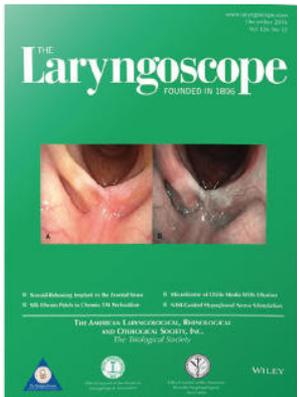




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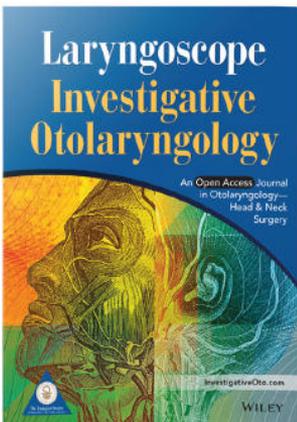


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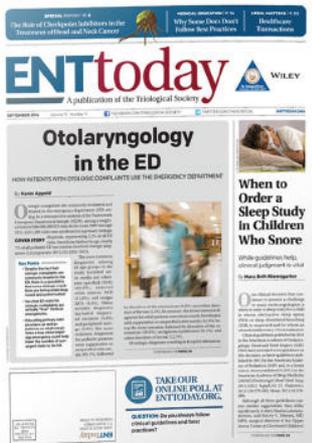


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# Antileukotrienes Improve Naso-Ocular Symptoms and Biomarkers in Patients With NARES and Asthma

Eugenio De Corso, MD, PhD ; Roberta Anzivino, MD; Jacopo Galli, MD; Silvia Baroni, MD; Walter Di Nardo, MD; Carla De Vita, MD; Antonio Salvati, MD; Chiara Autilio, CB; Stefano Settimi, MD; Dario Mele, MD; Gaetano Paludetti, MD; Joaquim Mullol, MD

**Objective:** The aim of our study was to analyze the montelukast effectiveness in improving oculonasal symptoms, patient-reported outcomes (PROs), and eosinophilic biomarkers in patients with nonallergic rhinitis eosinophilic syndrome (NARES).

**Methods:** We enrolled prospectively 80 symptomatic patients treated with 10 mg once a day of montelukast in monotherapy for 2 months. All patients were investigated before and after treatment. Nasal symptoms (nasal obstruction, rhinorrhoea, sneezing, nasal itching), ocular symptoms (redness/puffiness, watery eyes), and other PROs (olfactory dysfunction, difficulty going to sleep, nighttime awakenings, and nasal congestion on awakening) were scored by visual analogic scale. The following clinical scores were assessed: Total Nasal Symptom Score (T4NSS), Total Ocular Symptom Score (T2OSS), Total Symptom Score of Patient-Reported Outcomes (TSS-PROs), and a Composite Symptoms Score (CSS). Patients were classified as responders when a reduction of at least 50% of the CSS was observed. Before and after treatment, the eosinophilic biomarkers in nasal lavage were analyzed: nasal eosinophilia (number of eosinophils per high power field), eotaxin-1 and eotaxin-2.

**Results:** After treatment, significant reductions were observed for all the symptom scores. Forty-two of 78 patients were considered responders. A significant reduction of eosinophils in nasal mucosa and of levels of eotaxin-1 and eotaxin-2 in nasal lavage were observed after treatment in responder patients. Patients with asthma had an increased probability to be responders.

**Conclusion:** NARES patients may benefit from treatment with montelukast. In particular, the presence of concomitant asthma may be predictive of a greater efficacy.

**Key Words:** NARES, asthma, antileukotrienes, montelukast, eosinophils, eotaxin, precision medicine.

**Level of Evidence:** 2

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## INTRODUCTION

Cysteinyl-leukotrienes (cysLTs), including LTC<sub>4</sub>, LTD<sub>4</sub>, and LTE<sub>4</sub>, are proinflammatory mediators derived from arachidonic acid and synthesized by mast cells and eosinophils in response to stimuli such as allergens, proinflammatory cytokines, and other types of receptor-dependent stimuli.<sup>1</sup> After release into the circulation, cysLTs reach their targets in the upper and lower airways and interact with two main receptors (LT<sub>1</sub>R and LT<sub>2</sub>R), eliciting a number of responses including the recruitment of inflammatory cells (particularly eosinophils), cytokine

release, enhanced mucus production, mucosal edema, and activation of airway smooth muscle. Most of the proinflammatory activity seems to be attributed to mediation through LT<sub>1</sub>R, which are expressed on basophils; mast cells; dendritic cells; eosinophils; monocytes/macrophages; and a variety of structural cells such as airway smooth muscle, fibroblasts, epithelial, and endothelial cells.<sup>2</sup>

