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Does NSAID exacerbated respiratory disease (N-ERD) accompanying severe asthma affect biological treatment response? Efficacy of omalizumab and mepolizumab in N-ERD

Fatma Merve Tepetam, MD[a]*, Şeyma Özden, MD[a], Fatma Kübra Kılıç, MD[b], Cihan Örçen, MD[c] and Tuğçe Yakut, MD[d]

ABSTRACT

Introduction: Non-steroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (N-ERD) accompanies severe asthma in about 15% of the patients and may adversely affect the prognosis. Omalizumab and mepolizumab are biologics used in patients with severe asthma. The objective of this study is to assess the respiratory improvements, after these biologics in severe asthmatic patients stratifed by the presence of concomitant Non-erosive reflux disease (N-ERD) and the effect of omalizumab and mepolizumab in severe asthmatics with N-ERD.

Material & method: The population of this three-center, retrospective, cross-sectional, observational study comprised patients using omalizumab or mepolizumab for severe asthma. Patients administered these biologics for severe asthma were comparatively analyzed for the presence of N-ERD; asthma control test (ACT) scores, number of attacks, and the changes in forced expiratory volume in 1 s (FEV1) were assessed. Subsequently, patients who were found to have N-ERD were analyzed using visual analog scale (VAS) in terms of the changes in their nasal parameters (ie, nasal obstruction, facial pain, anterior-posterior rhinitis, and hyposmia), according to whether they use omalizumab or mepolizumab.

Results: The use of biologics resulted in a significant improvement in ACT and FEV1 and reduction in attacks in 28 severe asthmatics with N-ERD and 125 without N-ERD. Although both biologics resulted in a significant improvement in the respiratory parameters, omalizumab treatment resulted in a significant improvement in nasal parameters except hyposmia, mepolizumab treatment resulted in a significant improvement only in posterior rhinitis, and nasal obstruction among the nasal parameters.

[a]University of Health Sciences, Süreyyapasa Chest Diseases and Thoracic Surgery Training and Research Hospital, Department of Immunology and Allergy, Istanbul, Turkey
*Corresponding author. University of Health Sciences Sureyyapasa Chest Diseases and Thoracic Surgery Training and Research Hospital, Department of Immunology and Allergy, Basibuyuk Mahallesi, Maltepe, 34854, Istanbul, Turkey. E-mail: fatmamervealan@hotmail.com
MD Fatma Merve Tepetam: University of Health Sciences, Süreyyapasa Chest Diseases and Thoracic Surgery Training and Research Hospital, Department of Immunology and Allergy, Istanbul, Turkey. E-mail: fatmamervealan@hotmail.com **MD Şeyma Özden:** University of Health Sciences, Süreyyapasa Chest Diseases and Thoracic Surgery Training and Research Hospital, Department of Immunology and Allergy, Istanbul, Turkey. E-mail: seymaglhn@hotmail.com **MD Fatma Kübra Kılıç:** University of Health Sciences, Süreyyapasa Chest Diseases and Thoracic Surgery Training and Research Hospital, Department of Pulmonology, Istanbul, Turkey. E-mail: fkubrademir@gmail.com **MD Cihan Örcen:** University of Health Sciences, Derince Training and Research Hospital, Kocaeli, Turkey. E-mail: c_orcen@hotmail.com **MD Tuğçe Yakut:** University of Health Sciences, Diyarbakır Gazi Yasargil Training and Research Hospital, Diyarbakır, Turkey. E-mail: tugceyakut@gmail.com

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Conclusion: This study is the first to address both omalizumab and mepolizumab treatments in severe asthmatics with N-ERD. The improvement in nasal parameters was more pronounced in patients who were administered omalizumab. Large-scale randomized controlled studies are needed to corroborate the findings of this study.

Keywords: Anti-inflammatory agents, Non-steroidal (NSAID), Asthma, Aspirin-induced, Omalizumab, Visual analog scale (VAS)

INTRODUCTION

In 2014, risk factors associated with asthma attacks were identified introducing the concept of remission in asthma.[1,2] Treatment goals in asthma include not only symptom control but also prevention of remodeling by reducing the risk of future attacks, airway inflammation, and accelerated lung function declines.[3] Factors such as chronic rhinosinusitis (CRS), upper airway diseases such as nasal polyps, and high eosinophil levels confirmed nonsteroidal anti-inflammatory drug (NSAID) allergies are among the risk factors that activate asthma. Despite treating all these comorbidities, optimizing the risk factors, and administering high-dose inhaled corticosteroid (ICS) and long-acting beta-agonist (LABA) therapies, uncontrolled asthma persists in some patients. These patients, who constitute approximately 3–10% of asthmatic patients, are diagnosed with severe asthma.[1,4] The main treatment strategy in severe asthma patients is an individualized treatment approach based on their phenotypes. The presence of NSAID-exacerbated respiratory disease (N-ERD) is clinically compatible with Type 2 inflammation.[1]

N-ERD is a chronic eosinophilic inflammatory airway disease that occurs in patients with asthma and/or chronic rhinosinusitis with nasal polyps (CRSwNP). It is characterized by upper and/or lower airway symptoms. The N-ERD symptoms induced by the use of NSAIDs, including aspirin, vary from nasal discharge to wheezing, dyspnea, severe laryngospasm, and bronchospasm.[5]

In the pathogenesis of N-ERD, mast cells, basophils and eosinophils triggered by an increase in proinflammatory mediators such as cysteinyl leukotrienes (CysLTs) and prostaglandin D2 (PGD2) and a decrease in anti-inflammatory metabolites such as prostaglandin E2 (PGE2) and lipoxin A4, due to cyclooxygenase-1 (COX-1) inhibition induced by NSAIDs play a role.[6,7]

