

Very rapid improvement of extended nitric oxide parameters, associated with clinical and functional betterment, in patients with chronic rhinosinusitis with nasal polyps (CRSwNP) treated with Dupilumab

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Abstract

Background: Dupilumab, an anti-IL-4 receptor alpha monoclonal antibody, has been recently approved for the treatment of chronic rhinosinusitis with nasal polyps (CRSwNP) and moderate to severe asthma, demonstrating a rapid onset of clinical effects. CRSwNP is characterized by an extended type-2 inflammatory involvement that can be assessed by extended nitric oxide analysis.

Objective: In this study we investigated whether Dupilumab is associated with a rapid improvement in extended nitric oxide parameters, lung function and clinical outcomes in patients with CRSwNP.

Methods: Consecutive patients with CRSwNP and indication to be treated with Dupilumab were evaluated for extended nitric oxide analysis (exhaled, FE_{NO} ; bronchial, Jaw_{NO} and alveolar, $Calv_{NO}$ components; nasal, nNO) and lung function 15 and 30 days after treatment initiation, and for clinical outcomes (nasal polyps score, NPS; quality of life questionnaires; visual analogue scales, VAS, for main symptoms, asthma control test, ACT) after 30 days of treatment initiation.

Results: 33 patients were enrolled. All extended nitric oxide and lung function parameters significantly improved after 15 days of treatment remaining stable at 30 days. NPS, VAS for main CRSwNP symptoms, quality of life questionnaires and ACT significantly improved after 30 days of treatment initiation.

Conclusions: Dupilumab is associated with very rapid improvement in type 2 inflammation in all airway districts and this is associated with improved lung function and clinical parameters in patients with CRSwNP.

Keywords: Chronic rhinosinusitis. Nasal Polyps. Asthma. Dupilumab. Biologics. Nitric oxide. Breath analysis. Lung function

Resumen

Antecedentes: El dupilumab, un anticuerpo monoclonal anti-IL-4 receptor alfa, ha sido aprobado recientemente para el tratamiento de la rinosinusitis crónica con pólipos nasales (CRSwNP) y asma de moderada a grave, demostrando un inicio rápido de los efectos clínicos. La CRSwNP se caracteriza por un infiltrado extenso inflamatorio de tipo 2 que puede evaluarse mediante el análisis de óxido nítrico exhalado extendido.

Objetivos: En este estudio, investigamos si dupilumab se asocia con una mejora rápida en los parámetros de óxido nítrico extendido, la función pulmonar y los resultados clínicos en pacientes con CRSwNP.

Métodos: Se incluyeron pacientes consecutivos con CRSwNP e indicación para ser tratados con dupilumab y fueron evaluados mediante el análisis de óxido nítrico extendido (exhalado, FENO; bronquial, JawNO y alveolar, componentes CalvNO; nasal, nNO) y función pulmonar, 15 y 30 días después del inicio del tratamiento, y en el caso de las variables clínicas (puntuación del tamaño de los pólipos nasales (NPS); cuestionarios de calidad de vida; escalas analógicas visuales (EVA) para los principales síntomas principales, prueba de control del asma (ACT) solo después de 30 días de iniciado el tratamiento.

Resultados: Se incluyeron 33 pacientes. Todos los parámetros del análisis extendido del óxido nítrico y la función pulmonar mejoraron significativamente después de 15 días de tratamiento, permaneciendo estables a los 30 días de tratamiento. El NPS, las EVA para los principales síntomas de CRSwNP, el cuestionario de calidad de vida y el ACT mejoraron

significativamente después de 30 días de inicio del tratamiento.

Conclusiones: En pacientes con CRSwNP, el tratamiento con dupilumab se asocia con una mejoría muy rápida en la inflamación tipo 2 en todos los compartimentos de las vías respiratorias y esto se asocia con una mejor función pulmonar y los parámetros clínicos .

Palabras clave: Rinosinusitis crónica; Pólipos nasales; Asma; dupilumab; fármacos biológicos; Óxido nítrico; análisis del aire exhalado; Función pulmonar.