Clinical studies<sup>3,4</sup> have shown that LT<sub>1</sub>R selective antagonists such as montelukast and zafirlukast may be advantageously administered orally in patients with lower airway inflammation/bronchial obstruction or reactivity due to the reduction of eosinophil accumulation and infiltration in the bronchial wall. A recent meta-analysis suggests that, although inhaled corticosteroids remain the first-line treatment, leukotriene receptor antagonists in monotherapy significantly reduce severe exacerbations in chronic mild to moderate asthma.<sup>5</sup> The effectiveness of antileukotrienes has also been assessed in patients suffering from allergic rhinitis (AR) with or without concomitant asthma. The common outcome of studies in this field was the significant improvement in daytime and nighttime symptoms related to both perennial and seasonal AR in patients treated with montelukast in comparison to placebo.<sup>6,7</sup>

Currently, the effects of montelukast on symptomatic patients with nonallergic rhinitis (NAR), and in particular on NAR with eosinophilic syndrome (NARES), have not been investigated in the literature. Nonallergic rhinitis

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includes an extensive list of different phenotypes that differ in terms of pathogenic mechanisms and clinical features.<sup>8–10</sup> Several authors<sup>11–16</sup> have encouraged the detection of inflammation in patients affected by NAR because the type of inflammatory pattern may impact differently both the disease severity and therapeutic response. Therefore, we strongly suggest defining the different phenotypes of NAR, and in particular the presence of nasal eosinophilia, which causes the most severe symptoms and greater association with comorbidities.<sup>17,18</sup> Corticosteroids are effective in controlling nasal symptoms in these patients by directly inducing eosinophil apoptosis, inhibiting eosinophil recruitment and its migration into the nasal airways.<sup>19</sup> Nevertheless, the long-term usage of corticosteroids is limited in certain situations such as hemorrhagic diatheses, history of recurrent nasal bleeding, and ocular contraindications; for these, alternative therapeutical options may be useful.

Because cysLTs are produced by eosinophils and play an important role in eosinophilic inflammation, selective antagonists such as montelukast may represent an alternative option to control nasal symptoms in NARES patients. Nonetheless, there are no existing published studies examining the role of leukotriene modifiers in the treatment of NARES. Because LT<sub>1</sub>R antagonists have been shown to be effective in attenuating eosinophilic inflammation in the airways of asthmatic subjects and in the nasal mucosa of allergic subjects, we hypothesized that this drug could have a significant effect on the treatment of eosinophilic NAR patients.

The aim of our study was to analyze the effectiveness of montelukast, an LT<sub>1</sub>R selective antagonist, in the management of nasocular symptoms and PROs in patients with NARES. In addition, secondary objectives were to assess the effect of montelukast on nasal eosinophilic infiltration and eosinophilic biomarkers in nasal lavage while phenotyping NARES responder patients based on therapeutic response.

## MATERIALS AND METHODS

### *Study Population and Study Design*

This is a prospective open-label cohort study (therapeutic) of level 2. Symptomatic patients with a diagnosis of NARES were recruited and treated with 10 mg montelukast orally in monotherapy once a day for 8 weeks. Patients were followed between February 2018 and April 2018 at our rhinology unit of the head and neck department of A. Gemelli Hospital Foundation IRCCS (Institute of Treatment and Scientific Research). All the patients gave their informed consent to participate in the study. The study was approved by the ethics committee of our institution (ID1805).

Montelukast was safely tolerated: 78 of 80 patients completed the treatment period (53 females [67.9%]; mean age of 41 ± 14 years). Baseline characteristics of patients are shown in Table I. There were only two dropouts in total, and the reasons for discontinuation were minor adverse events (headache in one patient, gastrointestinal symptoms in another).

*Inclusion criteria.* The phenotyping of NARES patients was based on several inclusion and exclusion criteria. Inclusion criteria consisted of clinical symptoms of persistent rhinitis, negative skin prick test, negative specific IgE blood assays with

Radioallergosorbent test (RAST), negative intranasal allergen provocation test for principal inhalant allergens (including house dust mites, major Italian pollens, mold, dogs/cats epithelium), and eosinophilic infiltration in the sinonasal mucosa detected by nasal cytology greater than 20% of total inflammatory cells in at least 10 fields observed (diagnostic cutoff assumed by most authors in literature).<sup>17,18</sup>

*Exclusion criteria.* We excluded from the study patients presenting at least one of these conditions: Previous sinonasal surgery, local or systemic medical treatment such as intranasal or oral corticosteroid (during the previous 4 weeks), positive skin prick test, negative nasal cytology or eosinophil infiltration lower than the assumed diagnostic cutoff, evidence of nasal polyps at nasal endoscopy (Meltzer endoscopic score > 0),<sup>20</sup> or evidence of sinonasal occupancy at computed tomography scan (Lund-Mackay score > 0).<sup>21</sup>