It has been shown in patients with N-ERD that free immunoglobulin E (IgE) in the circulation tends to increase independently of atopy; on the other hand the increased local IgE in nasal polyps plays a role in mast cell activation.[8,9]

The prevalences of N-ERD in adult asthmatic and severe asthma patients have been reported as 8% and 15%, respectively.[10,11] Asthma patients with N-ERD are more likely to have lower lung functions and increased need for urgent referral. It may be useful to avoid NSAIDs that inhibit COX-1 in these patients. Rather, they should be administered the NSAIDs, the safety of which are verified by testing them with alternative COX-2 inhibitors, as well as leukotriene receptor antagonist therapy (LTRA). There is evidence that aspirin therapy after desensitization (ATAD) improves both nasal and respiratory symptoms in the absence of contraindications.[1,12] However, some patients may face respiratory, skin, and gastrointestinal problems during desensitization while others face such problems during ATAD. Biologics targeting Type 2 inflammation may be preferred if ATAD cannot be tolerated or if asthma control cannot be achieved despite ATAD.

It has been demonstrated that omalizumab (anti-IgE) improved nasal symptoms in patients with nasal polyps including N-ERD in a randomized controlled study, and both nasal and asthma symptoms in patients with N-ERD accompanied by severe asthma in an open-label study.[7,13,14]

Omalizumab reduces the free IgE in the circulation and inhibits the interaction of the high-affinity receptors for the Fc region (FcεRI) with IgE, resulting in reduced mast cell activation and thus reducing the synthesis of the cysteinyl leukotrienes (CysLTs).[15]

There are studies showing that patients with severe asthma accompanied by a nasal polyp with a more pronounced eosinophilia respond better to mepolizumab therapy, an anti-interleukin-5 (anti-IL-5) therapy.[1,16,17] The increase in interleukin-5 receptor alpha (IL-5Rα) expression in nasal polyp cells in patients with N-ERD suggests that IL-5 antagonists may also be beneficial in these patients.[18]

In this context, the objective of this study is to assess the clinical improvements in respiratory parameters in severely asthmatic patients stratifed by the presence of concomitant N-ERD after they were administered biologic agents, ie, omalizumab and mepolizumab, for at least 16 weeks. In addition, we aimed to investigate the clinical improvements in nasal and respiratory parameters after omalizumab and mepolizumab treatment in patients with N-ERD.

MATERIALS AND METHODS

Study design

This study was designed as a three-center, retrospective, cross-sectional, observational study. The study population consisted of severely asthmatic patients stratifed by the presence of concomitant N-ERD who received omalizumab and mepolizumab treatment for at least 16 weeks between 2012 and 2022. The study protocol was approved by the local ethics committee of the University of Health Sciences, Süreyyapaşa Chest Diseases, and the Thoracic Surgery Training and Research Hospital (Approval Number: 318). The study was conducted in accordance with the standards of good clinical practice and the ethical principles set forth in the Declaration of Helsinki. Patients with comorbid diseases such as nasal polyp without N-ERD, malignancies, rheumatological diseases, bronchiectasis, vasculitis, sarcoidosis, bronchopulmonary aspergillosis, or interstitial lung disease and pregnancy were excluded from the study. The data were collected from electronic or paper hospital medical records.

Study procedure

The patients were diagnosed with asthma according to the Global Initiative for Asthma (GINA) guidelines. Inhaler therapy compliance of patients with uncontrolled asthma that persisted despite high-dose ICS and LABA therapies was reviewed. They were recommended to avoid the risk factors that may trigger asthma, and treated for comorbidities to optimize their condition in the best way possible before they were treated for asthma. Accordingly, nasal steroid ± antihistaminic therapy was administered to patients with accompanying rhinosinusitis. Patients were diagnosed with severe asthma if uncontrolled asthma persisted during the 3–6 month follow-up period despite the addition of non-biological treatment options such as montelukast and/or long-acting muscarinic antagonist (LAMA). In the event that there were signs of Type 2 inflammation, specific treatment approaches, eg, ATAD in the case of N-ERD patients, were added to the treatment regimen, and then omalizumab or mepolizumab treatment was started according to the GINA guidelines, taking into account the availability of the biologics and dominant phenotypic features of the patients (Fig. 1: flow chart).

Patients over 18 years of age with a total IgE level of 30–1500 IU/mL, who had perennial allergen sensitivity as determined by specific IgE (ImmunoCap; Pharmacia Diagnostics AB, Uppsala, Sweden) or by skin prick test, were administered omalizumab therapy (Xolair, Novartis-Switzerland) subcutaneously biweekly/monthly at a dose adjusted according to their body weight and total serum IgE levels. On the other hand, patients with severe asthma who had a peripheral blood eosinophil level ≥150 cells/μL during systemic steroid therapy or at admission or ≥300 cells/μL in the previous year were administered mepolizumab therapy (Nucala, Glaxosmithkline-UK). Patients were treated with either biologics for at least 16 weeks and then analyzed in terms of concomitant N-ERD.