Introduction

Chronic rhinosinusitis (CRS) is an inflammatory disorder of the nose and the paranasal sinuses that lasts 12 weeks or longer [1] and it is a common condition in most of the world, affecting about 5-16% of the general population [1,2]. In general, CRS presents with nasal obstruction or nasal discharge and/or facial pain/pressure and/or hyposmia/anosmia. In addition to two or more of these symptoms, the diagnosis is confirmed upon the presence of consistent endoscopic and/or CT scan signs [1].

CRS occurs in two distinct phenotypes: CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP); CRSwNP is usually associated with high levels of morbidity and it also has an impact on lower airway disease status [3]. In fact, several studies suggest that CRSwNP is strongly associated with asthma, as the latter is found in 30-70% of CRSwNP patients [4]. Inflammation in the nasal mucosa and in the lower airways are directly related, with a significant correlation between nasal and bronchial inflammatory profiles [4,5].

CRSwNP is more frequently associated with adult-onset asthma rather than childhood-onset, which, on the other hand, is more likely to be linked to CRSsNP [6-8]. Furthermore, CRSwNP is more commonly associated with severe asthma than mild-to-moderate asthma, suggesting that the presence of nasal polyps in asthmatic patients may be a risk factor for asthma severity [4,9].

In Europe and the United States, the most dominant endotype of both CRSwNP and severe asthma is the type 2 inflammation, characterized by elevated levels of type 2 pro-inflammatory cytokines, such as interleukin-4 (IL-4), interleukin-13 (IL-13) and interleukin-5 (IL-5), produced by type 2 pro-inflammatory cells, being mainly T helper 2 cells and group 2 innate lymphoid cells [10,11]. Type 2 inflammation elicited by IL-4 and IL-13 results in the production of immunoglobulin E (IgE) and the increase of IL-5 with concomitant activation and proliferation of eosinophils, leading to mucus production and tissue remodeling consisting in polyp formation, goblet cells hyperplasia and epithelial barrier abnormalities, that account for the symptomatology, persistence and recurrence of CRS [10]. Interestingly, in Asian CRSwNP patients other endotypes (mainly type 1 or type 3, characterized by neutrophilic inflammation) are predominant [12], but there has been an increase in the type 2 endotype in the last 20 years [13], in conjunction with massive industrialization of Asian countries, suggesting that the interaction between genetic and environmental factors is crucial in the development of disease phenotypes and endotypes.

Due to its predominance in both CRSwNP and asthma, type 2 inflammation became a “treatable trait” for both upper and lower airway [14,15], in a precision and personalized medicine perspective [16] including the use of biologic agents targeting pivotal molecules of type 2 inflammation [17,19]. Dupilumab is a fully human IgG4 monoclonal antibody that

blocks IL-4 receptor alpha, the shared receptor component of IL-4 and IL-13, therefore inhibiting the signaling pathways of both these cytokines [19]. Dupilumab proved its efficacy in improving the most relevant outcomes of moderate-to-severe asthma [20,21], and severe uncontrolled CRSwNP [22]; a recently published post hoc analysis of phase 3 trials has demonstrated, in patients affected by moderate-to-severe asthma and severe CRSwNP, that the treatment with Dupilumab provides rapid, significant and clinically meaningful improvements of the most relevant outcomes that are sustained for the duration of the treatment. [23].

Fractional Exhaled Nitric Oxide (FE_{NO}) is an easy, non-invasive and rapid method to assess airway inflammation [24], it reflects type 2 inflammation [25] and it has been shown to be particularly elevated not only in asthmatics but also in patients with CRSwNP, irrespectively of having asthma as comorbidity [26]. Measuring FE_{NO} at different exhaled flow rates gives the possibility to differentiate the nitric oxide production at the bronchial and alveolar level: this is the so-called "extended nitric oxide analysis" [27]; using this approach, together with the measurement of nasal nitric oxide (nNO) [28] we were able to demonstrate that patients with CRSwNP had clear signs of type 2 inflammation at alveolar, bronchial and nasal level, also when asthma is not associated as comorbidity [5].

