particularly to inhaled corticosteroids (ICS), increases the risk of exacerbation and death, and places a higher burden on healthcare systems [6,7]. Patient and physician estimations of adherence are overstated [8⁹,9,10].

Our understanding of the heterogeneity of asthma has expanded over the past 20 years and led to the development of treatments targeting eosinophilic inflammation driven by Type 2 (T2) cytokines, of which fractional exhaled nitric oxide (FeNO) is an important biomarker of interleukin (IL)-4 and IL-13 mediated nitric oxide synthesis in

the airways [1,11,12]. In the era of costly biologic therapies, it is important that clinicians address and assess for adherence prior to committing patients to long-term (potentially life-long) complex treatments. This review will concentrate on the literature pertaining to FeNO and potential role in evaluation of adherence.

Fractional exhaled nitric oxide

FeNO is a noninvasive, near-patient test and increased levels can be seen in many patients with asthma [11,13]. Although it is not a diagnostic test for asthma, an elevated FeNO can support this diagnosis [14]. It is produced by airway epithelial cells and indicates the presence of local Type 2 inflammation driven by IL4/IL13 [15]. Importantly, FeNO

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KEY POINTS

- Nonadherence to inhaled corticosteroid treatment in asthma remains common and is important to assess in the uncontrolled asthmatic.
- Failure to assess for adherence may result in inappropriate escalation of therapy including long-term biologic agents in T2-high patients.
- FeNO suppression is useful in assessment of intentional and nonintentional nonadherence to inhaled corticosteroid treatment in T2-high patients.

elevation is not specific for asthma and can be demonstrated in patients with allergic rhinitis, rhinovirus infection and tends to be higher in men; it is estimated that one in five patients with an elevated FeNO do not have asthma [15,16]. Levels are lower in children, smokers and with exposure to ICS [15]. The American Thoracic Society (ATS) suggests cut-off points of less than 25 parts per billion (ppb) (low), 25–50 ppb (intermediate) and more than 50 ppb (high probability of Type 2 inflammation) [17]. In severe asthma, with background high-dose ICS or oral corticosteroids, GINA suggest that a FeNO more than 20 ppb and/or blood eosinophils more than 150/ μ l may indicate persisting Type 2 inflammation [1].

Application of fractional exhaled nitric oxide

Elevated FeNO correlates with other biomarkers of T2 inflammation (including sputum eosinophils) and is suppressed in response to ICS [18]. However, given the heterogeneous nature of airway inflammation in asthma, there is a subgroup of patients in which FeNO is not useful including smokers and patients with T2-low asthma in whom T2-driven eosinophilic inflammation is not present [17,19]. The mechanism of T2-low asthma remains unclear, but in severe asthma, a recent randomized control trial investigating a biomarker-led approach to corticosteroid reduction has suggested this phenotype is less prevalent than previously thought [20].

Although FeNO is not a 'stand-alone' diagnostic test for asthma, there is support for the use of FeNO in the diagnosis of T2-mediated asthma and more specifically determination of the likelihood of response to corticosteroids [1,16,17]. Many centres use FeNO routinely in clinical practice for the corticosteroid-naïve patient, as an aide in phenotyping patients and to monitor adherence to ICS [21].

Elevated FeNO is predictive of future severe exacerbations across all severities of asthma, so it is unsurprising that clinicians have utilized this

biomarker to titrate ICS dose and there is mounting evidence to support this approach at least in mild-to-moderate asthma [22,23]. In patients with mild asthma who were treated with short-acting bronchodilator (SABA) only, as-needed budesonide-formoterol led to a decrease in exacerbations alongside a reduction in FeNO [24]. A systematic review including 16 studies reported a reduction in exacerbations when treatment was adjusted using FeNO [25^{***}]. There was no significant difference in the ultimate ICS dose or symptom scores between FeNO tailored management versus usual practice, though there was trend to ICS reduction with the former strategy [25^{***}]. A 'real-world' clinical practice study from Hanania *et al.* [26] noted that clinical assessment was likely to underestimate airway inflammation, and that use of FeNO by clinicians altered their management plan in a third of cases. The recent CAPTAIN study reported greater reduction of moderate and/or severe exacerbations in biomarker high (FeNO and blood eosinophil) patients when ICS dose was increased [27].

