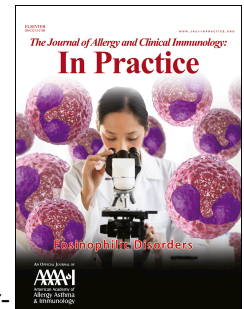


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Omalizumab-induced aspirin tolerance in N-ERD patients is independent of atopic sensitization

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Omalizumab-induced aspirin tolerance in N-ERD patients is independent of atopic sensitization

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Highlights:

1. What is already known about this topic?

- Aspirin-desensitization is currently the gold standard to induce aspirin tolerance in N-ERD patients.
- Clinical efficacy regarding omalizumab on asthma and nasal polyposis in N-ERD patients has been addressed, but the effect of anti-IgE therapy on prevention of aspirin-induced hypersensitivity especially in non-atopic N-ERD patients is less well known.

2. What does this article add to our knowledge?

- This is the first prospective study to demonstrate successful omalizumab-induced aspirin tolerance in both atopic and non-atopic N-ERD patients.
- Omalizumab exerts clinical effectiveness regarding improvement of asthma and nasal polyposis also in N-ERD patients who remain aspirin intolerant.

3. How does this study impact current management guidelines?

- This study adds comprehensive information of anti-IgE therapy in N-ERD patients thereby facilitating future treatment decisions in N-ERD patients without allergic sensitization and supports the use of omalizumab as an alternative treatment option in inducing aspirin tolerance in N-ERD patients.

81 List of abbreviations

- 82 CRSwNP: chronic rhinosinusitis with nasal polyps
83 CT: computed tomography
84 ECP: eosinophilic cationic protein
85 FESS: functional endoscopic sinus surgery
86 FEV1: forced expiratory volume in one second
87 IgE: immunoglobulin E
88 MEF 50: maximal expiratory flow at 50%
89 N-ERD: NSAID-exacerbated respiratory disease
90 NPS: nasal polyp score
91 NSAIDs: nonsteroidal anti-inflammatory drugs
92 SNOT-20 GAV: Sino Nasal Outcome Test German Adapted Version
93

Abstract

Background: NSAID-exacerbated respiratory disease (N-ERD) comprises the triad of chronic rhinosinusitis with nasal polyps (CRSwNP), asthma and intolerance to inhibitors of the cyclooxygenase-1-enzyme. The impact of omalizumab on prevention of aspirin-induced hypersensitivity in N-ERD patients with and without atopic sensitization has not been thoroughly addressed.

Objective: To investigate the effect of omalizumab treatment on aspirin tolerance in atopic and non-atopic N-ERD patients.

Methods: This single-center, prospective trial evaluated overall omalizumab-induced aspirin tolerability in N-ERD patients by performing aspirin challenge testing before and after 6 months of anti-IgE therapy. The impact of omalizumab on CRSwNP, asthma as well as serum and tissue biomarkers in patients with and without comorbid atopic sensitizations was further analyzed.

Results: Out of 33 patients included in the study, 56% developed complete aspirin tolerance and 18% tolerated higher dosages after 24 weeks. Polyp size and disease-specific symptoms (NPS:- 1.9 ± 0.3 , $p < 0.001$; SNOT-20:- 16.7 ± 3.7 , $p < 0.001$; ACT: $+3.2 \pm 0.7$, $p < 0.001$) improved in all patients irrespective of atopic sensitization. Effectiveness of omalizumab was accompanied by an increase in mean total serum IgE ($307.8 \pm 42 \text{ kU/L}$, $p < 0.001$) and a decrease in ECP ($-10.6 \pm 6.7 \text{ } \mu\text{g/L}$) and in relative eosinophilia ($-2.5 \pm 0.7\%$, $p < 0.01$). While there was a significant reduction of tissue IgE ($p < 0.05$) in all patients after 4 weeks, the number of local eosinophils decreased only in atopic individuals ($p < 0.05$).

Conclusion: Omalizumab induced complete aspirin tolerance in the majority (56%) of patients independent of atopic sensitization and demonstrated clinical efficacy in the treatment of CRSwNP and asthma. Inhibition of IgE can therefore be a promising treatment option in preventing NSAID hypersensitivity reactions in N-ERD patients.

Introduction

NSAID-exacerbated respiratory disease (N-ERD), also named AERD or NSIAD-ERD, comprises the triad of allergic asthma, chronic rhinosinusitis with nasal polyps (CRSwNP) and intolerance to nonsteroidal anti-inflammatory drugs (NSAIDs) severely diminishing patients' overall quality of life.¹ Upon exposure to aspirin/NSAIDs, patients experience severe symptoms predominantly affecting the upper and lower respiratory tract.² Disease-specific pathomechanisms include a decrease in the anti-inflammatory mediator prostaglandin E₂ upon NSAID-induced cyclooxygenase-1 inhibition and, subsequently, a preponderance of the cyclooxygenase-2 dependent pro-inflammatory mediator prostaglandin D₂ and its metabolites.^{1, 3-5} These events are accompanied by a metabolism of arachidonic acids that leads to an accumulation of leukotrienes further enhancing pro-inflammatory pathways and to an extensive eosinophilic mucosal type 2 inflammation in lower and upper airways.^{3, 6} Tissue-infiltrating mast cells are an important source of pro-inflammatory mediators such as cysteinyl leukotrienes or prostaglandin D₂ driving the eosinophilic inflammation also in stable N-ERD.^{1, 5} IgE, which is highly elevated in nasal mucosa in N-ERD, is thought to play a central role in the pathogenesis of polyposis by activating mast cells and further intensifying type 2 immunity. Interestingly, its nasal concentration is independent of total serum IgE levels and co-existing allergies.⁷ A subpopulation of patients with N-ERD exhibit elevated total and specific serum IgE-levels, but allergic sensitization to air-borne allergens, although frequently present, is not an aspect linked to the disease.⁸

