

Fractional Exhaled Nitric Oxide-Guided Algorithm for Children With Asthma

Summary. Fractional exhaled nitric oxide (FeNO) is a surrogate marker of eosinophilic airway inflammation in asthma. The randomized controlled parallel study published by Peirsman et al combined GINA guidelines and FeNO level in guiding drug treatment in children with mild to severe asthma. Their target was to control the FeNO level below 20 ppb. The FeNO group resulted in increasing the dosage of inhaled corticosteroid and the usage of leukotriene receptor antagonist. However, the study was not truly randomized and drug adherence was not reported. The FeNO-guided algorithm failed to improve the primary outcome, the symptom-free days, but did result in decreasing the number of acute exacerbations and unscheduled contacts. Unfortunately the authors did not demonstrate a persistent and significant difference in FeNO levels between both groups. As the final FeNO levels were not reported, it remains unclear whether their target was met. **Pediatr Pulmonol.** © 2014 Wiley Periodicals, Inc.

Key words: asthma; nitric oxide; algorithm.

Dear Editor:

I read the paper by Peirsman et al with interest.¹ The authors aimed to employ fractional exhaled nitric oxide (FeNO), a surrogate marker for eosinophilic airway inflammation, in guiding drug treatment for children with mild to severe persistent asthma. Patients were allocated into the clinical group or the FeNO group. This parallel study was carried out in a single-blinded manner. However, it was not truly randomized, as allocation was deliberately arranged by a research nurse to ensure equal distribution of patients with high and low FeNO in the two groups. While both groups divided patients into uncontrolled, partly controlled and controlled asthma according to GINA guidelines, the FeNO group also made use of a threshold of FeNO 20 ppb, above which preventive medications were to be stepped up irrespective of symptoms, frequency of rescue treatment or spirometric values. The effect was that mild asthmatics or asymptomatic patients with elevated FeNO whose treatment would otherwise be maintained in the clinical group, were given add-on therapy or higher dosage of inhaled corticosteroid (ICS) in the FeNO group. In other words, the targets of the FeNO group included a significant proportion of patients with subclinical eosinophilic airway inflammation. As both groups followed the GINA guidelines, it comes as no surprise that addition of a FeNO-guided algorithm did not cause further increase in

the symptom-free days (SFD), the primary outcome of the study. FEV1 and FEV1 reversibility were not different between both groups.

The authors were able to show that, compared with GINA guidelines, FeNO-guided algorithm resulted in an increased usage of leukotriene receptor antagonist (LTRA). Median daily dosage of ICS was also increased by 100 µg from a baseline of 320 µg. Unfortunately, drug adherence was not reported, so it was not possible to tell whether the clinical improvement was associated with genuine increase in the consumption of preventive medications. It was reported that optimal asthma control entails at least 80% of drug adherence.² Despite the lack of improvement in SFD, the FeNO group achieved a 49%

Financial Support: None

Conflict of interest: None

*Correspondence to: Qun Ui, Lee, MMed (Syd), Department of Paediatrics & Adolescent Medicine, Princess Margaret Hospital, Lai Chi Kok, Kowloon, Hong Kong. E-mail: leequnui@gmail.com

Received 14 July 2014; Accepted 1 August 2014.

DOI 10.1002/ppul.23115

Published online in Wiley Online Library
(wileyonlinelibrary.com).

and a 50% decrease in the number of acute exacerbations and unscheduled contacts, respectively, over one year. The explanation for the discrepant effect on the primary and secondary outcomes is wanting. The baseline daily ICS dosage of 320 µg was near the plateau of dose-response curve, allowing little room for improvement on the daily symptoms and lung function.³ Add-on LTRA to ICS also offers little additional benefit on asthma control and FEV₁.⁴ On the other hand, it has been shown that enhanced adherence to ICS may result in elevation of the threshold of asthma exacerbation.⁵ Increased ICS dosage and/or adherence in the FENO-group may have raised the threshold of exacerbations among asthmatics with subclinical eosinophilic inflammation without affecting the daily symptoms and lung function. A bronchial challenge test is one way to further delineate this threshold. This was not done in this study.

It must also be emphasized that the authors explicitly aimed at keeping the FeNO below 20 ppb. Thus it is crucial to prove that the resultant clinical improvement is accompanied by a concomitant decrease in FeNO level. Unfortunately the authors failed to prove a persistent and significant difference in the FeNO level between the two groups, although this may be the result of a type II error. Furthermore, since the exact FeNO values were not given, the readers cannot determine whether the algorithm-target was met. It was also unclear whether the clinical effect of the FeNO group was mediated by the control of

eosinophilic inflammation as reflected by a persistent lowering of the surrogate marker.

—Qun Ui, Lee MMED (SYD)

Department of Paediatrics & Adolescent Medicine
Princess Margaret Hospital
Lai Chi Kok, Kowloon, Hong Kong

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