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Original article

FeNO measurement as a new tool for increasing patient's adherence to SLIT

Le No exhalé est un nouvel outil pour augmenter l'adhérence du patient à une désensibilisation sublinguale

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Abstract

Background. – Sublingual immunotherapy (SLIT) is clinically effective, but, as any other long-term treatment, faces the problem of adherence. Measurement of fractional exhaled nitric oxide (FeNO) is a non-invasive exam for assessing inflammation in asthma. The aim of our study was to evaluate whether repeated FeNO measurements could increase adherence to SLIT.

Methods. – Forty-four patients (23 males and 21 females, mean age 25.5 years $\pm$ 12.9) with allergic rhinitis undergoing SLIT for house dust mites (HDM), were included in the study. They were divided in 2 groups: patients performing at least 2 FeNO measurements (FeNO-group) vs. patients who had never measured FeNO or had only one measurement (noFeNO-group). To evaluate adherence to therapy, we considered allergen immunotherapy renewal rate (number of vials) as a parameter.

Results. – The FeNO-group showed a significant higher renewal rate compared to the noFeNO-group, both in the first year and for all the duration of SLIT.

Conclusion. – We found a correlation between FeNO measurement and adherence to SLIT in terms of product reorders. These findings suggest that monitoring the disease with a clear numeric parameter, as FeNO, may help patients to understand their disease state and motivate their continuation of immunotherapy.

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Keywords: Patient adherence; Allergen immunotherapy; FeNO

Résumé

Objectifs. – L'immunothérapie par voie sublinguale (ITSL) est un traitement efficace qui se heurte comme tous les traitements de fond à des problèmes d'adhérence de la part du patient. La mesure du No exhalé (FeNO) est un examen non invasif qui permet de mesurer l'inflammation dans l'asthme. Le but de cette étude était d'évaluer si des mesures répétées du FeNO pouvaient augmenter l'adhérence au traitement.

Patients et méthodes. – Quarante-quatre patients (23 hommes et 21 femmes, de moyenne d'âge 25,5 $\pm$ 12,9 ans) victimes d'une rhinite allergique et désensibilisés par ITSL aux acariens ont été inclus dans cette étude. Ils ont été randomisés en 2 groupes : patients effectuant au moins 2 mesures du FeNO (groupe FeNO), vs patients n'ayant jamais effectué de mesure ou FeNO ou uniquement à une seule occasion (groupe noFeNO). L'adhérence au traitement a été appréciée par le nombre de demandes de renouvellement des extraits allergéniques.

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Résultats. – Le groupe FeNO a effectué un plus grand nombre de demandes de renouvellement des extraits de désensibilisation comparé au groupe noFeNO, à la fois lors de la première année de traitement et pour toute la durée de l'ITSL.

Conclusion. – Nous avons objectivé une corrélation entre les mesures du FeNO et l'adhérence à la SLIT basée sur le renouvellement du traitement. Ces résultats suggèrent que la surveillance de la maladie avec un paramètre numérique clair, tel que le FeNO, peut aider les patients à mieux comprendre leur état de santé et permet de les motiver pour poursuivre le traitement de fond.

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Mots clés : Adhérence au traitement ; Désensibilisation sublinguale ; NO exhalé

1. Introduction

Allergen immunotherapy (AIT) is a validated treatment option for allergic rhinitis (AR) and asthma in adults and children [1]. It is based on the administration of increasing doses of the causative allergen in order to reduce subject reactivity to the allergen itself. AIT is the only treatment acting on the causes of allergy and not only on its symptoms. The clinical efficacy of sublingual immunotherapy (SLIT) has been established in a number of clinical trials and meta-analysis, with a good safety profile using high allergen doses, both in adults and in children [2,3]. However as SLIT is a long-term therapy, self-administrated by patients without medical supervision, assessment of adherence to treatment is still a concern. Adherence has been defined as “the extent to which a person’s behavior, taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider” [4]. Poor adherence to long-term therapies leads to a decrease in treatment benefits and can cause an increase of the socioeconomic costs due to direct (e.g. symptomatic drugs, increased morbidity) and indirect costs (e.g. reduced productivity, poor quality of life). Concerning SLIT, contrasting data are available, because post-marketing studies reported adherence rates ranging from 75% to 95%, depending on age and on treatment duration [5], while a study based on Italian sales data of the two major manufacturers of SLIT products found that the renewal rate progressively decreased from 44% at the first year of therapy to 13% at the third year [6]. Some studies have attempted to investigate the reasons for these treatment withdrawal rates, suggesting that perception of clinical efficacy and absence of side effects are very important [7], and that timing and monitoring of control visits, and patient’s education are able to increase patient’s adherence [8,9]. The availability of an objective “marker”, able to help patients to follow their own improvement should represent a step forward in adherence optimization. Measurement of fractional exhaled nitric oxide (FeNO) is a non-invasive exam, which has been validated for asthma management [10].

