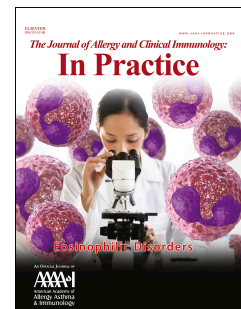


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**A low FEV1 confounds interpretation of FeNO as an eligibility criterion for
Dupilumab**

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Clinical Implication

A_{low} FEV₁ can confound interpretation of FENO values as a marker of type-2 inflammation making repeated FENO measurements mandatory in roughly half of patients with severe asthma when using the 25ppb FENO threshold to identify those eligible for dupilumab.

Asthma is a heterogeneous disease with respect to the inflammatory pathways that are activated (1). Recently, biologic agents targeting airway type-2 (T2) inflammation have been approved to treat uncontrolled T2 severe asthma (2). Among those agents, dupilumab, a monoclonal antibody directed towards the alpha subunit of the interleukin (IL)-4 receptor that blocks the signal transduction pathways activated by both IL-4 and IL-13 has recently become available (3). Several studies have documented the efficacy of dupilumab in reducing severe exacerbation rate and improving lung function in patients suffering from T2 moderate-to-severe asthma that remains uncontrolled despite optimal therapy (4, 5). This effect was larger in patients with elevated signals of T2 inflammation such as blood eosinophils (B-Eos) ≥ 300 cells/mm³ or baseline fractional exhaled nitric oxide (FENO) ≥ 25 ppb (5). A post hoc analysis suggested that patients with both B-Eos ≥ 150 cells/mm³ and FENO ≥ 25 ppb showed the greatest treatment benefits (5). The current EMA approval for dupilumab as from 2019 in patients aged ≥ 12 years specifies that it is approved as an add-on treatment for severe asthma in subjects with type 2 inflammation characterized by raised blood eosinophils and/or raised FENO, uncontrolled with high dose ICS as well as another medicinal product for maintenance treatment. The 25ppb FENO threshold shown to be a valuable predictor of dupilumab efficacy in the LIBERTY QUEST ASTHMA study (5) is used in most countries when FENO is considered to initiate dupilumab treatment often together with elevated B-Eos (≥ 150 -300/mm³). However, it was also demonstrated that FENO is significantly reduced when airway calibre is reduced (6) confounding its interpretation as an indicator of T2 airway inflammation. This airway calibre impact could make the selected FENO threshold inappropriate in severe asthma patients with lower FEV₁ values.

To this end, we evaluated the prevalence of FENO measurements < 25 ppb in patients suffering from T2 high uncontrolled severe asthma. We also investigated whether this could be linked to FEV₁ reduction.

The study, approved by the local ethic committee, was designed as a post-hoc analysis performed on a data base of patients attending the out-patient asthma clinic in Erasme University Hospital (Brussels, Belgium). FENO (in ppb), measured by chemiluminescence (Logan Research LTD, Rochester, UK) according to international standards (7), and FEV₁ measured using a Zan 300 spirometer (Zan®, Oberthulba, Germany) were recorded at each visit in 32 patients (n=342 visits separated by a median interval of 109days) suffering from severe eosinophilic asthma defined according to ERS guidelines on severe asthma (8) associated with B-Eos repeatedly > 300 /mm³. In a sub-population of 19 patients with at least

five visits recorded (median number of visits:12, range: 5-33 on a median time frame of 5years), the individual percentage of visits with a FENO value < 25ppb was computed. Patients characteristics are given in Table E1 of the Online Repository. Figure 1 shows that, of 342 visits, 47% of FENO measurements were lower than 25 ppb and that FENO and FEV₁ (%pred) are positively correlated. Of 19 patients with at least five visits, up to 50% of their FENO were lower than 25 ppb in 48% of the patients. Moreover, as shown on Figure 2, this individual percentage of low FENO values appeared to be negatively correlated ($r = -0.467$ (Pearson coefficient) , $P=0.045$) with the mean FEV₁ (%pred) over the patient's visits. Additionally, up to five and 11 measurements are needed to observe at least one FENO above 25ppb when 50 and 75% of FENO measurements below this threshold are expected, respectively. No association was found between OCS use (unpaired t-test) and individual percentage of FENO below 25ppb ($P=0.46$) or mean FEV₁%pred ($P=0.76$) but it should be noted that in the real life setting treatment adherence could not be fully assessed. Similarly, there was no influence of atopy, sex, BMI or pollen season noted. Our results show that, in this specific population of adults suffering from uncontrolled T2 high severe asthma, a significant proportion of patients frequently (> 50% of the measurements) displays FENO levels < 25 ppb selected as an eligibility criterion for treatment with dupilumab. Patients with the lowest FEV₁ were those most frequently exhibiting FENO levels < 25 ppb, suggesting an association with airway calibre reduction. This could impact some of the most severely affected patients. One could, however, argue that patients included in our study, who would have been considered as eligible for dupilumab regardless of baseline FENO, based on their high blood eosinophil count, might differ in terms of baseline FENO from patients with moderately elevated B-Eos that might reflect a lower T2 inflammation intensity. No difference in baseline FENO between patients with high (> 300/mm³) or moderately high blood eosinophils (150-300/mm³) count was however observed in the LIBERTY ASTHMA QUEST (5). Finally, it appears that no less than five FENO measurements should be carried out in patients exhibiting 50% of FENO measurements < 25 ppb to detect at least one value superior to the selected FENO threshold. A least 10 measurements should be carried in patients exhibiting 75% of FENO measurements < 25 ppb. These results further support the GINA guidelines statement that "FENO at one time point should be interpreted with caution" and should be repeated up to three times when used to identify T2 inflammation, especially in patients treated with OCS (9). In our study, we could not find any influence of the OCS use on the probability to observe FENO values below 25ppb.

These results add to the complexity of FENO as a marker of airway inflammation. Also the fact that the expense of FENO testing is not always reimbursed by health care providers suggest that more data are needed before definitive conclusions on FENO use to mark T2 inflammation can be drawn.

To conclude, low FEV₁ can confound interpretation of FENO as an indicator of T2 inflammation in severe eosinophilic asthma. This makes repeated FENO measurements advisable in about half of patients in the subgroup with moderately elevated blood eosinophil counts in which FENO is employed to identify dupilumab eligibility.

KEY WORDS: type-2 high severe asthma, dupilumab, exhaled nitric oxide, FEV₁.

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Legend to the figure

Figure 1: Significant relationship (dashed line, $p < 0.001$) between individual FENO measurements and FEV₁ (%pred); 47% of FENO values (open circles) are below 25ppb threshold (grey line). FEV₁ mean values (vertical lines) corresponding to FENO below (open circles) and above (closed circles) 25ppb, are 65 and 71%, respectively ($p = 0.001$, unpaired t-test)

Figure 2: Significant relationship ($p = 0.045$) between individual mean FEV₁ (in ordinate) and individual percentage of FENO values below 25ppb (in abscissa) in the 19 patients with, at least, five visits. Closed and open circles are patients with and without OCS, respectively. The figures in the box are derived from binomial law giving the number of consecutive measurements required to reach 95% probability of observing at least one FENO value above 25ppb as a function of the percentage of FENO values below 25ppb.

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