Type 2 high or Type 2 low severe asthma?

Optimizing treatment decisions with biologics based on regular FeNO home measurement

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Summary

This case study refers to a participant of the ongoing FeNO@home study. A patient with severe non-allergic asthma for whom repeated outpatient measurements of Type 2 inflammatory biomarkers (blood eosinophils and FeNO measured in medical practice) could not confirm the Type 2 nature of severe asthma, denying the patient access to the use of biologic drugs currently available in Italy. Regular FeNO home measurements revealed that on several days the patient had values above 25 ppb (cut-off for dupilumab eligibility[1]), with peaks as high as 88 ppb. At the end of the monitoring, the patient started treatment with dupilumab. **Frequent measurement of FeNO can help in the correct endotyping of severe asthmatic patients, allowing a personalized and precise choice of a biologic therapy.**

Case history

A 69-year-old woman with a history of non-allergic asthma that was well controlled with low-medium dose of inhaled corticosteroids (ICS) plus long-acting beta2-agonists (LABA) until 2021 when the patient started experiencing recurrent exacerbations with a need for oral corticosteroids (OCS) and poor asthma control in the Asthma Control Test (ACT score always around 9-15). The patient was re-assessed in terms of comorbidities (perennial rhinitis, no endoscopic and CT-scan signs of chronic rhinosinusitis; no gastroesophageal reflux symptoms or signs; no bronchiectasis; no obesity; no smoker), treatment adherence and inhalation technique (both were proven to be optimal). Therefore, according to Global Initiative for Asthma (GINA) guidelines[1], treatment step-up was done to use of Fluticasone furoate/Vilanterol 184/22 mcg, Tiotropium bromide via Respimat® device and Montelukast 10 mg/die. Despite this therapy, the patient was still experiencing recurrent asthma exacerbations (2 episodes per year with the need of OCS short courses) and poor asthma control (ACT score around 9-17) with a daily need for a short-acting beta2-agonist (SABA), salbutamol, as rescue treatment. The patient was therefore classified as being affected by severe asthma. Several blood cell counts were performed, always with blood eosinophils lower than 150 cells/mcl. Fractional exhaled Nitric Oxide (FeNO) was assessed in the clinic several times, always with values lower than 20 ppb, and only in one single occasion the result was 21 ppb (to be noticed that the latter assessment was done during an upper airway infection episode). Total Immuglobulin E (IgE) was 115.8 kU/l. Skin prick tests for airborne allergens and multiplex IgE array were performed, confirming that the patient was not sensitized to any allergen. Spirometry was normal (FEV1>80% predicted value, FEV1/FVC>80%).

Problem statement

The patient was not sufficiently controlled and having recurrent asthma exacerbation needing the intake of OCS, despite the highest level of inhaled and oral treatment according to GINA[1]. The patient was adherent with the prescribed therapy, with a proper inhalation technique, and without relevant comorbidities potentially affecting the severity of asthma. Therefore, the patient was a good candidate to start biologic therapy. However, the absence of evidence of Type 2 high biomarkers (no atopy, low eosinophils and FeNO) was limiting us in using available biologics (omalizumab, mepolizumab, benralizumab, dupilumab). Regular FeNO home measurement was proposed to the patient to confirm or rule-out the absence of Type 2 signature.

Investigation

The patient was included in the FeNO@home study[2]. The aim of the study was to investigate whether regular FeNO home measurements had an impact on patient compliance or behavior, variability of FeNO values over a longer period, correlation of FeNO values with symptoms, identification of asthma triggers, and treatment decisions. In this multicenter study, adult patients with diagnosed asthma performed FeNO measurements over a period of 12 weeks using the Vivatmo *me* measurement device for home use. They continued to take their currently prescribed asthma treatment, which could also be adapted. Daily symptoms, use of asthma medication, potential exacerbations, and Peak Expiratory Flow (PEF) were recorded in the device-associated Vivatmo *app*. After 12 weeks, the study ended with a final assessment of asthma control, symptoms, and lung function.