The aim of this pilot study was to assess whether repeated FeNO measurements could increase SLIT adherence. In a cohort of Italian individually identifiable patients the prescriptions were analyzed from 2009 to 2012 to evaluate the renewal rate for SLIT.

2. Methods

In this retrospective study we included 44 patients (23 males and 21 females, mean age 25.5 years $\pm$ 12.9) with AR, who

underwent SLIT therapy for HDM from 2009 until 2012. All patients received the same educational program based on the importance of environmental control aiming at reducing the exposure to HDM (e.g. aeration of the house, use of covers to encase bedding, removal of carpets, etc.) and were treated by 4 pressures/die of Staloral 300 IR, administering the following amount of major allergen dose: Der p 1 24 μ g, Der p 2 4.8 μ g, Der f 1 60 μ g. We divided the patients in 2 groups: patients performing at least 2 FeNO measurements (with FeNO) vs. patients who never measured FeNO or had only one exam (without FeNO). To evaluate adherence to therapy, we considered allergen immunotherapy renewal rate (number of vials) as the major parameter, considering that patients cannot comply SLIT if they have not obtained the prescribed drug. Vaccine renewal rate was obtained from the Stallergenes Italy’s database of pharmacy refill records. Patients who reordered at least twice in 2010 were considered adherent for the first year of therapy. Conversely, if a patient failed to reorder at least once a year was considered as non-adherent. The analysis of the database did not require patient informed consent or independent ethics committee approval of the analysis plan.

FeNO measurement was performed using an elettrochemoluminescent analyzer (NIOX MINO[®], Aerocrine, Sweden) with 50 mL/s flow rate, according to published guidelines from the American Thoracic Society (ATS). FeNO measurement was voluntary and its costs were charged to the patient.

Statistical analysis. Continuous parameters were expressed with mean $\pm$ SD, median, mode, minimum and maximum. Comparison of qualitative data was made by the χ^2 -test. The relationships between probability of reorder and the independent variables (age, sex, FeNO test) were assessed using logistic regression. *P* values < 0.05 were considered statistically significant. All statistical analysis was performed with the BMDP (v.8.1) software.

3. Results

Both groups were homogeneous for age and sex and were evaluated during the follow-up.

All patients in the FeNO-group had asthma, whereas in the group without FeNO measurement 12 patients had allergic rhinitis alone.

At baseline, mean FeNO value was 76 (SD 36.75) ppb in the patients, who did this exam, of group without FeNO. In the group with FeNO measurement, the mean baseline value was 59.45 (SD 18.75). The FeNO mean value significantly (*P* < 0.05) decreased at the end of the study: 21.69 (SD

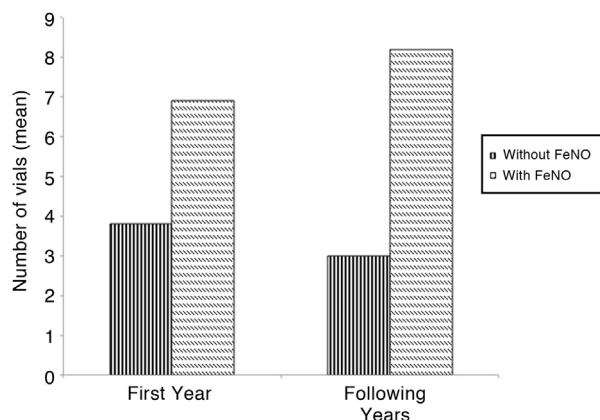


Fig. 1. Mean number of vials number used in patients performing fractional exhaled nitric oxide (FeNO) measurement (blue column) and not performing FeNO measurement (red column), in the first year and on the following years.

8.04). In the first year of therapy the group with FeNO measurements had a significant ($P < 0.05$) higher number of used vials per year compared to the group without FeNO measurements (Fig. 1). The difference was more evident ($P < 0.001$) in the successive years of therapy (II and III). FeNO was able to discriminate between who was likely to assume the allergen immunotherapy the next year and who will not: 85% of patients that performed FeNO measurement reordered at least one vial of allergen immunotherapy in the subsequent years, while this fell to only 40% in patients without FeNO measurements, as shown on Fig. 2. No patient reached the number of allergen immunotherapy vials needed to complete SLIT treatment (12 vials/year) as indicated in the package insert. Forty-five percent of patients from the group with FeNO reached the highest rate of adherence (9 vials/year). In the group without FeNO no one reached this high level of adherence to therapy ($P < 0.01$). The logistic regression analysis showed that only the FeNO test resulted as a significant parameter