In this study, we investigated whether dupilumab could induce a very rapid (at 15 and 30 days after treatment initiation) improvement of airway inflammation (assessed by extended nitric oxide analysis), together with improvement in clinical and functional parameters, in patients with severe CRSwNP, with or without associated asthma.

Methods

Study design and patients

All consecutive adult (≥ 18 years of age) patients evaluated by our Allergy or ENT units from March 2021 to January 2022 for severe uncontrolled CRSwNP and for which Dupilumab was prescribed, were enrolled in the study. According to the Italian drug agency (AIFA), patients with severe uncontrolled CRSwNP are eligible to be treated with Dupilumab when, despite chronic intranasal corticosteroid therapy and evidence of failure or previous systemic corticosteroid treatment (≥ 2 courses in the previous year) and/or endoscopic sinus surgery (relapse or complications), met the following criteria: NPS ≥ 5 and/or SNOT-22 ≥ 50 .

All patients received Dupilumab 300 mg subcutaneously every 15 days, apart from those with concomitant severe asthma that received a loading dose of 600 mg followed by 300 mg every 15 days.

Exclusion criteria were recent upper or lower airway infections and the intake of oral or systemic corticosteroid therapy in the 4 weeks preceding clinical evaluation.

The study was approved by our institutional Ethic Committee (Ethic Approval nr. 59/20). An informed consent was obtained from all enrolled participants. The study has been performed in accordance with the ethical standards laid down in the Declaration of Helsinki and its later amendments.

Demographic and clinical data have been collected from all subjects at the baseline visit.

Visual Analogue Scale (VAS) about nasal obstruction, hyposmia, hypogeusia, post-nasal drip, facial pain, headache, anterior rhinorrhea and sneezing [29], Sinonasal Outcome Test 22 (SNOT-22) [30], Nasal Polyposis Quality of Life questionnaire (NPQ) [31], Nasal Obstruction and Septoplasty Effectiveness Scale (NOSE) [32], Asthma Control Test (ACT) [33] were collected at baseline and 30 days after Dupilumab initiation. The images of the last sinus CT scan performed (in the previous 6 months) were viewed and the Lund-MacKay score (LMK) [34] was calculated.

All patients underwent an ENT evaluation including nasal endoscopy at baseline and 30 days after Dupilumab initiation, and Nasal Polyp Score (NPS) [35] was collected.

Patients were evaluated by extended nitric oxide analysis and lung function assessment at the baseline visit, after 15 days and a month after the start of treatment with Dupilumab.

Airway inflammation and lung function assessment

All the subjects underwent assessment of extended nitric oxide analysis, including FE_{NO} , nitric oxide alveolar concentration ($Calv_{NO}$) and bronchial output (Jaw_{NO}), and nNO measurement, at baseline, and 15 and 30 days after the initiation of Dupilumab therapy. FE_{NO} was measured at exhaled flow rates of 50, 100, 150 and 350 ml/sec with an electrochemical analyzer (FENO+, MediSoft, Belgium), following the most recent recommendations [24,36]. Jaw_{NO} and $Calv_{NO}$ were calculated using the linear model proposed by Tsoukias and George [37] using the three flow rates of at least 100 ml/sec, and corrected according to Condorelli et al. [38]. nNO was assessed by the same electrochemical analyzer

by asking the subjects to insert a nasal olive into one nostril and to inhale to total lung capacity for more than 2-3 seconds through open mouth, after which they closed their mouths and held their breath while nitric oxide was continuously measured at an aspiration flow rate of 350 ml/sec. nNO was assessed in both nostrils and the highest value was recorded, to limit biases due to anatomical faults.