Results and treatment

During the study no adjustment of medication was done. Asthma control was poor in most of the observation period (ACT score <20). The regular monitoring of FeNO revealed that frequently the levels were higher than normal (>25 ppb) with peaks up to 88 ppb (see figure below). Our expectation of serial FeNO measurement was fully met, as it revealed that Type 2 inflammation is the predominant endotype for this patient, despite the repeated single in-clinic assessment failed to show high FeNO values.
With these results on our hand, we were confident to prescribe dupilumab, an anti-IL4-receptor alpha monoclonal antibody, that showed greater efficacy in patients with high FeNO (>20 ppb) and/or high blood eosinophils (>150 cells/mcl)[3].

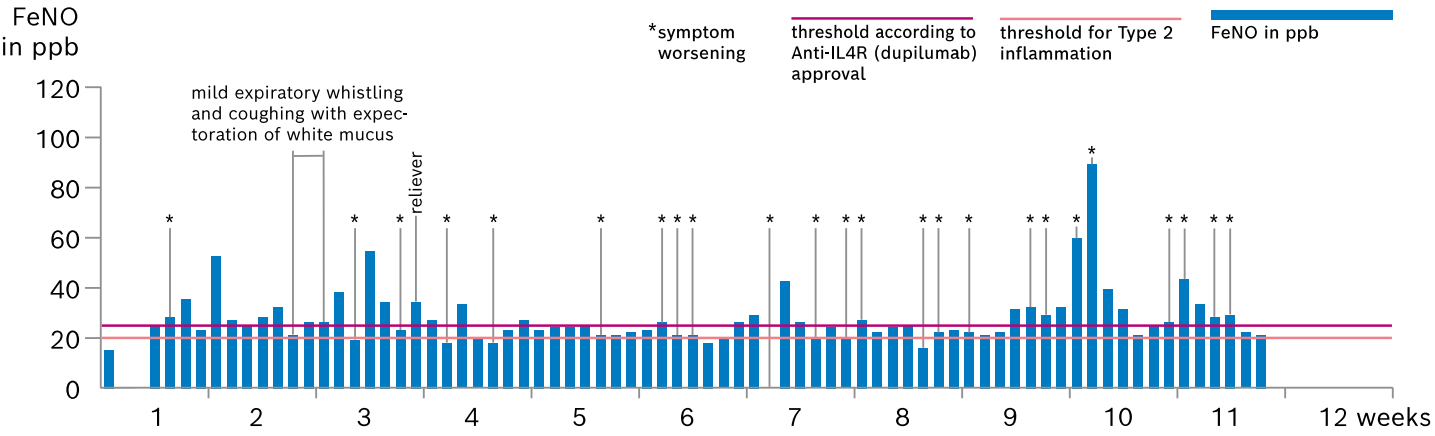

Figure: Course of the FeNO values based on regular home measurements by patients, thresholds according to GINA[1]

Discussion

Severe asthma is affecting an estimated proportion of about 3-5% of asthmatics, and it is characterized by non-adequate response to high dose of ICS plus another controller (LABA, LAMA, leukotriene receptor antagonists...).[4] Most of the patients with severe asthma have evident Type 2 signature[5], assessed mainly by means of the presence of atopy and/or high levels of blood eosinophils and/or FeNO. All the biologic drugs currently available for severe asthma target immunological mechanisms directly involved in the Type 2 inflammation, such as (IgE), interleukin-5 (IL-5) or its receptor, interleukin-4 (IL-4) receptor-alpha, or Thymic Stromal Lymphopoietin (TSLP)[6]. Only tezepelumab (an anti-TLSP monoclonal antibody) showed a certain degree of efficacy in patients with Type 2 low asthma, even if the better results are achieved in patients with high Type 2 biomarkers[7] (tezepelumab is still not yet available in Italy). Therefore, in the case of the described patient, FeNO home measurement was crucial for identifying the Type 2 signature (that was not evident in previous single in-clinic assessments) that led us to prescribe dupilumab.
These are some preliminary results since the study is still ongoing. Thus, only a single patient case is reported. The completion of the study is needed to strengthen the beneficial effects of FeNO home measurement for physicians and asthma patients.

Conclusion

In conclusion, this case report shows that FeNO home measurement could be useful for better understanding the real endotype in patients with apparent Type 2 low severe asthma, opening to the clinician the opportunity to start a targeted biologic treatment.

References

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