### *Efficacy Outcomes*

*Nasal symptoms and patient-reported outcomes.* Patients were asked to complete a rhinological questionnaire at baseline and at end of treatment to score, using a visual analogical scale (VAS) ranging from 0 to 10 cm, their main nasal symptoms (nasal obstruction, rhinorrhoea, sneezing, and nasal itching); ocular symptoms (redness/puffiness, watery eyes); and other PROs such as olfactory dysfunction, sleeping difficulties, nighttime awakenings, and nasal congestion on awakening. For each symptom, the patients had to indicate, using a scale ranging from 0 to 10, their answer to the question: “How troublesome is your symptom?” Patients were notified that 0 indicated “absence of symptom” and 10 indicated “symptom extremely bothersome.” For each patient, we calculated the T4NSS by adding the scores of the four main nasal symptoms, the T2OSS by adding the scores of the two main ocular symptoms, and the TSS-PROs by adding the scores of the other four PROs (olfactory dysfunction, difficulty going to sleep, nighttime awakenings, and nasal congestion on awakening). Finally, the CSS was also calculated by adding the T4NSS, T2OSS, and TSS-PROs scores. The efficacy was assessed comparing values of symptom scores at baseline and at the end of 8 weeks of treatment. Patients were classified as responders to treatment when there was at least 50% improvement in the CSS compared to baseline. We lastly performed unimodal logistic regression analysis based on clinical patient phenotypes (familiar history for sinonasal eosinophilic inflammation, associated asthma, and blood hypereosinophilia) to establish the relative risk (RR) of good response to the therapy.

*Eosinophilic infiltration of nasal mucosa by nasal cytology.* Nasal leukocyte counts were performed on scraped nasal tissue, obtained from the inferior turbinate bilaterally. Scraping was performed using Rhinoprobe (Farmark s.n.c, Milan, Italy). The sample was gently spread on glass slides and immediately fixed in 95% ethyl alcohol and stained with May-Grünwald-Giemsa. The slides were examined under oil immersion by light microscopy at a magnification of ×1000. Nasal tissue eosinophil infiltration was measured as eosinophil count per high power field (Ec-hpf), and reported as the mean of at least 10 high-powered fields observed at nasal cytology.<sup>3,12,13,17,18</sup>

*Nasal lavage fluid collection and processing of eosinophilic biomarkers.* Nasal lavage fluid was obtained from subjects with the head bent down, based on methods previously described.<sup>22</sup> Each nostril was washed by instilling 5 mL of saline solution (NaCl 0.9%) prewarmed to 35 °C. The fluid was collected by asking the subjects to lean forward and blow the nasal

TABLE I.  
Clinical Characteristics and Eosinophilic Biomarkers of Patients at Baseline

|   | All Patients N = 78 | Responders N = 42 | No Responders N = 36 | P Value |
|---|---------------------|-------------------|----------------------|---------|
| Age, years (mean ± SD)                  | 41 ± 14             | 40 ± 13           | 42 ± 15              | > 0.05  |
| Gender (females)                        | 53 (67.9%)          | 28 (66.7%)        | 25 (69.4%)           | > 0.05  |
| <i>Clinical factors</i>                 |                     |                   |                      |         |
| Family history of sinonasal disorders   | 30 of 78 (38.5%)    | 14 of 42 (33.3%)  | 16 of 36 (44.4%)     | > 0.05  |
| Duration of rhinitis, years (mean ± SD) | 7.2 ± 3.0           | 6.1 ± 3.0         | 8.2 ± 2.0            | > 0.05  |
| Asthma                                  | 22 of 78 (28.2%)    | 15 of 42 (35.7%)  | 7 of 36 (19.4%)      | < 0.05  |
| Peripheral blood ipereosinophilia       | 22 of 78 (28.2%)    | 10 of 42 (23.8%)  | 12 of 36 (19.0%)     | > 0.05  |
| <i>Eosinophilic biomarkers</i>          |                     |                   |                      |         |
| Eosinophils, Ec-hpf (mean ± SD)         | 54.1 + 8.1          | 65.9 ± 10.2       | 43.9 ± 8.1           | < 0.05  |
| Eotaxin-1, pg/mL (mean ± SD)            | 22.8 + 6.1          | 29.1 + 8.5        | 21.1 ± 7.5           | > 0.05  |
| Eotaxin-2, pg/mL (mean ± SD)            | 136.6 + 23.2        | 145.6 + 19.5      | 126.6 + 20.5         | > 0.05  |

P values of comparison between responder and nonresponder are reported.  
SD = standard deviation.

contents gently into a funnel connected to a 30 mL universal container. The lavage fluid was filtered to remove any nasal mucus, centrifuged immediately at 4 thousand rpm for 5 minutes, and then divided into aliquots and frozen at  $-80^{\circ}\text{C}$  until assay.