Adherence to inhaled corticosteroids

Nonadherence to ICS and other asthma-controlling medications has been well recognized for many years [28], but fast-forward to the present day and patients' adherence with treatment remains a major challenge across the spectrum of asthma severity despite increased clinician awareness of the scale of the problem [6,8^{***},29^{*}]. Consideration of suboptimal adherence at all treatment steps is now firmly embedded in asthma guidelines [1,16]; however, there is no standardized approach to assessment, reflective of variable healthcare systems, poor quality evidence about the optimal intervention and a multitude of patient-related factors [1,16,30]. The estimated prevalence of nonadherence in a 'difficult-to-treat' asthma population is estimated at around 50% with little suggestion that this has changed over time [4,9], and considering these patients might otherwise proceed to biologic agents there are substantial economic implications. As mentioned above, nonadherence is a major risk factor for asthma morbidity and mortality [6,7] and potentially exposes patients to the unfavourable effects of inappropriate steroid use risking further escalation in healthcare consumption [31]. The reasons for nonadherence are complex, variable and have been previously reported but beyond the scope of this article [32].

Assessment of adherence

There are a number of methods whereby adherence is assessed in routine care. The simplest method, but

perhaps the least accurate, is patient-reported adherence, which tends to be an overestimate when verified by objective methods such as electronic monitoring [10]. Interestingly, nonadherence can remain 'undetected' despite careful assessment by asthma healthcare specialists [9]. Many asthma centres use prescription refills as a surrogate marker for adherence, though prescribing or dispensing records of inhalers does not necessarily correlate with use [4,29].

More objective methods include the use of digital inhaler monitoring, which has been shown to 'unmask' nonadherence though not all inhalers are compatible for such devices [8⁹,9]. As discussed above, nonadherence can be unintentional secondary to suboptimal inhaler technique and a large meta-analysis of device errors in asthma and chronic obstructive pulmonary disease noted a high error rate for both metered-dose inhalers (MDIs) and dry-powder inhalers (DPIs) [33]. Factors associated with device errors were increased age of patient, lower educational achievement, female sex and lower socioeconomic class [33]. Maintenance of inhaler technique may also lessen with time, suggesting regular review is required especially where disease control lessens [34].

Addressing nonadherence

It can be challenging to introduce a change in patient behaviour and their approach to regular treatment, which involves working in partnership with the patient to address the contributory factors to poor adherence [32]. Whereas nonintentional adherence *may* be amenable to reviewing inhaler choice and technique, wilful avoidance of treatment poses a more difficult scenario. Strategies for managing suboptimal adherence vary from concordance interviews to intensive inhaler monitoring [35,36]. A simpler dosing schedule may also help and in mild-to-moderate asthma there may be benefit from single inhaler LABA/ICS, also termed 'maintenance and reliever therapy' (MART) [37]. Another means of simplification is a once-a-day inhaler and a study in paediatric patients reported reduced emergency department attendance and steroid boosts with the use of a once-daily inhaler in patients with poor adherence; similarly, an adult study of mild-to-moderate asthma comparing a once-daily inhaler to a twice-daily confirmed increased adherence rates with the once-a-day device [38,39]. Some studies have employed reminder alarms or directly observed dosing, but the latter is time-consuming as a long-term solution [36]. Future solutions may include the use of real-time feedback to patients using 'connected' inhalers alongside smartphone technology

and may provide novel insight into adherence especially when they are available in the 'real world' clinic setting [40,41].

Fractional exhaled nitric oxide 'suppression' test

An early study utilizing FeNO in the assessment of nonadherence involved comparison of the change in FeNO with directly observed inhaled corticosteroid (DOICS) between patients assessed as adherent or nonadherent on the basis of prescription refills [42]. Nonadherent patients had a significantly greater reduction in their FeNO following 7 days of DOICS, which was evident by Day 4, and on the basis of these data, the 'FeNO suppression' test was developed.

A later study involved the use of integrated remote monitoring technology to deliver FeNO suppression testing, and correlated with short-term clinical outcome with patients having a positive FeNO suppression test being T2-biomarker low (blood eosinophils/FeNO) with tendency to greater improvement in FEV₁ [8⁹]. The FeNO suppression test and relation to longer term adherence and clinical outcome is also being studied in a clinical trial assessing adherence supported with a digital technology compared to standard care (www.clinicaltrials.gov; NCT02307669) [8⁹]. This methodology can be used to differentiate patients who are likely to respond to optimized ICS from those with refractory Type 2 inflammation who will most likely require biologic agents to achieve disease control. However, not all patients are able to engage with monitoring of inhaled treatment nor use inhaler technology competently [8⁹,9], illustrating the complexity in this patient population and other solutions may be needed [43].

Application of fractional exhaled nitric oxide to biologic assessment

Biologic therapies for asthma are drugs targeting specific aspects of the T2-inflammatory pathway, such as anti-IgE (omalizumab), anti-IL-5 (mepolizumab/reslizumab), anti-IL-5 receptor- α (benralizumab) and anti-IL-13/IL-4-receptor- α (dupilumab) [12]. At present, these drugs are indicated for patients with severe refractory asthma who remain uncontrolled despite high-dose ICS and long-acting bronchodilator [1]. There is a 'disconnect' between FeNO and the response to the anti-IL5 agents, whereby their administration decreases blood eosinophils but does not affect FeNO levels [15]. FeNO does not appear to correlate with the likelihood of response to the anti-IL5 agents; however, there is

evidence of a greater reduction in exacerbations with omalizumab and dupilumab in 'FeNO-high' patients [12,44]. An elevated FeNO in a patient who is self-administering dupilumab, where this was previously suppressed, might prompt the clinician to review adherence to their biologic.