N-ERD diagnosis and management

Asthma patients with concomitant CRSwNP and who exhibited upper and/or lower airway symptoms ranging from mild rhinorrhea, wheezing, and shortness of breath to severe laryngospasm and bronchospasm after receiving NSAIDs from at least

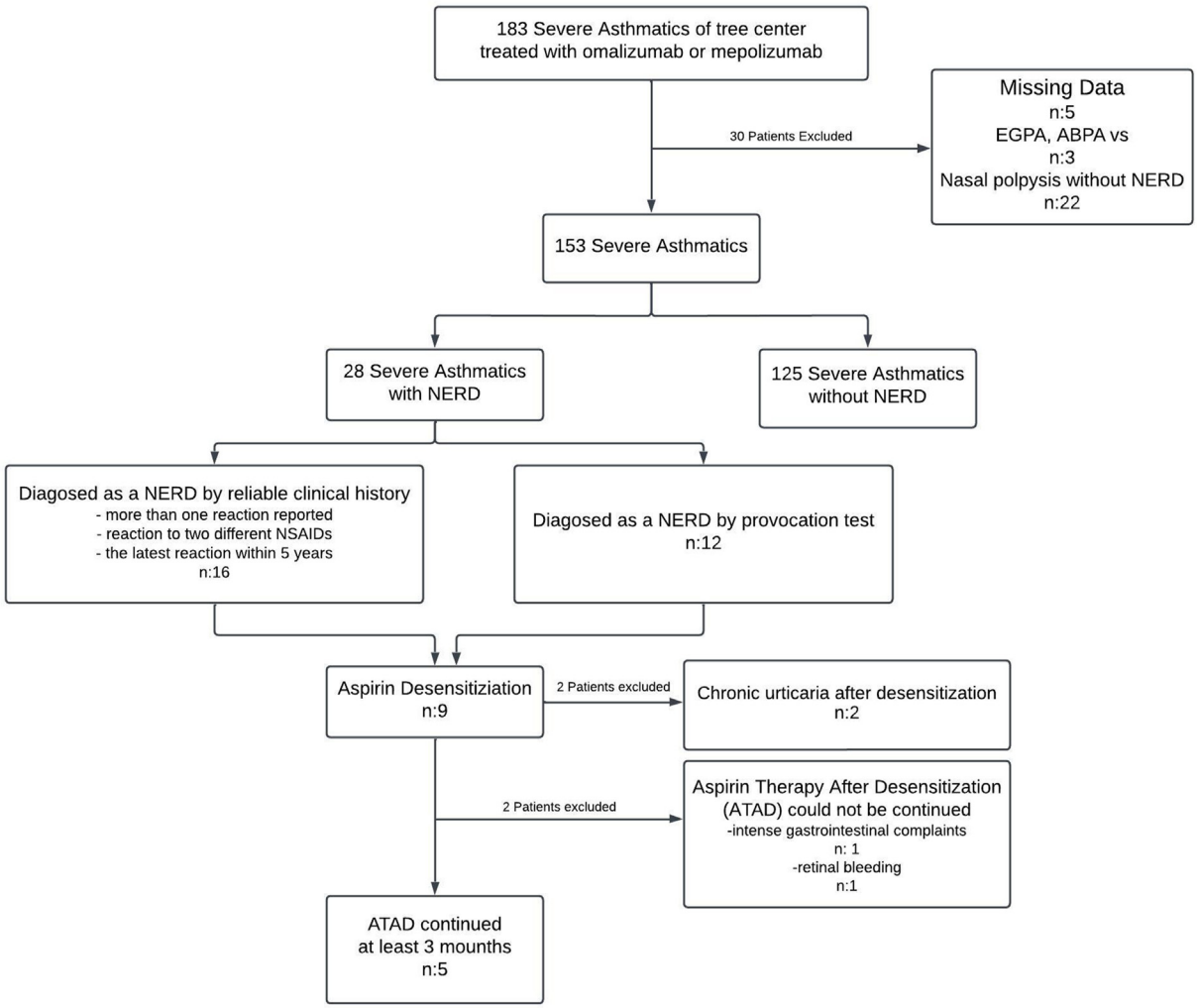

Fig. 1 Flow chart of the study design. The study population consisted of severely asthmatic patients stratifed by the presence of concomitant non-steroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (N-ERD) who received omalizumab or mepolizumab treatment for at least 16 weeks. Diagnostic process of patients with NERD and aspirin desensitization treatment status before starting biologics were recorded.

2 different chemical groups were clinically diagnosed with N-ERD. Patients with unconvincing respiratory symptoms were subjected to the forced expiratory volume in 1 s (FEV1) test upon patients' consent. Consequently, patients with a FEV1% of more than 70% were administered the aspirin preovulation protocol. Accordingly, they were administered a placebo on the first day, and an initial dose of 10 mg of aspirin on the second day, which was gradually increased every 90 min to a maximum dose of 500 mg. Patients' blood pressure and FEV1 values as well as their skin, ocular, nasal, and bronchial reactions were monitored during the procedure. The diagnosis of N-ERD was confirmed if upper and/or lower respiratory tract symptoms developed and/or a 20% or more decrease was observed in FEV1 ratio. First, a provocation test was performed with reliable alternative partial selective and/or selective COX-2 inhibitors. To this end, meloxicam, nimesulide, or celecoxib was used depending on availability. Ear, nose, and throat department was consulted in terms of CRSwNP. Medical therapy, ie, oral corticosteroids, or surgical polypectomy was performed based on the recommendation of the ear, nose, and throat department.[5] Immediately afterwards, four-week ATAD protocol was applied to patients who had no contraindications (FEV1 >60% or 1.5 lt) and gave consent for the treatment. Accordingly, they were given an initial dose of 25 mg of aspirin, which was gradually increased every 90 min to a maximum dose of 650 mg. Subsequently, 650 mg aspirin was given every 12 h for a month, and the dosage was

gradually reduced according to the asthma control achieved and the desired effect, provided that the minimum dose was not reduced below 300 mg/day. The decision to continue ATAD protocol was made taking into account the efficacy and side-effects of the treatment protocol as well as the patient's preference.[5,19] Changes in nasal and respiratory parameters after ATAD protocol were evaluated at least for 3 months. Patients in whom asthma control could not be achieved during the follow-up period were started on biologic agents.

Comparative analysis of severely asthmatics according by the presence of N-ERD

Severely asthmatic patients with and without N-ERD were compared in terms of baseline characteristics, including age of asthma onset, duration of disease, smoking history, presence of atopy, body mass index (BMI) values, asthma control test (ACT) scores, number of asthma attacks that required at least 3 days of systemic corticosteroid therapy, resulted in emergency admission or hospitalization, FEV1 and forced expiratory flow between 25 and 75% of vital capacity (FEF25-75) values in ml and percentage (%), total periferic eosinophil counts (TEC), total IgE levels and duration of treatment with biologic agents.