**CCL24 (eotaxin-2) and CCL11 (eotaxin-1) immunoassay.** CCL24 and CCL11 were assayed according to the manufacturer's instructions (R&D Systems, Minneapolis, MN) by Quantikine Human CCL24 and CCL11 Immunoassay ELISA kits designed to measure CCL24 and CCL11 levels in cell culture supernatant, serum, and plasma. All samples, standards, and controls were assayed in duplicate, and mean values were calculated as in our previous experience.<sup>23,24</sup> The coefficient of variation of duplicates was always less than 7%. The sensitivity of the CCL24 assay was 2.5 pg/mL, and the range was from 2.5 to 2,500 pg/mL. The sensitivity of the CCL11 assay was 5.0 pg/mL, and the measuring range was from 5.0 to 1,000 pg/mL.

### Statistical Analysis

Statistical analysis was performed using SPSS package version 22.0 (IBM Corp., Armonk, NY). Baseline and posttreatment scores were compared by two-tailed Student *t* test for paired data. The limit for statistical significance was set at  $\alpha = 0.05$  because the *P* value < 0.05 was considered significant. The RR of good outcome (probability to be a responder to montelukast treatment) was established for clinical factors by binominal regression analyses. In our study, we chose to perform a binomial logistic regression because the dependent variable was dichotomous. The outcome was coded as "0" or "1," leading to the most straightforward interpretation. In our series, "1" represents responder to treatment, "0" represents nonresponder to treatment. The results were considered significant for a *P* value < 0.05.

## RESULTS

### Efficacy Outcomes

**Symptoms control.** In Figure 1, we report the values of mean VAS scores for nasal symptoms, eye symptoms, and patient's reported outcomes in all patients before and after treatment. We observed a significant reduction in all mean scores after treatment for each item analyzed ( $P < 0.05$ ). Furthermore, we identified a significant

decrease in mean T4NSS (Fig. 1A) (from  $26.0 \pm 8.0$  to  $12.8 \pm 5.4$ ,  $P < 0.05$ ) in mean T2OSS (Fig. 1B) (from  $8.3 \pm 4.1$  to  $2.7 \pm 1.5$ ,  $P < 0.05$ ) and in mean TSS-PROs (Fig. 1C) (from  $11.8 \pm 4$  to  $4.6 \pm 3$ ,  $P < 0.05$ ). Finally, a significant decline of the mean value of CSS from  $46.0 \pm 15.6$  to  $20.3 \pm 15.2$  ( $P < 0.05$ ) was ascertained. In evaluating the efficacy of montelukast for individual patients, 42 of 78 patients (53.8%) were considered responders, whereas 36 of 78 patients (46.2%) did not have good control of symptoms and were considered nonresponders. We did not find a significant difference between responders and nonresponders in terms of median age and gender ratio.

**Eosinophilic infiltration of nasal mucosa.** A significant difference between mean Ec-hpf before and after treatment was observed in all patients ( $54.1 \pm 8.1$  vs.  $42.3 \pm 7.1$ ,  $P < 0.05$ ), especially in responders ( $65.9 \pm 10.2$  vs.  $33.5 \pm 8.4$ ,  $P < 0.05$ ), as shown in Figure 2. No differences were found in nonresponders before and after treatment ( $43.9 \pm 8.1$  vs.  $51.7 \pm 9.9$ ).

**Eosinophilic biomarkers in nasal fluid pre- and post-treatment.** Although eotaxin-1 concentrations in nasal lavage were unchanged after montelukast treatment ( $22.8 \pm 6.1$  pg/mL vs.  $23.4 \pm 6.9$  pg/mL), a significant reduction ( $29.1 + 8.5$  pg/mL vs.  $19.9 \pm 8.1$  pg/mL,  $P < 0.05$ ) was observed in responders, whereas no considerable changes were observed in nonresponders ( $21.1 \pm 7.5$  pg/mL vs.  $29.6 \pm 8.1$  pg/mL) (Fig. 3). Similar findings account for eotaxin-2 concentration, a significant decrease in responders ( $145.6 + 19.5$  pg/mL vs.  $115.4 + 18.1$  pg/mL,  $P < 0.05$ ) but no difference in nonresponders ( $126.6 + 20.5$  pg/mL vs.  $145.8 + 21.5$  pg/mL) or in the overall population ( $136.6 \pm 23.2$  pg/mL vs.  $134.6 \pm 22.4$  pg/mL) (Fig. 4).