Recently, the humanized anti-IgE monoclonal antibody omalizumab has been approved for the treatment of CRSwNP after demonstrating clinical efficacy in a proof-of-concept study as well as two phase 3 trials.⁹⁻¹¹ Omalizumab exerts its therapeutic effect in allergic asthma by depletion of IgE from airways and simultaneous reduction of tissue-infiltrating eosinophils thereby impairing type 2 immune responses.^{9,12, 13} Similar disease-modifying mechanisms might thus be employed when treating CRSwNP, as effectiveness of omalizumab in improving nasal and asthmatic symptoms in N-ERD patients has already been reported.^{10,14-17} It is unclear, however, whether IgE inhibition might be a useful tool for preventing NSAID-induced hypersensitivity reactions as well.¹⁷⁻¹⁹ So far, data are only available for atopic N-ERD patients exhibiting at least one allergic sensitization. By performing aspirin

challenge testing before and after 6 months of anti-IgE therapy, we (i) sought to verify overall
omalizumab-induced aspirin tolerability in N-ERD patients, (ii) investigate the impact of omalizumab
treatment on CRSwNP, asthma, eosinophilia, and serum and tissue IgE levels of patients and (iii)
analyze differences of omalizumab treatment in N-ERD patients with and without atopic sensitization
against aeroallergens.

Methods

Study design and patients

This study was conducted as an investigator-initiated, prospective single center trial between February 2017 and April 2020 at the Department of Dermatology at the Medical University of Vienna, Austria. It was approved by the local ethics committee (EK 1732/2017) and registered at EudraCT (2017-003119-21). Written informed consent was obtained from all patients before study participation. Inclusion criteria comprised age ≥ 18 years, diagnosis of N-ERD (CRSwNP, asthma, aspirin intolerance) and a medical history of more than one endoscopic sinus surgery (ESS). CRSwNP was diagnosed according to the 2012 European Position Paper on Rhinosinusitis and Nasal Polyps Guidelines and asthma was diagnosed based on Global Initiative for Asthma guidelines.²⁰⁻²² NSAID intolerance was confirmed by hypersensitivity reactions during oral aspirin challenge before study inclusion. Omalizumab was given subcutaneously biweekly/monthly for a total of 6 months adjusted to body weight and total serum IgE levels as used for asthma treatment. During the study period, all patients maintained their usual topical/systemic asthma medication and nasal treatment regimen (Table 1). None of the patients received concomitant aspirin desensitization treatments or other biologicals.

Aspirin provocation testing

Aspirin intolerance, confirmed at baseline, was re-evaluated after 24 weeks of omalizumab treatment by oral exposure to aspirin (Fig. E1A). Aspirin provocation testing was performed in accordance with previously established protocols starting with a dose of 125mg that was gradually increased every two hours to a maximum of 500mg while closely monitoring vital signs.^{3, 23} Spirometry was performed 30 minutes before and after each drug intake and additionally in association with respiratory symptoms when necessary. Positive reactions were evaluated by a respiratory function test and/or clinical symptoms (nasal and/or extra-pulmonary symptoms). Positive reactions were categorized into groups based on the type of respiratory reaction to aspirin: lower respiratory reaction (decrease in forced

expiratory volume in 1 second [FEV1] > 20%), upper respiratory reaction (symptoms of nasal congestion, rhinorrhea, sneezing, nasal/eye itching, or eye redness/tearing); combined upper and lower respiratory reaction (decrease in forced expiratory volume in 1 second [FEV1] by 10 to 20% with presence of nasal congestion, rhinorrhea, sneezing, nasal/eye itching, or eye redness/tearing) and no respiratory reaction. Oral challenges were stopped when a positive reaction was noted or when the highest dose of aspirin had been administered. In case of hypersensitivity reactions, the patient received appropriate emergency treatment for anaphylaxis. Patients were observed for at least 12 hours after the last dose of aspirin in order to exclude late anaphylactic reactions.

Study measures

Our primary endpoint was the proportion of intolerant atopic and non-atopic patients developing tolerance to aspirin as examined by oral provocation testing at baseline and after 24 weeks (Fig. E1A). Nasal polyp size was graded by nasal endoscopy using nasal polyp score (NPS) with higher points indicating more severe disease (NPS, 0-8 points) at baseline and up to 24 weeks.^{24, 25} Quality of life was recorded using the patient-oriented German version SNOT-20 GAV of the validated Sino-Nasal Outcome Test-20 (SNOT-20, range 0-100) at baseline and up to 24 weeks.²⁵⁻²⁷ The 20 questions were further grouped in four subcategories: nasal, otologic, sleep and emotional symptoms.²⁵

Where CT pictures were available, we assessed sinus computed tomographic scans at baseline and after 6 months of treatment using the Lund-Mackay CT score to analyze changes in severity of CRSwNP.^{24, 28} Changes in asthmatic symptoms were measured by spirometry at baseline and after 12 and 24 weeks of therapy. The forced expiratory volume in one second (FEV1%) and the maximal expiratory flow at 50% (MEF50) were measured. As patient-oriented asthma questionnaire, we assessed the asthma control test (ACT) at each visit. In order to divide patients into allergic and nonallergic subgroups, we performed skin prick tests and specific IgE to air-born allergens at baseline. Peripheral blood eosinophil counts, serum total immunoglobulin E (IgE) levels and eosinophilic cationic protein (ECP) were assessed in patients' sera at baseline, after 12 and 24 weeks of treatment. Finally, we documented potential drug-related side effects at each visit.