Characteristic features of severe asthmatics with N-ERD and evaluation of the effect of aspirin therapy after desensitization (ATAD) in this population

In patients with N-ERD, the type of diagnosis, ie, whether it was clinical diagnosis or diagnosis based on provocation test results, the number of nasal polypectomy procedures performed, ATAD history, the status of receiving aspirin treatment, and the changes in nasal and respiratory parameters after aspirin treatment before starting biologic agents, were analyzed.

Assessment of the efficacies of biologic agents in severe asthmatics with and without N-ERD

Respiratory parameters

The efficacy of the biologic agents was assessed using the ACT, numbers of asthma attacks, and FEV1 (mL) values.

Assessment of the efficacies of omalizumab and mepolizumab in severe asthmatics with N-ERD

Nasal parameters

In the visual analog scale (VAS), rhinosinusitis is assessed in terms of 5 parameters, ie, nasal obstruction, facial pain, anterior and posterior rhinitis, and hyposmia, which are assigned a score between 0 and 10 (0: no discomfort, 10: most discomfort).[14,20] The changes induced by the biologic agent treatments in nasal parameters were evaluated by comparatively analyzing patients' pre-treatment and post-treatment VAS scores of patients with N-ERD that used omalizumab or mepolizumab treatment.

Respiratory clinic parameters

The improvement in ACT scores and the decrease in asthma attacks were evaluated separately in patients with N-ERD that were on omalizumab or mepolizumab treatment. The rate of patients in whom systemic steroid and aspirin treatments were discontinued after omalizumab or mepolizumab treatment were noted.

Statistical analysis

Statistical analyses were performed using the SPSS 21.0 (Statistical Product and Service Solutions for Windows, Version 21.0, IBM Corp., Armonk, NY, U.S., 2012) software package. The independent samples *t*-test or the Mann-Whitney *U* test was used to analyze demographic and baseline characteristics in the case of numerical variables determined to conform and not to conform to the normal distribution, respectively. Parametric and non-parametric variables were expressed as mean and standard deviation values and as median and minimum-maximum (min-max) values, respectively. Pearson's chi-squared test was used in the analysis of categorical variables such as number or percentage of patients.

The paired samples *t*-test or the Wilcoxon signed-rank test was used to analyze the changes in clinical physiological parameters and peripheral blood eosinophil levels of asthma patients with and without N-ERD in terms of improvement in nasal and respiratory parameters after treatment with omalizumab and mepolizumab, in the case of numerical variables determined to conform and

	Severe Asthmatics with NERD n:28	Severe Asthmatics without NERD n:125	P value
Age (years old),mean ± SD	49.74 ± 12.46	46.57 ± 11.16	0.218[a]
Sex,male, n (%)	10 (34.50)	18 (14.50)	**0.025**[b]
Asthma Onset Age, median (25–75% percentile)	33.50 (21.00–37.00)	33.00 (20.00–43.50)	0.299[c]
Asthma Duration Time, (months) median (25–75% percentile)	15.00 (9.50–22.75)	15.00 (7.50–25.00)	0.707[c]
Treatment time (months) median (25–75%. percentile)	15.50 (6.00–40.00)	29.00 (14.00–57.50)	0.078[c]
Presence of Atopy, n (%)	18 (64.3)	103 (82.4)	0.061[b]
BMI (kg/m^2), median (25–75% percentile)	27.76 (24.28–31.14)	29.38 (25.04–32.87)	0.370[c]
Smoking History, n (%) Current Smoker Exsmoker Nonsmoker	 4 (14.3) 9 (32.1) 15 (53.6)	 6 (4.8) 39 (31.2) 80 (64.0)	 0.169[b]
Comorbidities, n (%) A.rhinitis Gastro- oesophageal reflux disease	 25 (89.3) 11 (39.3)	 95 (76.0) 31 (24.8)	 0.197[b] 0.187[b]
ACT, mean ± SD	11.61 ± 3.563	11.11 ± 3.279	0.473[a]
Asthma Attack, median (25–75% percentile)	4.50 (4.00–6.00)	5.50 (4.00–9.00)	0.319[c]
TEC (cells/µl),median (25–75% percentile)	485.00 (225.00–1055.00)	300.00 (162.50–752.50)	0.088[c]
FEV1 (mL), mean ± SD	2074.74 ± 823.36	1937.06 ± 697.744	0.213[a]
FEV1%, mean ± SD	71.13 ± 21.33	71.30 ± 21.19	0.972[a]
FEF25-75 (mL) mean ± SD	1790.00 ± 1070.37	1789.42 ± 957.67	0.998[a]
FEF25-75 (%) mean ± SD	49.33 ± 29.76	51.28 ± 23.17	0.960[a]
Total IgE (IU/mL), median (25–75% percentile)	246.00 (131.75–711.75)	211.00 (87.50–477.50)	0.183[c]
Omalizumab/mepolizumab n (%)	19/9 (67.9/32.1)	92/33 (73.6/26.4)	0.703[b]

Table 1. Baseline demographic characteristics in severe asthmatics with N-ERD and without N-ERD. *Abbreviations: ACT: Asthma Control Test, BMI: Body mass index, TEC: Total Peripheral Eosinophil Account. [a]Independent Sample T Test. [b]Chi Square Test. [c]Mann Whitney U test.*

not to conform to the normal distribution, respectively. Two-way repeated measures analysis of variance (ANOVA) was used to calculate the probability (p) statistics for comparisons between cohorts. Accordingly, two-sided p values of <0.05 were deemed to indicate statistical significance.