### Phenotyping of NARES Patients Based on Treatment Response

Distribution of clinical conditions commonly associated with nonallergic eosinophilic rhinitis is reported in Table I. We evaluated the RR of good response to

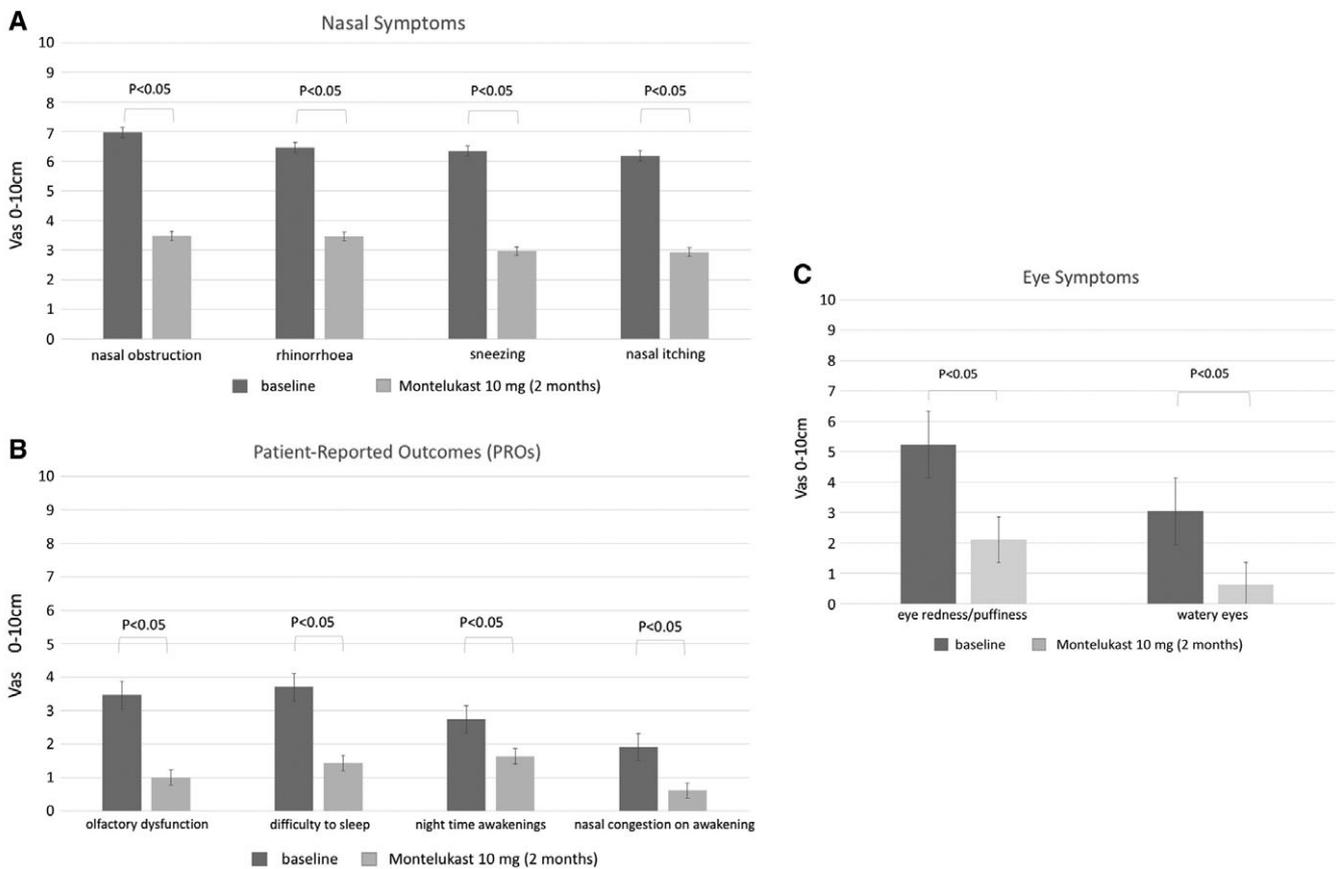


Fig. 1. Severity of nasal-ocular symptoms and PROs before and after montelukast treatment in nonallergic rhinitis eosinophilic syndrome patients: (A) nasal symptoms, (B) Patient-Reported Outcomes (PROs), and (C) Eye Symptoms.

treatment in the presence of asthma, blood hypereosinophilia, and family history of eosinophilic sinonasal inflammation using binominal logistic regression analyses. Patients with asthma showed an increased probability of a good outcome (RR: 1.59 [1.05–2.41],  $P < 0.05$ ), whereas a nonsignificant risk was observed for both blood hypereosinophilia (RR: 0.90 [0.48–1.33]) and family history of rhinitis (RR: 0.80 [0.51–1.26]) (Fig. 5).