Biopsies and immunohistochemistry

Polyp tissue biopsies were obtained by an ENT specialist under local anesthesia from 12 patients with a total NPS score of >2 at baseline and after 4 weeks of omalizumab therapy. Biopsies were approximately 3mm in size and transferred to RPMI solution, imbedded in OCT medium, snap-frozen in liquid nitrogen and stored at -80°C until further processing. Immunohistochemistry on frozen tissue was performed as described before.²⁹ In brief, antibodies against IgE (Southern biotech, IgG1K, Clone B3102E8), FcεRI (Biolegend, IgG2b, Clone AER-37 (CRA-1)) and eosinophilic major basic protein (MBP, IgG1, clone BMK-13, BioRad) were incubated overnight and visualized by Dako Autostainer Link 48. In all staining experiments, appropriate isotype controls (IgG1K, Sigma and IgG2b, Sigma) served as negative controls. Positively stained cells were quantified by using Aperio Image Scope 12.3.3.5048 and counted per mm².

Statistical analysis

Mean and standard deviation were calculated for continuous variables and absolute and relative frequencies were calculated for categorical variables. Tolerated aspirin dosages at baseline and after 24 weeks were summarized in a shift-table. Using an exact test for symmetry, we tested the null-hypothesis that a shift towards higher tolerated aspirin levels was equally likely as a shift towards lower aspirin levels. McNemar's tests were applied to assess whether the proportion of patients with either upper-, lower or combined respiratory tract reactions to aspirin exposure provocation was reduced after treatment compared to baseline. To assess changes in continuous outcome variables, linear mixed models were calculated including a fixed effect for each visit and a random intercept term for the factor patient. To further analyze if treatment changes may differ between allergic and nonallergic patients, the mixed models were extended to include a fixed effect for allergy status and its interaction with different timepoints. The same approach was used to compare changes in continuous outcome variables between patients with and without improvement in aspirin tolerance. Patients with missing values in a particular outcome variable were excluded in the calculation of respective summary

statistics. Hypothesis tests regarding aspirin provocation were performed including all patients with complete provocation data at baseline and after 24 weeks. In mixed models, all patients with observations for at least one time-point were included. Hypothesis tests other than the exact symmetry test for the primary endpoint were considered as exploratory and hence no multiple testing adjustment was applied. P-values of <0.05 were considered statistically significant. All statistical calculations were performed using R 3.6. Analysis of immunohistochemical stainings of nasal tissue was done using Graphpad prism (v8.0.1) software applying paired t- test for statistical significance of group comparisons.

Results

Baseline population

After assessment of eligibility (Fig. E1B), 33 patients (9 male, 24 female) with N-ERD and conclusive history of nasal and asthmatic symptoms were enrolled (Table 1). At baseline, all patients showed hypersensitivity reactions to aspirin (Table 1). Most patients (46%, n=15) presented with isolated upper respiratory tract reactions such as nasal congestion, rhino-conjunctivitis or rhinorrhea, whereas 36% (n=12) of patients showed isolated lower respiratory tract disorders (pulmonary obstruction, coughing or dyspnea) and 18% (n=6) demonstrated a combination of both reactions (Fig. 1, Table 1). At baseline, 18 patients showed hypersensitivity reactions to an aspirin dosage of 125mg, 14 patients to 250mg and one patient to 500mg (Table 1). Six patients discontinued omalizumab treatment before week 24 and were not re-subjected to aspirin provocation testing (Fig. E1B). All patients underwent standard skin prick testing including relevant inhalant allergens and subsequent analysis of specific IgE to air-born allergens (Table E1). Patients with positive results were accordingly classified as atopic (42%, n=14) and patients with negative results as non-atopic (58%, n=19) (Table 1). A substantial proportion of patients displayed specific IgE antibodies against staphylococcus enterotoxin A (15%, n=5) and B (21%, n=7) irrespective of their allergic sensitization to inhalants (Table 1).

Induction of aspirin tolerance after omalizumab treatment

Compared to baseline, only 12 of 27 patients (44%) showed hypersensitivity reactions to aspirin challenge after 24 weeks of omalizumab treatment (Fig. 1). Of these patients, 9 had isolated upper-, none had isolated lower-, and three patients showed a combination of upper/lower airway reactions (Fig. 1). Five patients (19%) tolerated higher dosages at re-exposure compared to baseline and 7 patients (26%) did not show any symptom improvements reacting at aspirin 125mg (n=3) and 250mg (n=4) (Fig. 2). Fifteen patients (56%) received the highest cumulative dose of aspirin 875mg without developing any hypersensitivity reactions ($p<0.001$), indicating omalizumab-induced aspirin tolerance

(Fig. 1, 2). None experienced a worsening of symptoms after oral re-exposure (Fig. 2). Omalizumab was generally well tolerated (Table E2).

Overall clinical effectiveness of omalizumab

After 24 weeks of omalizumab treatment, polyp size and patient-reported outcomes of CRSwNP were significantly reduced as evaluated by mean values of NPS (-1.9 ± 0.3 , $p < 0.001$) and total SNOT-20 (-16.7 ± 3.7 , $p < 0.001$) compared to baseline (Fig. 3A, B). When SNOT-20 was stratified in subcategories, we noticed significant improvement in nasal ($p < 0.001$), otologic ($p < 0.001$) and sleep symptoms ($p < 0.05$), but not in emotional symptoms ($p = 0.07$) (Fig. E2A-D). Spirometric data demonstrated a mild improvement of asthmatic symptoms by week 24 of omalizumab treatment, as measured by mean MEF 50 ($+0.5 \pm 0.2$, $p < 0.05$) and FEV1% ($+2.1 \pm 1.6$, $p = 0.209$) (Fig. 3C, D). The patient-oriented questionnaire ACT supported a highly significant relief in subjective pulmonary symptoms ($+3.2 \pm 0.7$, $p < 0.001$), (Fig. 3E). The overall clinical amelioration of CRSwNP was corroborated by a clear, although not significant reduction in the mean Lund-Mackay CT score by 1.8 points after 24 weeks ($p = 0.326$) (Fig. 3F).