As discussed above, FENO suppression may have use in preventing inappropriate progression to biologics by unmasking of suboptimal adherence. Faruqi *et al.* [45[■]] reported on a 6-month follow-up of patients with elevated who met criteria for biologic initiation. Following FENO suppression with supervised ICS treatment, 19 out of 46 patients were deemed 'nonadherent' and 14 of these did not need to proceed to biologic therapy [45[■]]. There will of course be a proportion of patients with refractory disease who fail to suppress their FeNO or eosinophils despite adequate adherence and are appropriate to progress to biologic therapy. Another group to consider are those with persisting Type 2 inflammation and suboptimal adherence despite targeted intervention to address nonadherence. Adherence to inhaled therapy is clearly a highly desirable criterion, but in risk-high patients there may need to be a pragmatic approach.

One concern regarding administration of biologics to the nonadherent patient is an inferior response in terms of exacerbation rate and oral corticosteroid withdrawal. A recent observational study noted a greater impact on oral corticosteroid and exacerbation rate reduction in adherent patients (assessed by prescription records) [29[■]]. Just under one-fifth of patients on biologics were classed as nonadherent, representing a sizeable proportion of the cohort, and unsurprisingly prior poor adherence seemed to predict future poor adherence [29[■]]. Patients with poor adherence were more likely to be classed as a 'treatment failure'; therefore, it seems intuitive that adherence should be suspected in patients who fail to respond as anticipated to these therapies. There was no significant difference in FeNO between those with good versus intermediate or poor adherence, which was assessed only by prescription records, suggesting that, at least in this centre, raised FeNO did not help predict suboptimal adherence [29[■]]. However, it is noted that FeNO was quite high in both groups potentially reflecting the refractory nature of the group, in that 'optimised' FeNO was high, but may also reflect challenges using prescription records as the only method of adherence assessment. The same group have suggested that an eosinophil depleting antibody (benralizumab) may be more forgiving of poor adherence to background ICS when on biologic therapy [46] and a clinical trial is underway to assess if patients established on anti-IL5RA therapy

(benralizumab) can successfully reduce ICS/LABA dose (www.clinicaltrials.gov; NCT04159519).

FeNO may also have a role in oral corticosteroid stewardship by aiding clinicians in differentiation of infective from asthmatic exacerbations in patients on mepolizumab [47]. In this study, low FeNO (<20 ppb) had 100% negative predictive value for identifying a noneosinophilic exacerbation, whereas a FeNO more than 50 ppb had a high correlation with an eosinophilic event (77% positive predictive value) [47]. A similar study is ongoing for benralizumab (www.clinicaltrials.gov; NCT04102800).

Adherence to biologics; the next pitfall?

In recent months, severe asthma services have tried to respond to unprecedented barriers to current chronic disease management posed by COVID-19 by moving care away from hospital, including biologic 'homecare', where biologics are administered by the patient, carer or a community healthcare team. Although self-administration of biologics is widely accepted in other disease areas, there is at least some concern that a propensity to nonadherence to inhaled therapies could extend to biologics [43]. Data for adherence to biologics for other diseases vary; this may in part be due to availability in particular healthcare systems and patient contribution to drug cost. A large systematic literature review from the USA suggested low adherence and persistence with biologic therapies in rheumatological disorders, compared with a large Scottish database of Homecare patients, which suggested over 80% adherence [48,49]. Undoubtedly, adherence to self-administered asthma biologics in severe asthma will be investigated over the coming years and should be considered in biologic 'failures' when treatment is not directly administered as well as considering poor adherence to background ICS treatment. This is greatly facilitated with the availability of T2 biomarkers (FeNO and blood eosinophil count), which are helpful at identifying poor adherence to all these therapies targeting the T2 cytokine axis.

CONCLUSION

Nonadherence in asthma, like all chronic disease, remains a common problem despite enhanced awareness by asthma healthcare professionals. Although potentially time-consuming to identify, given the potential impact on exacerbation frequency and risk of asthma death, it remains fundamental in the assessment of the poorly controlled asthmatic and is essential prior to committing a patient to long-term biologic therapy. In patients

with Type 2 inflammatory biology, FeNO suppression with monitored ICS treatment using digital inhaler technologies is a useful tool for assessing the presence of latent nonadherence and differentiating patients who would respond to regular ICS treatment from true refractory biology who are likely to require treatment with targeted biologic therapies.

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