## DISCUSSION

Several studies<sup>25,26</sup> have demonstrated that leukotriene receptor antagonists may inhibit bronchoconstriction and attenuate eosinophilia in the lower airway mucosa of asthmatic patients. Moreover, over the years montelukast has become the object of controlled clinical trials evaluating its efficacy and safety in the treatment of AR with or without concomitant asthma. Consequently, it has been

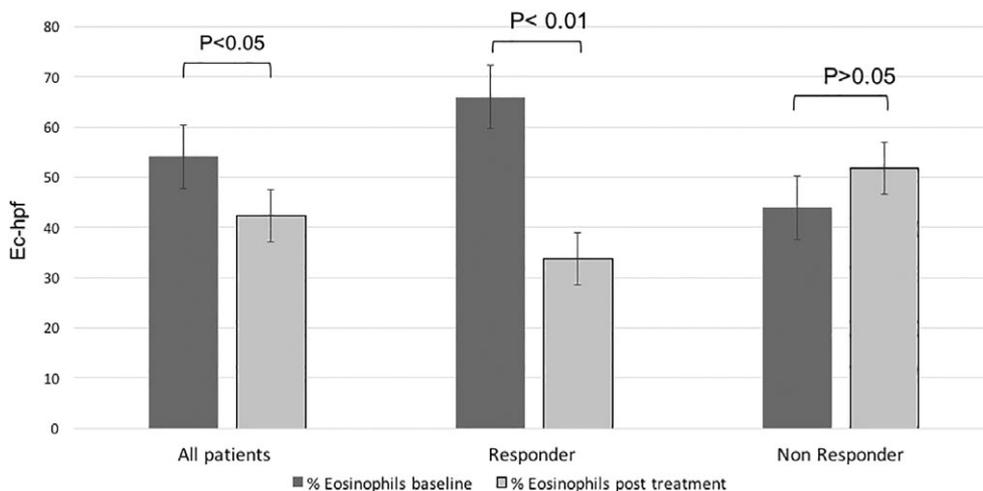


Fig. 2. Nasal mucosa eosinophil infiltration (Ec-hpf) before and after montelukast treatment in nonallergic rhinitis eosinophilic syndrome patients: all patients, responders, and nonresponders. Ec-hpf = eosinophilic count per high power field.

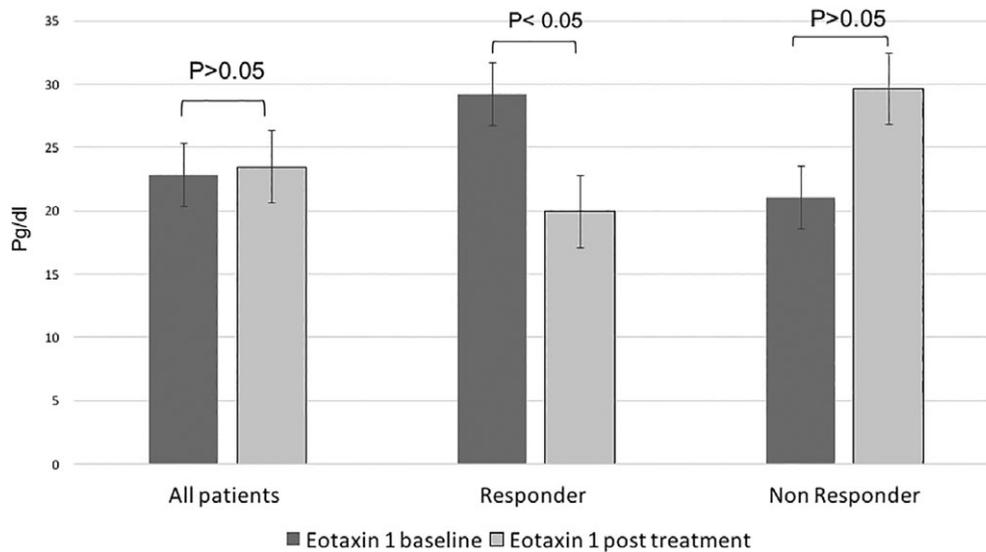


Fig. 3. Eotaxin-1 (A) and eotaxin-2 (B) levels (pg/dl) before and after montelukast treatment in nonallergic rhinitis eosinophilic syndrome patients: all patients, responders, and nonresponders.

approved by the U.S. Food and Drug Administration for the treatment of both seasonal and perennial AR.<sup>27</sup> It is well known that cysLTs are synthesized via 5-lipoxygenase metabolism of arachidonic acid by mast cells and basophils during the AR early phase in response to antigens, and by eosinophils and macrophages during the AR late phase. Studies on murine experimental AR model have demonstrated a significant decrease in the number of eosinophils in nasal mucosa after treatment with montelukast not only by a reduction in tissue recruitment but also as a result of limited eosinophilopoiesis that is IL-5 dependent, with effects on several stages of cellular differentiation and maturation.<sup>28</sup>