RESULTS

The population of this three-center, retrospective, cross-sectional, observational study comprised 183 patients with severe asthma using omalizumab or mepolizumab. Of these patients, 153 patients

who met the study inclusion criteria were included in the study sample. The mean age of the study group, of whom 125 (81%) were female, was 49.16 ± 12.264 years. There were a total of 28 (18.3%) patients with N-ERD. Analysis of the patients with N-ERD in terms of the centers where this study was conducted revealed that 12 of the 75 in Istanbul, 9 of the 58 in Kocaeli, and 7 of the 20 severe asthmatics in Diyarbakır had N-ERD.

Comparison of baseline characteristics of severe asthmatics according to whether they had N-ERD

The analysis of the baseline characteristics of the patients revealed that the patients with and without N-ERD did not significantly differ in terms of demographic characteristics including age, age of asthma onset, disease duration, BMI value, smoking history, and comorbidities, clinical characteristics including ACT scores and frequency of attacks, and biophysiological characteristics including FEV1 and FEF25-75 ratios. There were significantly more males in the group of patients with N-ERD than in the group of patients without N-ERD (34.5% vs 14.5%, p: 0.025). In addition, TEC and total IgE levels were higher, whereas the atopy rate was lower, albeit not statistically significantly, in those with N-ERD compared to those without N-ERD. Most of the patients, 67.9% in the group of patients with N-ERD and 73.6% in the group of patients without N-ERD, were using omalizumab. There was no significant difference between the groups in terms of treatment duration (Table 1).

Type of N-ERD diagnosis, whether they received ATAD and evaluation of the period they received ATAD in patients with N-ERD

Of the 28 patients diagnosed with N-ERD, 16 (57.14%) were diagnosed based on their clinical history and 12 (42.85%) were diagnosed based on aspirin provocation. There were 14 patients with a history of surgical polypectomy at the time of admission. The median number of polypectomy these patients had was 3 (min. 1, max. 10). Six patients stated that they had undergone medical polypectomy with systemic steroid therapy at least once for at least 2 weeks. Sixteen patients were recommended polypectomy since they had active polyps at admission based on the recommendation of the ear, nose, and throat department. Of these patients, 10 and 6 patients were recommended surgical and medical polypectomy, respectively. Aspirin desensitization was administered to 9 patients who had adequate nasal passage opening and no contraindications upon their consent. ATAD could not be started in 2 patients who developed chronic urticaria after desensitization. ATAD could not be continued in 1 patient due to intense gastrointestinal complaints, and in another patient due to retinal bleeding during the period of ATAD. Pre- and post-treatment nasal and respiratory scores of 5 patients who continued ATAD therapy for at least 3 months were recorded (Table 2). Given that asthma control could not be achieved in these patients despite ATAD, omalizumab treatment was started in 3 patients and mepolizumab treatment was started in 2 patients.

Assessment of the efficacies of biologics in severe asthmatics with and without N-ERD

Significant improvements in ACT scores were observed in both the group of patients with N-ERD and group of patients without N-ERD. There was no significant difference between the groups in terms of the level of improvement in ACT scores (p: 0.966) (Fig. 2). There was a significant decrease in median of asthma attacks in severe asthmatics with and without NERD respectively (4.5–0, $p < 0.001$; 5.5 to 0, $p < 0.001$). There was no significant difference between the groups in terms of the decrease in number of asthma attacks (p: 0.521) The improvement in FEV1 was significant in the group of patients with and without N-ERD (Fig. 3). However, there was also no significant difference between the groups in terms of the improvement in FEV1 (p: 0.254).

Assessment of the efficacies of omalizumab and mepolizumab treatments in severe asthmatics with N-ERD

Of the severe asthmatics with N-ERD, 19 used omalizumab treatment and 9 used mepolizumab treatment. Of the 9 patients who used mepolizumab treatment, 2 had switched from omalizumab treatment to mepolizumab treatment. The respiratory parameters improved significantly in all patients treated with a biologic agent, regardless of whether it was omalizumab or mepolizumab. On the other hand, the improvement in nasal parameters was more pronounced in the group of patients who received omalizumab treatment.

Diagnosis of NERD, n (%)		
Reliable history of reaction to two different NSAIDs		16 (57.14)
Oral provocation with aspirin		12 (42.85)
A history of previous of nasal polypectomy, n (%)		
Medical		6 (21.42%)
Surgery		14 (50%)
Number of poly-pectomy, median (min-max)		3 (1–10)
Aspirin desensitization, n (%)		9 (32.14)
Aspirin therapy discontinued (adverse effects)		4 (14.28)
Duration of aspirin therapy until biological initiation (months)		3.80 ± 0.84
Aspirin therapy after desensitization (ATAD) n (%) 5 (17.85)	**Baseline**	**After aspirin treatment**
Nasal Parameters, mean ± SD		
Rhinosinusitis (VAS), range 0–10		
Anterior rhinitis	9.40 ± 1.34	7.20 ± 4.20
Posterior rhinitis	8.80 ± 1.30	7.60 ± 2.51
Nasal obstruction	8.60 ± 1.67	7.0 0 ± 4.12
Hyposmia	8.80 ± 1.78	6.80 ± 3.97
Facial pain	6.80 ± 1.92	3.60 ± 1.67
Asthma Control Test, mean ± SD	5.60 ± 0.90	7.40 ± 1.52

Table 2. Characteristic features of severe asthmatics with N-ERD and evaluation of the effect of aspirin therapy after desensitization (ATAD) in these population.