Improvement of symptoms and induction of aspirin tolerance occurs in atopic and non-atopic patients

IgE inhibition may lead to more profound treatment responses in atopic N-ERD patients. It is noteworthy that subgroup analysis revealed a more pronounced reduction in CRSwNP (NPS: -2.2 ± 0.5 ; $p < 0.001$) and better quality of life, as evaluated by SNOT-20 (-19.2 ± 4.8 ; $p < 0.001$) in patients without concomitant atopic sensitization as compared to atopic patients (NPS: -1.5 ± 0.5 , $p < 0.01$; SNOT-20: -13.4 ± 5.7 , $p < 0.05$) (Fig. 4A, B, Table E3). FEV1% scores showed a trend of increase in non-atopic patients after 24 weeks of treatment, whereas ACT scores equally improved in both subgroups (Fig. 4C, D, Table E3). Noteworthy, acquisition of aspirin tolerance was completely independent of the patients' atopic sensitization (Table E4).

Clinical improvement is independent of induction of aspirin tolerance

Baseline characteristics of patients who completed the study and were re-subjected to aspirin provocation testing after 6 months (n=27) showed no significant differences between aspirin tolerant and intolerant patients, but, interestingly, aspirin-tolerant patients exhibited more pronounced eosinophilia and slightly elevated levels of IgE and ECP (Table E5). Additional analysis of both subgroups revealed comparable improvement of asthmatic symptoms (MEF 50, FEV1%, ACT), whereas overall amelioration of nasal symptoms was more pronounced in aspirin-tolerant patients at week 24 (Table E6). None of the parameters analyzed showed significant differences in mean changes between the two groups after 24 weeks of treatment (Table E6).

Changes in blood and nasal tissue biomarkers during omalizumab treatment

As already reported for chronic spontaneous urticaria and asthma, omalizumab may considerably alter serum IgE levels, thereby linking clinical responses to changes in total IgE.^{30, 31} During the course of treatment, we detected a highly significant increase in mean total IgE in all patients after 24 weeks compared to baseline ($307.8 \text{ kU/L} \pm 42$, $p < 0.001$) (Fig. 5A). Differences between baseline and week 24 IgE levels were more distinct in aspirin-intolerant patients ($+440.8 \text{ kU/L} \pm 85.6$, $p < 0.001$) than in those acquiring aspirin tolerance after 6 months ($+265.8 \text{ kU/L} \pm 50$, $p < 0.001$) (Table E6). Elevation of IgE was accompanied by a decrease in mean ECP levels ($-10.6 \pm 6.7 \text{ } \mu\text{g/L}$, $p = 0.13$) and mean percentages of relative eosinophilia ($-2.5 \pm 0.7\%$, $p < 0.01$) over the course of time (Fig. 5B, C). Whereas initial mean serum IgE levels in atopic and non-atopic patients were comparable, ECP and eosinophils were more elevated in non-atopic patient reaching comparable values after 24 weeks of therapy (Figure 5D-F, Table E4).

In order to explore if omalizumab differently affects local tissue IgE and infiltrating eosinophils in N-ERD patients, we used immunohistochemistry for analyzing IgE, its corresponding high affinity receptor FcεRI and eosinophilic MBP for eosinophils in biopsies taken from 6 atopic and 6 non-atopic patients

at baseline and after 4 weeks of treatment (Fig. 5G- I). Tissue was retrieved as soon as after 4 weeks of treatment to (i) gain insight into early effects of anti-IgE therapy and (ii) to ensure sufficient polyp size for sampling. As demonstrated in Fig. 5J, the number of IgE⁺ cells at baseline were comparable in atopic (116 cells/mm²±65.5) and non-atopic (139 cells/mm²±90) patients. After 4 weeks of omalizumab therapy, we noticed an overall significant reduction of IgE (85 cells/mm²±61) ($p<0.05$) that due to small sample size did not reach statistical significance in subgroup analysis (atopic 79 cells/mm²±31; non-atopic 90 cells/mm²±85) (Fig. 5J). Numbers of the corresponding high affinity IgE receptor, FcεRI, were similar in atopic (66 cells/mm²±44) and non-atopic (68 cells/mm²±39) patients at baseline and after 4 weeks of treatment (allergic: 55 cells/mm²±29; nonallergic: 81 cells/mm²±38) (Fig. 5K). Interestingly, we found a significant reduction in the number of eosinophils in atopic (before 451 cells/mm²±152, after: 185 cells/mm²±130) ($p<0.05$), but not in non-atopic individuals (before: 286 cells/mm²±193, after: 332 cells/mm²±261) (Fig. 5L).

Discussion

In this prospective single center study, we demonstrate clinical effectiveness of omalizumab in N-ERD patients with and without atopic comorbidity. Of note, aspirin tolerance was successfully induced in 56% of N-ERD patients after 6 months of treatment and 18% of patients tolerated higher aspirin dosages as compared to baseline. Omalizumab treatment was also accompanied by clinical improvement of nasal and pulmonary symptoms in most patients. Whereas efficacy of omalizumab on asthmatic and CRSwNP in N-ERD has been demonstrated in previous trials and case series, its impact on prevention of aspirin-induced hypersensitivity has been infrequently addressed.^{9, 10, 17-19, 32, 33} In addition, N-ERD patients included in most former studies exhibited at least one relevant allergy to aeroallergens thereby fulfilling label criteria of omalizumab treatment. A substantial proportion of N-ERD patients, however, show elevated total serum IgE in the absence of specific allergies to inhalants, thus likely rendering them eligible to anti-IgE treatment.³⁴ Although the underlying cause for this elevation has not been identified, it has been proposed that these patients might be sensitized either to yet unknown components or to rarely tested bacterial allergens such as *Staphylococcus aureus* endotoxin and other microbial epitopes which can act as amplifiers of local polyclonal IgE formation.³⁵⁻³⁸ In N-ERD, aspirin exposure-independent IgE-FcεRI interaction may lead to constant activation of mast cells, as levels of prostaglandin D2 and leukotriene E₄ (LTE₄), both known as markers of mast cell activation, are elevated in sputum and urine of stable disease.^{1, 5, 39} Omalizumab exerts its effect by binding to free serum IgE, which again blocks interaction of IgE with its receptors (FcεRI and FcεRII) on cells involved in allergic inflammation such as mast cells, eosinophils or dendritic cells.⁴⁰ During aspirin challenge urinary LTE₄ concentrations in omalizumab-, but not in placebo-treated patients, are significantly reduced indicating inhibitory effects on mast cell activation and, subsequently, reduced leukotriene release thereby potentially resulting in attenuated hypersensitivity symptoms.¹⁸ This hypothesis is corroborated by *in vitro* studies showing that dissociation of prebound IgE from its receptor FcεRI by omalizumab leads to rapid mast cell inhibition.^{41, 42}