In 2010, Mullol et al.<sup>29</sup> investigated the anti-inflammatory effects of montelukast in an in vitro model of upper-airway eosinophil inflammation and demonstrated

the reduction of proinflammatory cytokines from nasal mucosa and polyp epithelial cells, as well as lower eosinophil survival primed by epithelial cell secretions. Montelukast had a strong inhibitory effect on Fetal Bovine Serum (FBS)-induced GM-CSF, IL-6, and IL-8 secretion but not on ICAM-1. These anti-inflammatory effects on epithelial cell cytokine secretion and on eosinophil survival suggest that montelukast may contribute to the reduction of eosinophilic inflammation in upper-airway inflammatory diseases such as rhinitis and nasal polyposis.<sup>30</sup>

In contrast to the extensive amount of information found in the literature on AR, there is limited data on the treatment of NAR,<sup>8</sup> for which the intense symptoms can negatively affect the patient's quality of life. Our preliminary results suggest for the first time that some NARES patients may significantly benefit from treatment with

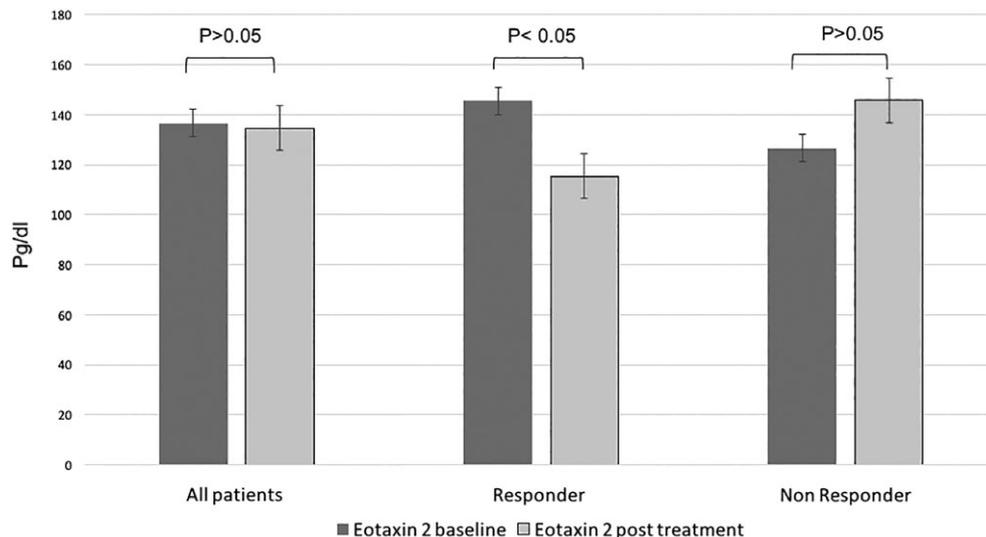


Fig. 4. Eotaxin-2 levels (mean values in pg/dl) in nasal lavage before and after montelukast treatment in nonallergic rhinitis eosinophilic syndrome patients: all patients, responders, and nonresponders.

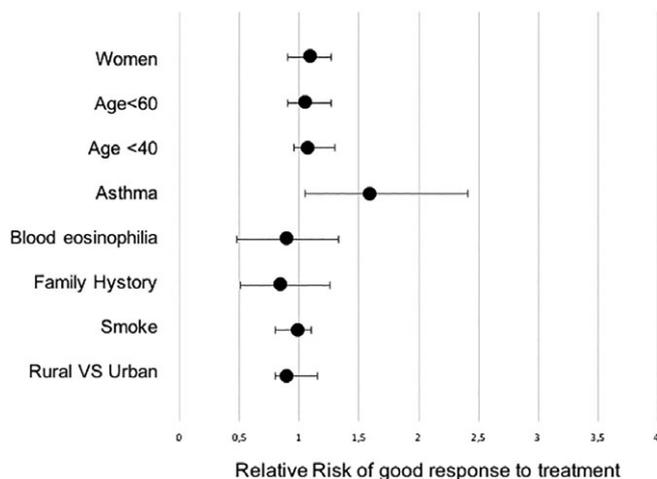


Fig. 5. Forest plot showing RR of good response to montelukast treatment based on clinical characteristics of nonallergic rhinitis eosinophilic syndrome patients. Clinical factors analyzed and RR with 95% confidence interval are shown. RR = relative risk.

montelukast 10 mg once a day. Considering all the patients enrolled, we observed a significant improvement of scores of nasal symptoms, eye symptoms, and PROs, with a significant reduction in the percentage of eosinophilic infiltration in the sinonasal mucosa following treatment. Analyzing the efficacy of montelukast in single patients, we observed a decrease of at least 50% of the CSS in approximately half of the treated patients, who were considered responders. In responder but not in nonresponder NARES patients, we also observed a significant reduction of eosinophil infiltration into the nasal mucosa. In this series, montelukast showed a good safety profile with the absence of any severe side effects, as also demonstrated in previous studies.<sup>25,26</sup> We confirmed good patient compliance and good tolerance to montelukast for 8 weeks in most of the patients and only minor side effects in two patients (headache and gastrointestinal symptoms).