At baseline, 15 and 30 days after Dupilumab treatment initiation, also lung function was performed through a portable spirometer (CareFusion®, San Diego, CA, USA) in all enrolled patients, regardless of the presence or not of asthma as known comorbidity, and the following parameters were collected: Forced Expiratory Volume in the first second (FEV₁) as absolute value and as percent of predicted value, Forced Vital Capacity (FVC) percent of predicted value, Tiffeneau index (FEV₁/FVC), and Forced Expiratory Flow at 25–75% of forced vital capacity (FEF₂₅₋₇₅) percent of predicted value. Patients received the indication to fast for 12 hours before airway inflammation lung function assessments, to stop any intranasal or oral corticosteroid treatment at least 10 days before the enrollment and to stop eventually maintenance asthma treatment 48 hours before the measures.

Statistical analysis

Statistical analysis was performed using SPSS 20.0 software (SPSS, Chicago, IL, USA). The Kolmogorov-Smirnov test was used to evaluate the normality of distribution of each continuous variable, and the Paired Student t-test test was used to compare continuous variables. Values were presented as mean ± Standard deviation.

A p-value of <0.05 was considered statistically significant.

Results

A total of 33 patients were enrolled: mean age was 54.2 ± 11.2 years, 20 (60.6%) were females, 20 (60.6%) were atopic, 29 (87.9%) had asthma as a comorbidity (10, 30.3% of which with severe asthma), and 20 (60.6%) had Non-Steroidal Anti Inflammatory Drugs (NSAIDs) hypersensitivity and therefore affected by NSAIDs-Exacerbated Respiratory Disease (N-ERD) [36]. All patients were no smokers (45.4% ex-smokers, all with a time since quitting smoking of over 5 years). Twenty-six patients (78.8%) had a clinical history of at least one previous surgery for CRSwNP, with a mean of 3.3 ± 0.8 surgical interventions per patient. Mean peripheral eosinophil count according to the latest available complete blood count was 475.0 ± 252.7 cells/mcl. Mean baseline NPS, NOSE score, SNOT-22, NPQ and LMK were 6.5 ± 1.4 , 14.5 ± 5.3 , 66.8 ± 15.1 , 73.5 ± 25.9 , and 20.1 ± 3.3 , respectively.

Mean baseline FE_{NO} , Jaw_{NO} , $Calv_{NO}$ and nNO were 40.5 ± 30.6 ppb, 2.25 ± 1.73 nl/sec, 8.7 ± 4.6 ppb and 455.8 ± 360.4 ppb, respectively.

No difference was found for any baseline parameter comparing ex-smokers and never smokers, patients with and without asthma, or severe asthma, or those with and without previous history of surgery for CRSwNP.

All airway inflammatory parameters derived by the extended nitric oxide analysis (FE_{NO} , Jaw_{NO} , $Calv_{NO}$, nNO) and lung function parameters (FEV_1 , FVC, FEV_1/FVC , FEF₂₅₋₇₅) significantly improved at 15 days after Dupilumab treatment initiation, while no further improvement was seen between 15 and 30 days of treatment (Table I and Figure 1). FEV_1 as

absolute value improved to a mean of 260 ml after 15 days ($p < 0.001$) and of further 100 ml after day 30 ($p = 0.083$) (Table I).

Statistically significant improvements in NPS, NOSE score, SNOT-22, NPQ, VAS about nasal obstruction, hyposmia, hypogeusia, post-nasal drip, facial pain, headache, and anterior rhinorrhea, and ACT, were found comparing baseline values to those obtained after 30 days of Dupilumab treatment (Table II).