In our study, patients with omalizumab-induced aspirin tolerance showed a trend in higher levels of serum IgE, ECP and an elevated relative number of eosinophils at baseline as compared to intolerant patients suggesting that peripheral signs of eosinophilic allergic inflammation might be indicative of omalizumab response. Our data is in line with recently published results demonstrating that N-ERD patients exhibiting marked eosinophilia and concomitant IgE-mediated asthma had a more pronounced improvement of asthmatic symptoms when treated with omalizumab.¹⁶ Likewise, Th2-associated biomarkers including high levels of exhaled nitric oxide, peripheral eosinophils and serum periostin, correlated with a better response to omalizumab in allergic asthma.¹³ Similar results are also reported in chronic spontaneous urticaria, where omalizumab nonresponders exhibited significantly lower baseline IgE levels than responders.³⁰

After 6 months, we noticed a similar reduction in NPS scores (-1.9 points) as compared to results from placebo-controlled trials after 16 (NPS -2.67) and 24 weeks (NPS -1.08 and -0.9) of treatment.^{9, 10} Asthmatic symptoms also changed for the better as shown by an increase in MEF50 (+0.5) and subjective ACT score (+3.2 points) after 24 weeks.¹⁸ Confirming other study results, all clinical parameters rapidly improved within the first 4 weeks of treatment.^{9, 18} Interestingly, overall amelioration of CRSwNP was more pronounced in patients with omalizumab-induced aspirin tolerance than in aspirin-intolerant patients, whereas asthmatic symptoms improved to a similar extent in both groups. It is thus tempting to speculate that omalizumab exerts its anti-inflammatory effects in aspirin-tolerant patients primarily by binding to IgE in nasal tissue thereby reducing inflammation and polyp size alike and stabilizing the threshold for rapid mast cell and eosinophil degranulation after aspirin challenge. In patients with persisting aspirin intolerance, however, a preponderance of non-IgE-mediated pro-inflammatory Th2 immune pathways might overweight inhibitory and anti-inflammatory effects of omalizumab.

We identified 42% of patients with allergic sensitization in our patient population as opposed to 58% without detectable allergic propensities. Specific serum IgE to *Staphylococcus aureus* enterotoxins was present in 15%-21% of our patients irrespective of atopic sensitization, a lower number than reported

before.⁹ Somewhat unexpected, whereas non-atopic patients demonstrated similar baseline IgE levels as atopic patients, they showed a more pronounced baseline elevation of ECP and eosinophils indicating eosinophilic inflammation. It is important to note that tissue IgE levels of nasal polyps do not correlate with levels of serum IgE or positive allergy skin prick testing.⁴³ Confirming this observation in N-ERD patients, we found a similar number of IgE+ and FcεRI+ cells in atopic and non-atopic individuals when examining polyp tissue before omalizumab therapy. At week 4 overall tissue IgE, but not FcεRI levels, were significantly reduced by omalizumab with similar reduction in atopic and non-atopic individuals. Strikingly, the number of tissue-infiltrating eosinophils in atopic individuals was not only higher at baseline, but was also significantly reduced after omalizumab treatment as compared to non-atopic patients. The clinical relevance of this observation has yet to be clarified, as omalizumab successfully induced aspirin tolerance in both patient subsets independent of their allergic sensitization. Our findings corroborate and extend earlier results from a placebo-controlled trial showing clinical efficacy of omalizumab on asthma and CRSwNP in both atopic and non-atopic patients.⁹ Since licensing in 2004, the use of omalizumab in asthma has generally been restricted to allergic respiratory disease.^{44,45} Increasing evidence suggests, though, that also non-atopic patients with severe eosinophilic asthma might benefit from inhibiting IgE.⁴⁶ Based on our results, we propose that concomitant allergic sensitization is irrelevant for successful omalizumab therapy in N-ERD patients.

As a main limitation of this study, the lack of a placebo group must be mentioned, which was not included for ethical reasons as our patient population had already failed several treatment attempts. Nonetheless, our results support those of recently published placebo-controlled trials.¹⁸

In summary, we show that inhibiting IgE successfully induces aspirin tolerance in the majority (56%) of N-ERD patients and ameliorates nasal and asthmatic symptoms independent of concomitant atopy. Patients exhibiting eosinophilia and an elevation of IgE and ECP at baseline are prone to more favorable treatment responses. Further identification of biomarkers in N-ERD patients will be essential for implementing tailored treatment strategies especially in the current era of newly available biologics.

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Table Legend

Table 1: Baseline characteristics

Figure Legends

Fig 1. Respiratory reactions to aspirin provocation. Graph shows patient numbers reacting with different types of respiratory reactions (upper;dark blue/lower;blue/both;purple/none;yellow) to oral aspirin exposure at baseline before omalizumab and after 24 weeks of treatment. *P-values* < 0.05 are considered significant. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Fig 2. Overall reactions to aspirin provocation at baseline and after 24 weeks. The vertical column on the left shows ascending dose from 125mg to 500mg at baseline, while the horizontal lines portray ascending aspirin dosages after 24 weeks of treatment. Number of patients who tolerated higher dosages after 24 weeks of omalizumab treatment are shown in green (n=20), while patients with no symptom improvement are marked in grey (n=7). Symptom worsening after re-exposure is displayed in the red field (n=0).