Many studies<sup>23,24,31</sup> have shown that the measurement of chemokine levels in nasal secretions may be useful in evaluating the degree of chronic nasal inflammation and consequently the response to therapy. Peric et al.<sup>32</sup> observed that nasal secretion levels of certain chemokines (MCP-1, MCP-3, and RANTES) correlated with nasal symptoms and degree of eosinophilia in patients with NARES and perennial AR. Similarly, we have previously demonstrated an important correlation with the levels of eotaxins and degree of eosinophilia and clinical symptoms in eosinophilic patients.<sup>23,24</sup> In the present series, we have observed that the levels of eosinophilic biomarkers were modified according to outcomes. After treatment, we observed significantly lower levels of eotaxin-1 and eotaxin-2 in responders, whereas an increasing trend was observed in nonresponders, although the difference did not reach statistical significance. These results were congruent with nasal mucosa eosinophil infiltration data. The evaluation of these objective parameters partially excluded a placebo effect in our series because we observed a significant reduction of eosinophilic biomarkers only in responders. The placebo effect could

potentially have some impact on the improvement of subjective outcomes (PROs, symptoms, VAS), whereas it is difficult to explain its effect on objective outcomes (eosinophilic biomarkers). Recent reviews on placebo effects in clinical trials suggest that objective changes following placebo treatments may not exist, or at least have been considerably overestimated. Meissner et al.<sup>33</sup> concluded in a review of clinical trials that placebo interventions can improve physical disease processes of peripheral organs more easily and effectively than biochemical processes.

Analyzing the response to therapy based on associated clinical factors, it was possible to identify different subgroups of patients who were presumed to belong to different phenotypes. Patients with asthma were the best responders to monotherapy with montelukast. Logistic regression analyses showed that they had an increased probability of good response to treatment with an RR of 1.59 ( $P < 0.05$ ). These results are in concordance with previous studies in which montelukast treatment was reported to be of greater benefit in patients with asthma associated with rhinitis or rhinosinusitis.<sup>34,35</sup> Philip et al.<sup>36</sup> observed that patients with AR benefited the most from montelukast treatment (based on global evaluations) and achieved the greatest improvement for asthmatic patients. Yazici et al.<sup>37</sup> studied the effects of montelukast in patients affected by nasal polyposis with a history of asthma. They observed an improvement of Rhinosinusitis Disability Index scores with montelukast in association with intranasal corticosteroids within this patient population. The findings of our study seem to follow a similar direction, suggesting that antileukotrienes may be useful to treat other multimorbidities such as NARES + asthma.

## CONCLUSION

Our data suggest that, for the first time it has been demonstrated that montelukast may be an effective treatment option in patients affected by NARES to control their nasal and ocular symptoms, as well as other disease PROs such as olfactory dysfunction and nighttime disturbances. We also observed a significant reduction of nasal mucosa eosinophil infiltration and biomarkers (eotaxin) in responders compared to nonresponder patients. Finally, according to the emerging need for proper phenotyping of chronic rhinitis patients, going towards a precision medicine approach,<sup>38</sup> we identified different subgroups of NARES patients based on the response to antileukotriene treatment. Interestingly, the presence of concomitant asthma may be considered a predictive factor for montelukast efficacy. This is the first study in the literature demonstrating any efficacy of antileukotrienes on NARES patients. Unfortunately, this is an open-label nonplacebo controlled trial and that is the main limitation of our study. Based on the present study, future randomized placebo-controlled trials are nonetheless needed to confirm the efficacy and tolerability of antileukotrienes in eosinophilic NAR patients, especially in those with concomitant asthma, and potentially in comparison with standard treatments such as intranasal corticosteroids.

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Jacopo Galli: involved in drafting the manuscript or revising it critically for important intellectual content; gave final approval of the version to be published.

Silvia Baroni: substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; gave final approval of this manuscript version to be published.

Walter Di Nardo: involved in the drafting the manuscript or revising it critically for important intellectual content; gave final approval of this manuscript version to be published.

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Gaetano Paludetti: involved in drafting the manuscript or revising it critically for important intellectual content; gave final approval of this manuscript version to be published.

Joaquim Mullol: substantial contributions to conception and design, acquisition of data, analysis and interpretation of data; gave final approval of this manuscript version to be published.

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