Nine patients (27.3%; seven out of nine were asthmatics, two of which with severe asthma) had baseline FE_{NO} lower than 20 ppb (mean: 15.1 ± 4.4 ppb); in this subgroup of patients, no statistically significant improvement was seen in any extended nitric oxide analysis nor in lung function parameters at 15 and 30 days of treatment, while after 30 days of treatment significant improvement was seen for NPS (6.43 ± 1.72 vs 3.57 ± 2.57 , $p = 0.04$), NOSE score (15.7 ± 3.5 vs 6.7 ± 3.5 , $p < 0.001$), SNOT-22 (71.4 ± 12.1 vs 34.6 ± 19.1 , $p < 0.001$), NPQ (67.8 ± 28.7 vs 36.7 ± 22.1 , $p = 0.001$), and VAS for nasal obstruction (8.1 ± 1.5 vs 2.8 ± 1.5 , $p < 0.001$), hyposmia (9.9 ± 0.3 vs 3.1 ± 3.0 , $p < 0.001$), hypogeusia (7.4 ± 4.0 vs 2.7 ± 2.7 , $p = 0.007$), post-nasal drip (6.2 ± 3.3 vs 2.4 ± 2.0 , $p = 0.03$), facial pain (6.8 ± 3.2 vs 2.9 ± 3.0 , $p = 0.03$). Moreover, these 9 patients did not significantly differ in any baseline parameters, including blood eosinophils or smoking status (ex-smokers vs never smokers), with patients having FE_{NO} greater than 20 ppb.

Discussion

The results of our study showed that Dupilumab therapy in patients with CRSwNP, with or without associated asthma, is associated with a very rapid reduction of airway inflammation in all considered districts (nasal, bronchial, alveolar), associated with an

equally rapid improvement in lung function parameters, and reduction of the extent, symptoms and impact on patients' quality of life of CRSwNP.

These results indirectly confirm that type 2 inflammation in CRSwNP extends to all respiratory districts, from upper to lower airways, as we previously described [5], and that the associated nitric oxide production is IL-13 dependent through the activation of the inducible isoform of nitric oxide synthase [40], as the blockade of IL-4 receptor alpha and its consequent inhibition of the IL-13 pathway was associated with an extremely rapid reduction in the production of nitric oxide in the airways.

According to data from the phase III studies of Dupilumab for moderate to severe asthma, high levels of FE_{NO} have been associated with a better clinical response to the drug [20,41]. In our study, mean FE_{NO} values were approximately 40 ppb, significantly higher than the 20 ppb cut-off used in phase III trials to stratify the level of clinical response [41]; in the 9 patients from our study with FE_{NO} lower than 20 ppb, we did not find a significant improvement in the parameters of extended nitric oxide analysis or lung function, while all the outcomes strictly related to CRSwNP significantly improved, suggesting that, opposite to what happens for moderate to severe asthma, baseline FE_{NO} and its extended parameters cannot be used as a predictive biomarker of response for CRSwNP outcomes.

It is well known that FE_{NO} is the first parameter to improve after the establishment of corticosteroid therapy in asthmatic patients, even before symptoms and lung function [42]. In our study, this finding is confirmed also for Dupilumab, but surprisingly also lung function improved significantly after a single drug administration, suggesting that bronchial obstruction in patients with CRSwNP and asthma is strictly dependent on type

2 airway inflammation. Notably, FEV1 significantly improved of about 260 ml fifteen days after Dupilumab therapy initiation, and an additional 100 ml was gained after a further 15 days of therapy, albeit the level of statistical significance was not reached (probably due to the small number of patients treated), being far superior to the commonly considered minimal clinically important difference of 100 ml [43,44]. Furthermore, FVC also significantly improved already at 15 days of therapy, suggesting the presence of air trapping [45] responsive to Dupilumab therapy, probably due to the presence of a relevant component of small airway dysfunction [46] associated with type 2 inflammation.

In our patients, 15 days after starting Dupilumab therapy, nNO was also significantly improved; this is at least partly surprising since the reduction of nNO in CRSwNP is supposed to depend on both the damage of the ciliated epithelium of the paranasal sinuses, and the obstruction of sinus ostia that reduces the passage of high levels of nitric oxide from the sinuses into the nasal cavity [28].

In conclusion, taking all the results together, our study is in line with the finding of rapid improvement in CRSwNP outcomes and lung function parameters observed in patients treated with Dupilumab in clinical trials [23, 47], but adds information on the extremely rapid onset of action of the drug on type 2 inflammatory component of the airways, both upper and lower. Furthermore, the results suggest that extended nitric oxide analysis, including measurement of nNO, may be an early marker of the rapid response of Dupilumab in patients with CRSwNP, to define a potential role of airway oxide measurement as a guide to biological therapies that act directly on type 2 inflammation [48].