Fig 3. Clinical effectiveness of omalizumab. Analysis of various clinical scores evaluating CRSwNP and allergic asthma at baseline and after 24 weeks of omalizumab treatment in all patients. **A)** Nasal polyp score (NPS) **B)** Total Sino Nasal Outcome Test (total SNOT-20) **C)** Maximal expiratory flow at 50% (MEF50) **D)** Forced expiratory volume in one second (FEV1%) **E)** Asthma control test (ACT) **F)** Lund-Mackay CT score. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Fig 4. Analysis of clinical effectiveness in atopic (red) and non-atopic (blue) patients. Differences in **A)** Nasal polyp score (NPS) **B)** Total SNOT score **C)** Forced expiratory volume in one second (FEV1 %) **D)** Asthma control test (ACT) in atopic (red) and non-atopic (blue) patients between baseline and up to 24 weeks are displayed. Significance of changes between baseline and 24 weeks of treatment is indicated. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Fig. 5. Analysis of biomarkers in serum and nasal polyp tissue.

A-C) Changes in blood biomarker levels during omalizumab therapy in total population (n=33). **A)** Course of total serum IgE levels in all patients up to 24 weeks. **B)** Course of ECP in all patients up to 24 weeks. **C)** Course of relative eosinophilia in all patients up to 24 weeks.

D-F) Changes in **D)** serum IgE levels, **E)** ECP levels and **F)** relative eosinophilia in atopic (red) and non-atopic (blue) patients between baseline and week 24. Significance of changes between baseline and 24 weeks of treatment is indicated. **G-L)** Comparison of immunohistochemical stainings for IgE, FcεRI and eosinophilic MBP in nasal polyp tissue at baseline and after 4 weeks of omalizumab treatment. Pictures display representative stainings of an atopic patient. **G)** Tissue infiltrating IgE+ cells at baseline (left) and at week 4 (right), **H)** FcεRI+ cells at baseline (left) and at week 4 (right) of omalizumab treatment and **I)** eosinophilic MBP+ cells before (left) and after 4 weeks (right). Positively stained cells are displayed in red (arrows). Magnification x200 **J)** Number of IgE+ cells (cells/mm²) in nasal polyps of all patients (green, $p = 0.054$), atopic (blue, $p = 0.14$) and non-atopic patients (purple, $p = 0.218$) at baseline and week 4 of treatment. **K)** Number of FcεRI+ cells (cells/mm²) in all patients (green, $p = 0.909$), atopic (blue, $p = 0.437$) and non-atopic patients (purple, $p = 0.562$) at baseline and week 4. **L)** Number of eosinophilic MBP+ cells in all patients (green, $p = 0.132$), atopic (blue, $p < 0.05$) and non-atopic patients (purple, $p = 0.473$) at baseline and week 4. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.
ECP: eosinophilic cationic protein; MBP: major basic protein; NS: not significant

Table 1. Baseline characteristics

	Overall population n=33	Atopic population n=14	Non-atopic population n=19	p value
Age years (Min-Max; Mean)	23–70; 47.6	43.9 (10.8)	50.26 (11.14)	0.111
Sex m/f	9/24	5/9	4/15	0.442
Reaction to aspirin provocation n	33			
Upper respiratory tract reaction	15	5	10	0.118
Lower respiratory tract reaction	12	4	8	
Both (upper/lower)	6	5	1	
125mg aspirin	18	6	12	0.286
250mg aspirin	14	8	6	
500mg aspirin	1	0	1	
Scores at baseline	Mean value (SD¹)			
Nasal polyp score (0-8)	3.8 (2.5)	4.1 (2.6)	3.5 (2.4)	0.459
Sinus nasal outcome test-20 (0-100)	40.4 (18.2)	37.1 (17.9)	42.9 (18.5)	0.377
Lund Mackay CT score (0-24)	18 (5.2)	17 (6.4)	18.9 (4.1)	0.46
Asthma control test (0-25)	19.1 (5)	17.4 (5.4)	20.3 (4.4)	0.106
FEV1 ^a %	70.9 (8.3)	72 (9.8)	70.2 (7.4)	0.588
MEF50 ^b l/s	2.4 (1.1)	3 (1.2)	2 (0.7)	0.029**
Biomarkers at baseline	Mean value (SD¹)			
Total IgE ^c kIU/L	188.2 (145.8)	189.9 (122.9)	186.9 (163.9)	0.952
ECP ^d µg/L	57.8 (33.8)	42.6 (23.2)	66.6 (36.3)	0.036*
Eosinophilia (relative) %	6.6 (3.9)	4.1 (2.4)	8.2 (3.9)	0.003**
Omalizumab dosages / month sc	n			
150mg	10	2	8	0.364
300mg	11	6	5	
450mg	4	2	2	
600mg	8	4	4	
Previous therapies				
Aspirin desensitization n	8	1	7	0.098
Functional endoscopic sinus surgery	33	14	19	
IgE to Staphylococcus enterotoxin A kIUa/L, n; mean (SD)	5; 0.1(0.3)	1; 0.1 (0.2)	4; 0.2 (0.3)	0.424
IgE to Staphylococcus enterotoxin B kIUa/L, n; mean (SD)	7;1.1 (3.9)	2; 0.5 (0.7)	5; 1.4 (4.7)	0.487
Concomitant therapies n				
Nasal corticosteroids	17	8	9	
Long-acting inhalant β-agonist	15	5	10	
Leukotriene receptor antagonists/antihistamines	18	11	7	
Inhaled corticosteroids	6	1	5	