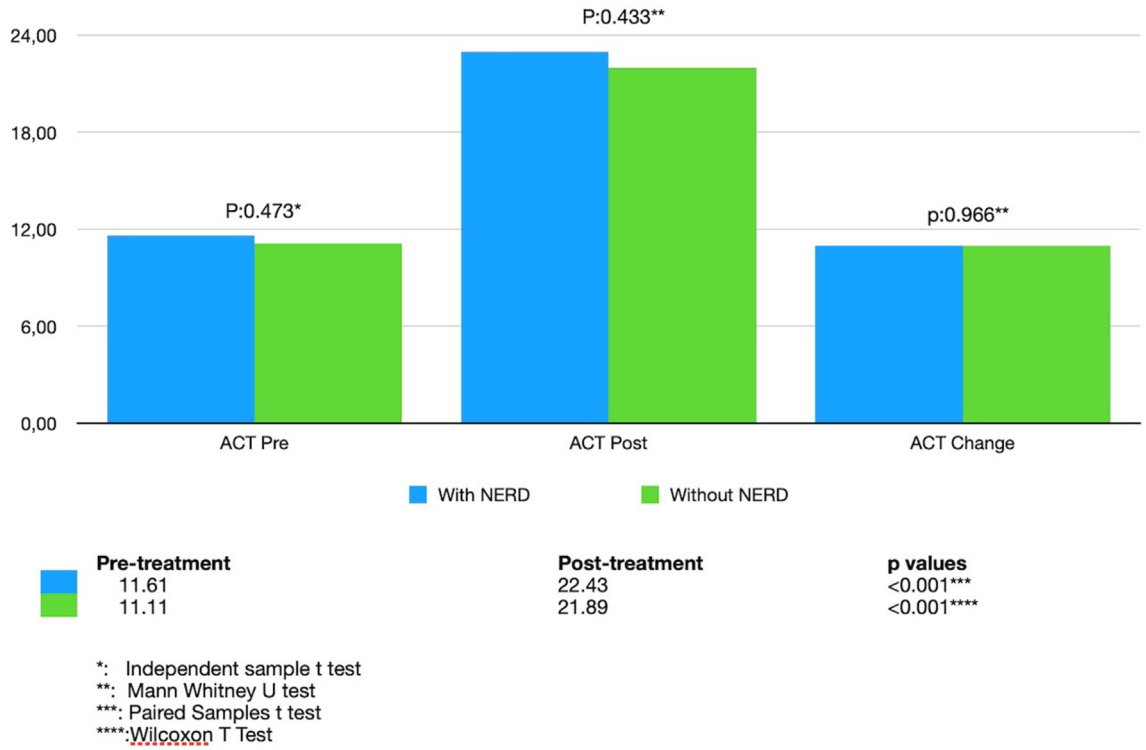

Fig. 2 Assessment of the efficacies of biologics in severe asthmatics with and without N-ERD in terms of the level of improvement in ACT. Asthma Control Test (ACT): Pre-treatment, post-treatment (omalizumab or mepolizumab) and the change from baseline, in patients with severe asthma with non-steroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (N-ERD) and without N-ERD.

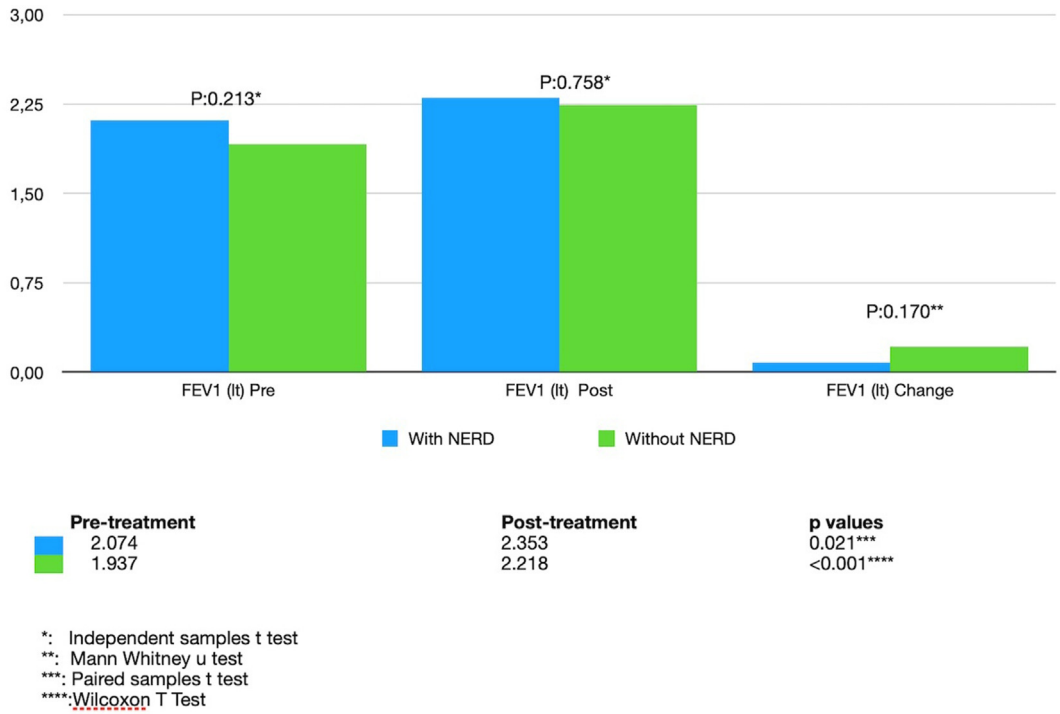

Fig. 3 Assessment of the efficacies of biologics in severe asthmatics with and without N-ERD in terms of the level of improvement in FEV1. Lung function assessed via forced expiratory volume in 1 s (FEV1) (lt): Pre-treatment, post-treatment (omalizumab or mepolizumab) and change from baseline, in patients with severe asthma with non-steroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (N-ERD) and without N-ERD.

