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### **Aerocrine statement on exhaled NO study in the Lancet, September 2008 (Szeffler et al)**

The largest trial to date of exhaled nitric oxide (F<sub>ENO</sub>)-guided asthma management was recently published in the Lancet [1]. The authors conclude that "The addition of fraction of exhaled NO as an indicator of control of asthma resulted in higher doses of inhaled corticosteroids, without clinically important improvements in symptomatic asthma control". The design of the study and the authors' interpretation of their results deserve some comments.

First, the higher doses of inhaled corticosteroids (ICS) seen in the F<sub>ENO</sub> group was an unavoidable effect of the study design since the exhaled NO value could only lead to a step-up in treatment and not to down-titration of ICS. This outcome on ICS use, which is entirely due to the study design, is unfair to NO measurements since exhaled NO has previously been shown to enable marked reductions in ICS use without affecting asthma control [2].

Second, it is now appreciated that symptoms, lung function and inflammation (F<sub>ENO</sub>) represent different domains of asthma. When managing asthma with anti-inflammatory agents (for example ICS) as in the study by Szeffler *et al*, it is logical to use an objective marker of inflammation as the primary guide to treatment, and F<sub>ENO</sub> is a well recognized marker of eosinophilic, steroid-sensitive inflammation. Instead, the authors used traditional guideline-based management strategies (symptoms and lung function) in both study groups, with the mere addition of F<sub>ENO</sub> measurements on top of the decision algorithm in the F<sub>ENO</sub> group. Thus, both the intervention and the primary endpoint were based on symptoms. Furthermore, exhaled NO values were reduced to close to normal already during the run-in period and together with the first point above (the F<sub>ENO</sub> value could only lead to a step-up in treatment), very little room was left for F<sub>ENO</sub> to exert any effect. This is visualized by the fact that treatment was modified on the basis of NO measurements at only 26% of the visits in the F<sub>ENO</sub> group.

Third, it is clear that elevated exhaled NO values can be used to define patients that will respond clinically to ICS treatment [3, 4]. It has also recently been described that exhaled NO is significantly related to asthma control over time, meaning that an improvement in asthma control is seen only when the F<sub>ENO</sub> value is clearly reduced [5]. These two features of exhaled NO have not at all been considered in the Lancet article. Instead, the exhaled NO values are almost identical in the two groups, probably due to the reasons mentioned above, and thus the basis for a difference in asthma control between the two groups is not even present. It would have been highly clinically relevant to study the effect of transition to the study medication on exhaled NO and the relation to symptom reduction during the run-in phase.

Fourth, the authors have chosen not to highlight several positive findings in the study. Most importantly, the proportion of patients requiring at least one course of oral corticosteroids in the F<sub>ENO</sub> group was 24% lower compared to the control group, supporting findings in other studies that F<sub>ENO</sub>-guided asthma management leads to fewer exacerbations [2, 6]. Furthermore, in two important and relatively large subgroups, the primary outcome of the study (maximum number of days with symptoms) was significantly reduced. Thus, patients with a BMI of  $\geq 30$  representing 28% of all patients had 0.6 fewer maximum days with symptoms ( $p=0.0245$ ), and patients with total IgE of  $\geq 460$  kU/L (33% of patients) had 0.5 fewer maximum symptom days ( $p=0.0296$ ). With the obese patients probably being proportionally distributed below and above a total IgE of 460 kU/L, this means that these two subgroups represent about 50% of all patients in the study! Finally, F<sub>ENO</sub> was closely related to treatment adherence, with a mean value of 23.9 ppb in patients with adherence of  $\geq 50\%$  and 30.8 ppb in patients with adherence of  $<50\%$  ( $p<0.0001$ ).

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In conclusion, Szeffler *et al* have performed a major clinical study on the use of exhaled NO in asthma therapy monitoring. The study show significant clinical benefits in terms of fewer exacerbations considering all patients, and fewer symptoms in subgroups representing approximately 50% of the patients in total, by the addition of FE<sub>NO</sub> measurements. However, the promising potential of exhaled NO to improve treatment adherence, to assess the response to anti-inflammatory treatment and the effect of environmental triggers, and to point towards diagnoses other than asthma was not explored in this study.

### Summary

1. Exhaled NO measurements led to a reduction in the proportion of patients experiencing at least one steroid burst by 24%.
2. In the exhaled NO group, the primary endpoint (maximum number of days with symptoms) was significantly reduced in patient subgroups (obese or highly IgE sensitized), together representing approximately 50% of the total patient number.
3. Exhaled NO followed symptom score in both groups, and was related to treatment adherence.
4. The study design forced ICS use to increase in the exhaled NO group, and left otherwise little room for the NO value to affect the treatment level.
5. The potential of exhaled NO to check for treatment adherence, to assess response to anti-inflammatory treatment and the effect of allergen exposure, and in differential diagnosis was not addressed in this study.

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### References

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