¹SD: Standard deviation^aFEV1: Forced expiratory volume in one second^bMEF50: Maximal expiratory flow at 50%^cIgE: immunoglobulin E^dECP: Eosinophil cationic protein

* p<0.05

** p<0.01

Fig. 1

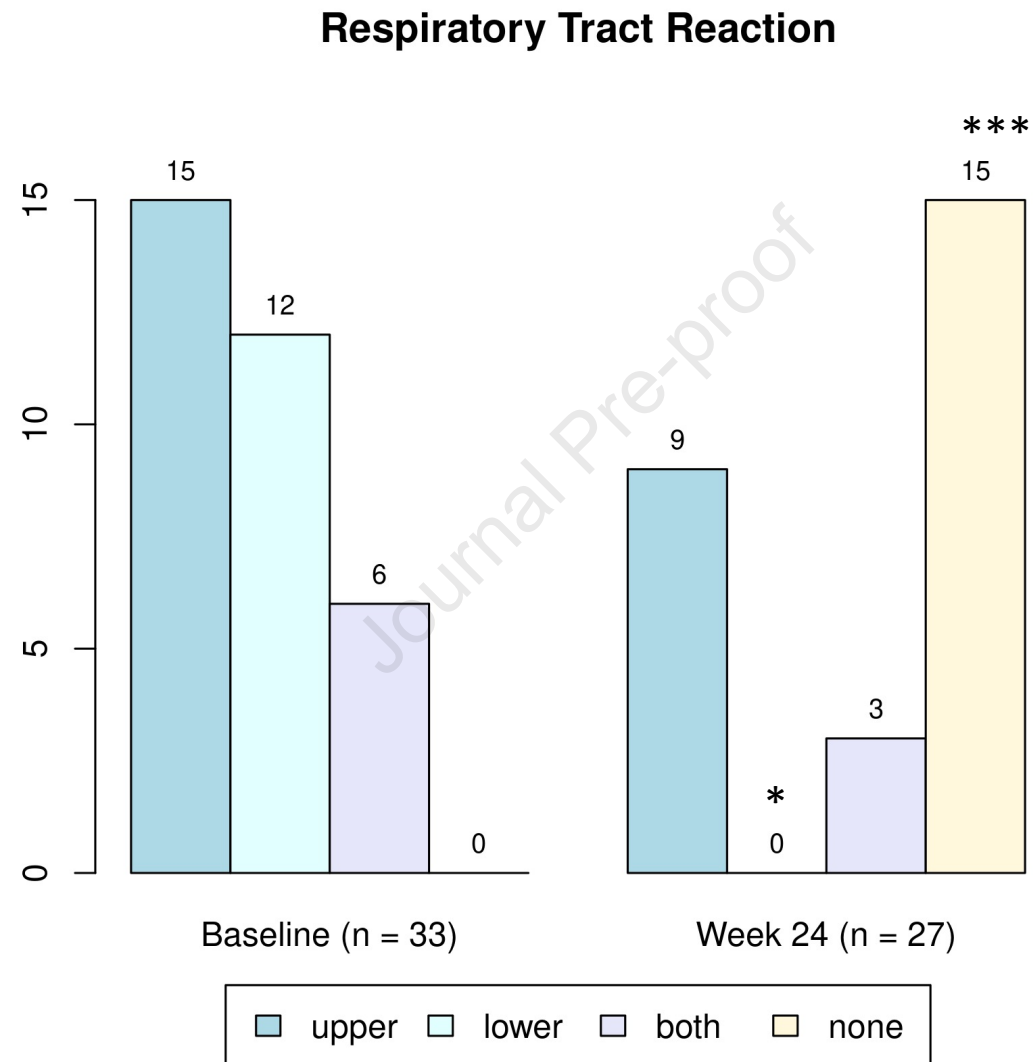
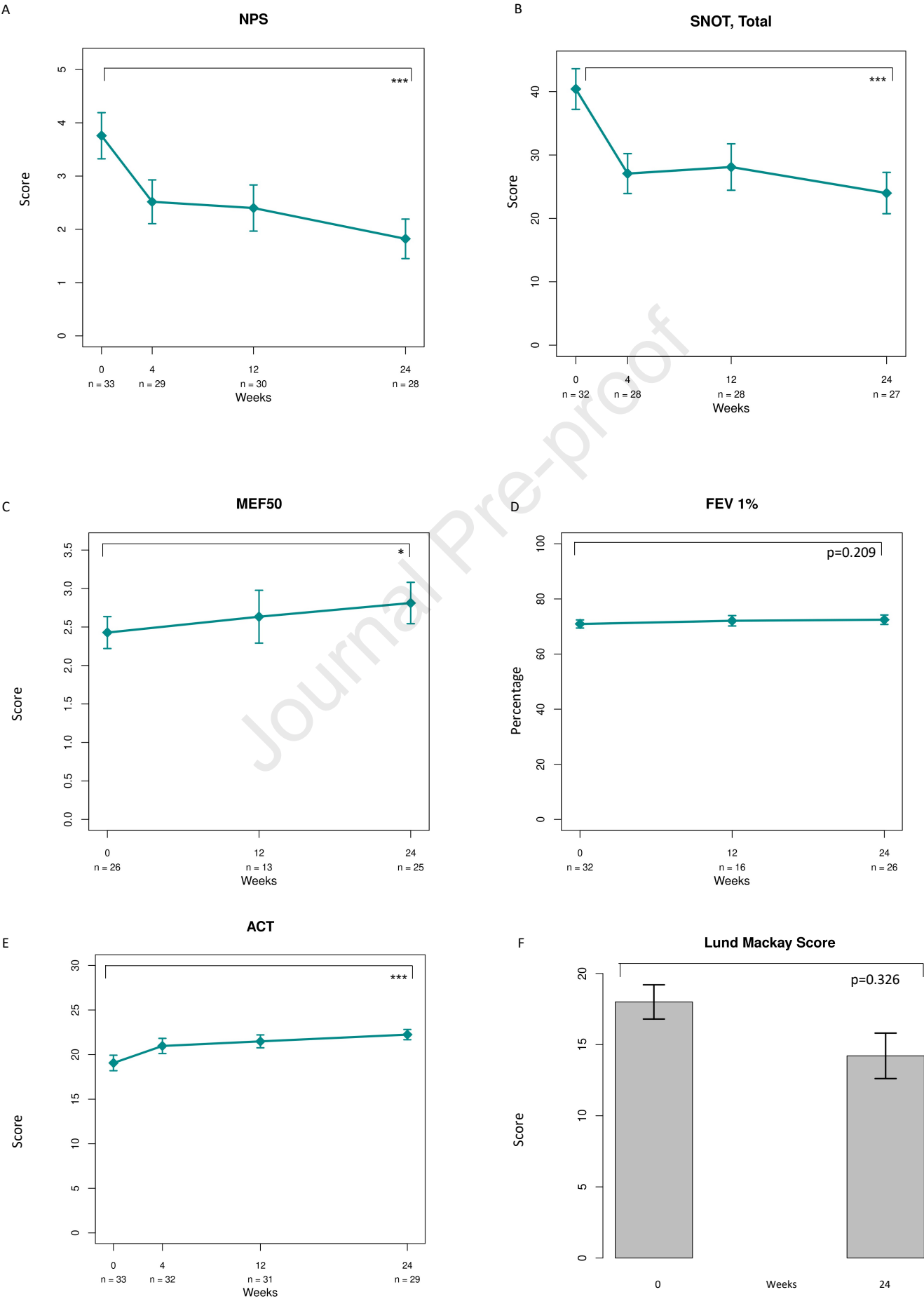