Switching from omalizumab treatment to mepolizumab treatment enabled the discontinuation of steroid therapy in 2 steroid-dependent patients (Table 3). In addition, aspirin therapy was discontinued in 2 patients who received omalizumab treatment at their own request.

DISCUSSION

The findings of this retrospective, multicenter study with respect to the changes in respiratory parameters induced by a biologic agent, either omalizumab or mepolizumab, indicated significant improvements in ACT scores, FEV1, and significant decreases in number of asthma attacks in severe asthma patients with and without N-ERD. Of the 28 severe asthma patients with concomitant N-ERD, only 9 could be desensitized. Additionally, given its side effects, ATAD could only be applied to 5 of these 9 desensitized patients for at least 3 months. Omalizumab or mepolizumab treatment was started in all these patients regardless of whether they received this specific ATAD, since asthma control could not be achieved in any severe asthma patients with concomitant N-ERD. There was a significant increase in asthma control and a decrease in attacks after treatment with either of these biologics. On the other hand, while omalizumab treatment resulted in a significant improvement in all nasal parameters but the hyposmia score, mepolizumab treatment resulted in a significant improvement only in posterior rhinitis and nasal obstruction among the nasal parameters. In terms of the rescue medications, systemic steroid therapy could be discontinued in 2 steroid-dependent patients who were switched from omalizumab treatment to mepolizumab treatment. Two patients exhibited the need to discontinue aspirin therapy, whereas one patient had an increase in nasal obstruction after the omalizumab treatment. However, none of the patients that received omalizumab or mepolizumab required repeat medical or surgical polypectomy.

Studies on the use of biologics in patients with N-ERD associated with nasal polyp progression are limited. The studies on the use of biologics were often conducted with severe asthma patients accompanied by CRSwNP.[21]

In comparison, in this study, the N-ERD diagnosis was confirmed clinically or by oral provocation, and other nasal polyp patients were excluded

	OMALIZUMAB n:19			MEPOLIZUMAB n:9		
Treatment Duration (months), Mean ± SD	37.11 ± 27.68			8.22 ± 4.66		**P value** <0.001[a]
Rhinosinusitis (VAS), range 0–10 Mean ± SD or median (25–75 percentile)	**Pre-treatment**	**Post-treatment**	**P value**	**Pre-treatment**	**Post-treatment**	**P value**
Anterior rhinitis	6.25 ± 3.65	1.81 ± 1.72	**<0.001**[c]	6.11 ± 3.37	4.11 ± 2.27	0.077[c]
Posterior rhinitis	5.50 (0.00–8.75)	1.00 (0.00–3.50)	**0.008**[b]	10.00 (7.50–10.00)	2.00 (1.00–2.50)	**0.008**[b]
Nasal obstruction	7.50 ± 2.40	2.19 ± 1.52	**<0.001**[c]	9.00 (5.50–10.00)	1.00 (0.00–2.50)	**0.023**[b]
Hyposmia	8.50 (0.75–10.00)	4.00 (0.00–9.00)	0.102[b]	6.55 ± 3.24	4.33 ± 3.43	0.206[c]
Facial pain	4.00 (3.00–4.75)	1.00 (1.00–2.00)	**0.001**[b]	3.11 ± 1.54	2.67 ± 1.32	0.466[c]
Respiratuar clinic parameters						
ACT, mean ± SD	11.26 ± 3.26	22.21 ± 2.39	**<0.001**[b]	12.33 ± 4.24	22.89 ± 1.61	**<0.001**[b]
Asthma attack, median (%25–75 percentile)						
	5.00 (4.00–7.00)	0.00 (0.00–2.00)	**<0.001**[a]	4.00 (3.50–4.50)	0.00 (0.00–1.00)	**0.007**[a]
Need for additional treatment (n)						
Systemic steroid	2	2	N/A	5	3	N/A
Aspirin	3	1		2	2	

Table 3. Assessment of omalizumab-mepolizumab treatment efficacy in severe asthmatics with N-ERD. *N/A:Not available.Abbreviations:VAS: visual analog scale.* [a]*Independent Sample* t-*Test.* [b]*Wilcoxon* t-*Test.* [c]*Paired Sample* t-*Test.*

to rule out any confounding factors. While improvements in respiratory clinical and spirometric improvements did not differ significantly according to the presence or absence of N-ERD, the improvement in FEV1 tended to be less, albeit not significantly, in the group of patients with N-ERD [85.00 mL (−25.00 mL–372.50 mL) vs. 210 mL (30.00 mL–362.50 mL), p:0.170]. The lack of statistical significance can be explained by the low number of patients with N-ERD.