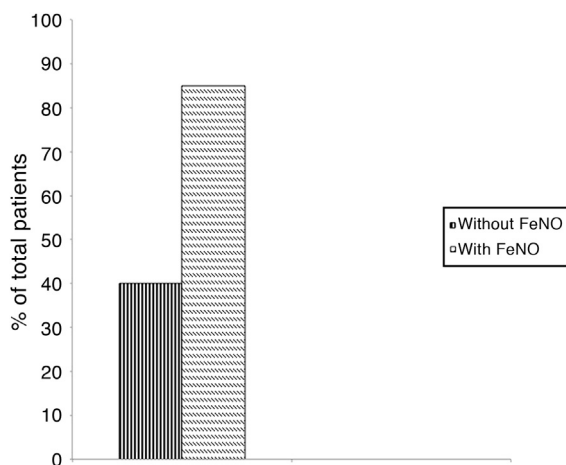


Fig. 2. Renewal probability of AIT in patients not performing fractional exhaled nitric oxide (FeNO) measurement (left column) and in patients performing FeNO measurement (right column).

influencing renewal probability. In other words, patients not performing FeNO measurement had significantly lesser probability $< 1\%$ of renewal in comparison with patients performing FeNO measurement.

4. Discussion

Adherence is influenced by several factors, including social and economic factors, the health care system, the characteristics of the disease, the various disease therapies and patient-related factors [11]. Adherence remains a problem for AIT and new methods to increase patient adherence to therapy have to be assessed. There is no consensual standard that represents an acceptable adherence rate: however, some trials consider that an adherence greater than 70–80% is adequate for most treatments [12,13]. These rates are probably influenced by the patient's knowledge that the measurement of their adherence to the treatment is the aim of the study. In the real practice the percentage of adherence to SLIT seems lower, as reported in a study based on Italian sales data of the two major manufacturers of SLIT immunotherapy [6]. Renewal rate for the first year of therapy was around 44% and decreased to 30% in the second year, with only 13% of initial patients that completed the prescribed 3-year immunotherapy cycle. Among the factors investigated as possible reasons for these treatment withdrawal rates, perception of clinical efficacy and absence of side effects seem of central importance [7]. Some other factors that can influence adherence are closely related to AR pathology such as variability in symptoms, which are related to the seasonal/perennial presence of causative allergens, and induce patients to stop treatment when symptom free. Moreover, the frequent administration regimen required for SLIT could also reduce adherence. The availability of an objective marker, able to help patients to follow their own improvement, should represent a step forward in adherence optimization. FeNO offers characteristics fitting with such aim. NO is a signaling molecule implicated in many processes in the airway tract, including eosinophilic inflammation. It is produced by the conversion of L-arginine to L-citrulline by a class of enzymes called NO synthases (NOS), which can be expressed constitutively (cNOS) by airway epithelia cells or induced (iNOS) by inflammatory cytokines (TNF- α , IFN- γ and IL-1 β) [14,15]. It is possible to measure levels of NO in both the lower and upper airway, using a hand-held device, with high precision and ease of use. Also very young patients can successfully perform this measure. The resulting value, expressed in part per billion (ppb) of NO molecules, has been demonstrated to help physician to adjust inhaled corticosteroids (ICS) treatment and reduce the risk of asthma exacerbations. The exam, resulting in a clear numeric parameter, could also increase patient's perception of the disease state and efficacy of the treatment prescribed [10]. In our study, the adherence to SLIT in patients undergoing FeNO measurement was around 75% and was significantly higher than the adherence in patients not monitored with FeNO. We found a correlation between FeNO measurement and adherence to SLIT therapy in terms of renewal rate. These

findings suggest that monitoring the disease with a clear numeric parameter, as FeNO, may help patients to understand their disease state and motivate their continuation of immunotherapy, whatever the measured value of FeNO. Patients who perceive their disease status and treatment efficacy are more actively engaged in the care process and are prone to have better adherence behavior and health outcomes. On the other hand, the cost charge of FeNO measurement could explain the reduced adherence: in fact, people with limited financial means have less access to visits and also to treatment, including SLIT.

5. Conclusions

Improving adherence to prescribed therapy with new efficacious interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments [16]. Taking regular FeNO measurements during AIT treatment could help to improve patient adherence to therapy. Using FeNO as a marker of his airway inflammation status, the patient has a more precise perception of the disease state and of AIT treatment efficacy in controlling AR. Moreover, the physician could use FeNO measurement in AR patient to better adapt the therapy. Overall, FeNO measurement offers a clear outlook on disease progression that improves AIT follow-up and patient adherence to therapy, and may thus be expected to improve overall AIT efficacy.

Disclosure of interest

Ilaria Dell'Albani and Farnco Frati are employees of Stallergenes Italy Srl.

Cristoforo Incorvaia and Giorgio Ciprandi are scientific consultant for Stallergenes Italy Srl.

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