Fig. 2

		Week 24			
		125mg	250mg	500mg	no
Baseline	125mg	3	4	1	7
	250mg	0	4	0	7
	500mg	0	0	0	1
	no	0	0	0	0

Fig. 3



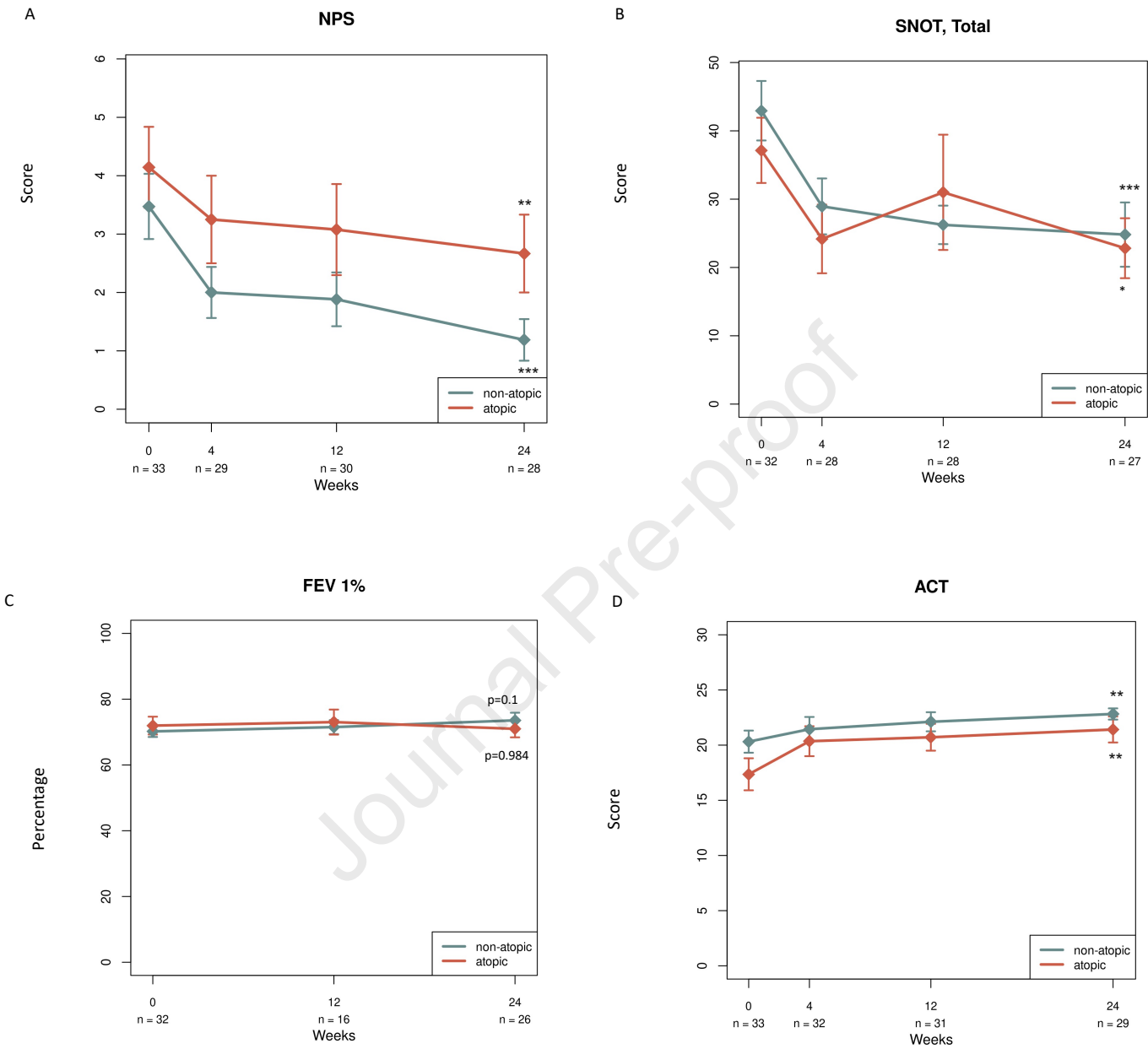


Fig. 5