In a sub-analysis featuring 12 N-ERD patients among 23 asthma patients with CRSwNP comorbidity, 16 weeks of omalizumab treatment resulted in a significant improvement in both nasal and respiratory symptoms, independent of atopy, compared to placebo.[22] In contrast, a similar sub-analysis was not performed in our study, since mepolizumab was started mostly in non-atopic N-ERD patients. Compared to the mepolizumab treatment which resulted in a significant improvement only in posterior rhinitis and nasal obstruction complaints from among nasal parameters, omalizumab treatment in patients with atopic N-ERD resulted in significant improvements also in parameters such as anterior rhinitis and facial pain. Then again, the fact that the number of patients who received mepolizumab treatment was nearly half of the number of patients who received omalizumab treatment is an important limitation. In the study mentioned above, unlike our study, the patient population did not consist of patients with severe asthma, and the improvement in asthma control or the decrease in asthma attacks was not evaluated. In a case series conducted with 29 patients, where the need for steroids and short-acting bronchodilators was evaluated after severe asthma-related omalizumab treatment in patients with N-ERD, there was a significant decrease in the need for treatment only in atopic asthmatic patients.[23] This finding suggests that the treatment responses and therefore the underlying pathogenesis of atopic and nonatopic N-ERDs may, in fact, differ. However, there is no randomized controlled study conducted with severely asthmatic patients who received mepolizumab treatment that features the subanalysis of patients with N-ERD. In a retrospective study conducted with patients who received at least 3 doses of mepolizumab due to severe asthma, it was observed that the smell and nasal obstruction scores of 17 patients whose N-ERD diagnosis was confirmed with aspirin challenge significantly decreased after mepolizumab treatment.[24] In contrast, no significant improvement was observed in the hyposmia scores of the patients who were treated with either omalizumab or mepolizumab in our study. As can be seen, studies evaluating biologic agents in NERD included a small number of patients and different biologics were not compared. In a recently published retrospective pilot study including 74 patients with NERD, the efficacy of 5 biologic agents (omalizumab, mepolizumab, reslizumab (anti−IL-5), benralizumab (anti−IL-5 receptor alpha [anti−IL-5Rα]) and dupilumab (anti−IL-4 receptor alpha [anti−IL-4Rα]) approved by the US Food and Drug Administration (FDA) was compared. It was shown that sense of smell/taste scores improved for each subgroup following initiation of biologic therapy, but this difference was statistically significant only for the anti−IL-4Rα subgroup. While the success of reducing subjective symptoms was similar with dupilumab and omalizumab, 50% of the patients using anti-IL-5/IL-5Rα did not have response (no improvement or worsening of symptoms).[25]

There is no study that compared biologic agents and ATAD head-to-head in patients with N-ERD. In an open-label, prospective study in which N-ERD diagnosis was confirmed by nasal-oral provocation of acetylsalicylic acid, patients that received ATAD was deemed as the control group, and while improvement was observed in both asthma control and nasal scores in the omalizumab treatment group, the nasal polyp scores did not change in the ATAD group.[14] In comparison, although a statistically significant evaluation of the efficiency of ATAD could not be made in our study due to the small sample size, it was determined based on the ACT scores that uncontrolled asthma persisted after ATAD and that nasal VAS scores decreased in all parameters. In addition, only 5 of the 9 desensitized patients were able to continue to receive the ATAD. The primary drawbacks of the ATAD are the respiratory, cutaneous and gastrointestinal side effects observed both during the desensitization and intervention period. In addition, the fact that it requires incessant administration and hence that re-sensitization is required before resuming the therapy after it is discontinued due to procedures such as surgery adversely affects its success.

The multicenter design of this study was among its primary strength. Additionally, the fact that N-ERD diagnosis in severely asthmatic patients using omalizumab or mepolizumab was confirmed by oral provocation in the case patients with a history of a single NSAID reaction and clinically in the case patients with a history of at least two different NSAID reactions was another strength of this study. In addition, changes in both nasal and respiratory parameters after aspirin, omalizumab and mepolizumab treatments were evaluated. On the other hand, this study's primary limitation was the low number of patients receiving biologic agent treatment and secondary limitation was the fact that nasal polyp scores were not evaluated by endoscopic or imaging methods.

CONCLUSION

In patients with severe asthma, the concomitant N-ERD does not affect the clinical and spirometric response to omalizumab or mepolizumab treatments. ATAD is not beneficial in the long term due to both side effects and drug compliance issues. This study is the first to address both omalizumab and mepolizumab treatments in severe asthmatics with N-ERD. While significant improvement was observed in asthma clinics after treatment with either biologic agent, the improvement in nasal parameters was more pronounced in patients who were treated with omalizumab. Nevertheless, large-scale, randomized, controlled studies are needed to corroborate the findings of this study.

Abbreviations

ACT, Asthma control test; Anti-IgE, Anti-immunoglobulin E; Anti-IL-5, Anti-interleukin-5; Anti−IL-5Rα, Anti−interleukin-5 receptor alpha; Anti−IL-4Rα, Anti−interleukin-4 receptor alpha; ATAD, Aspirin therapy after desensitization; BMI, Body mass index; COX-1, Cyclooxygenase-1; CRS, Chronic rhinosinusitis; CRSwNP, Chronic rhinosinusitis with nasal polyps; CysLTs, Cysteinyl leukotrienes; FcεRI, High-affinity receptors for the Fc region; FDA, Food and Drug Administration; FEF25-75, Forced expiratory flow between 25 and 75% of vital capacity; FEV1, Forced expiratory volume in 1 second; ICS, Inhaled corticosteroid; IgE, Immunoglobulin E; IL-5Rα, Interleukin-5 receptor alpha; LABA, Long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; LTRA, Leukotriene receptor antagonist therapy; NSAID, Non-steroidal anti-inflammatory drug; N-ERD, NSAID-exacerbated respiratory disease; PGD2, Prostaglandin D2; PGE2, Prostaglandin E2; TEC, Total periferic eosinophil counts; VAS, Visual analog scale.

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- The conception and design of the study, or acquisition of data, or analysis and interpretation of data.
- Drafting the article or revising it critically for important intellectual content.
- Final approval of the version to be submitted.

Ethics approval

The study protocol was approved by the local ethics committee of University of Health Sciences, Süreyyapasa Chest Diseases and Thoracic Surgery Training and Research Hospital, (Approval Number: 318).

Author consent

All authors consented for publication.

Declaration of competing interest

None.

Author details

[a]University of Health Sciences, Süreyyapasa Chest Diseases and Thoracic Surgery Training and Research Hospital, Department of Immunology and Allergy, Istanbul, Turkey. [b]University of Health Sciences, Süreyyapasa Chest Diseases and Thoracic Surgery Training and Research Hospital, Department of Pulmonology, Istanbul, Turkey. [c]University of Health Sciences, Derince Training and Research Hospital, Kocaeli, Turkey. [d]University of Health Sciences, Diyarbakır Gazi Yasargil Training and Research Hospital, Diyarbakır, Turkey.

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