A potential limitation of this study is the relatively low number of patients evaluated, however, the results obtained are highly significant and therefore we believe that they can be a starting point for developing larger studies, preferably in real-life and registry-based [49,50], to explore whether the rapid reduction of FE_{NO} (and its extended analysis) is present only in patients responsive to Dupilumab therapy, thus becoming a reliable, easy, non-invasive and relatively inexpensive method for monitoring the response to Dupilumab in patients with CRSwNP. Finally, studies that evaluate a longer follow-up of inflammatory biomarkers and clinical outcomes in real-life, will allow to confirm or not the persistence of the benefit obtained so quickly and described in our study.

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Conflict of interest

Giovanni Paoletti received fees for speaker activities and/or advisory boards participation from Novartis, Lusofarma, outside the submitted work.

Luca Malvezzi received fees for speaker activities and/or advisory boards participation from Sanofi, AstraZeneca, Novartis, outside of the submitted work.

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Giorgio Walter Canonica received fees for speaker activities and advisory boards participation from Menarini, Alk Abello', Anallergo Boehringer Ingelheim, Chiesi, Circassia, Genentech, Guidotti Malesci, GSK, Hal Allergy, Meda, Merck, Merck Sharp and Dome, Novartis, Recordati-InnuvaPharma, Roche, Sanofi, Stallergenes, UCB Pharma, Uriach Pharma, Teva, Astrazeneca, Thermo Fisher, Valeas, Vibor Pharma, outside the submitted work.

Enrico Heffler received fees for speaker activities and/or advisory boards participation from Sanofi, Regeneron, GSK, Astrazeneca, Novartis, Circassia, Stallergenes-Greer, Nestlè Purina, Chiesi, outside the submitted work.

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TABLES

Table I – Change in extended nitric oxide and lung function parameters 15 and 30 days after the initiation of Dupilumab treatment.

FE_{NO}: Fractional Exhaled Nitric Oxide; Jaw_{NO}: bronchial output of nitric oxide; Calv_{NO}: alveolar concentration of nitric oxide; nNO: nasal nitric oxide; FEV₁: Forced Expiratory Volume in the 1st second; FVC: Forced Vital Capacity; FEF₂₅₋₇₅: Forced Expiratory Flow at 25–75% of forced vital capacity.

	Baseline	After 15 days	p-value (Baseline vs After 15 days)	After 30 days	p-value (15 days vs 30 days)
FE _{NO} , ppb (mean ± SD)	40.5 ± 30.6	26.6 ± 23.3	0.001	25.5 ± 16.4	0.749
Jaw _{NO} , nl/sec (mean ± SD)	2.25 ± 1.73	1.33 ± 1.37	0.014	1.48 ± 1.26	0.412
Calv _{NO} , ppb (mean ± SD)	8.7 ± 4.6	5.3 ± 5.3	0.026	5.8 ± 5.0	0.874
nNO, ppb (mean ± SD)	455.8 ± 360.4	656.5 ± 329.8	0.020	677.0 ± 343.0	0.759
FEV ₁ , liters (mean ± SD)	2.60 ± 0.90	2.86 ± 0.79	<0.001	2.96 ± 0.74	0.083
FEV ₁ % (mean ± SD)	82.4 ± 21.1	93.1 ± 19.1	<0.001	95.3 ± 17.0	0.635
FVC% (mean ± SD)	97.4 ± 17.1	104.0 ± 17.1	0.003	102.7 ± 24.9	0.682
FEV ₁ /FVC (mean ± SD)	69.2 ± 10.7	73.3 ± 9.7	0.002	74.2 ± 16.8	0.737
FEF ₂₅₋₇₅ % (mean ± SD)	52.0 ± 24.5	64.2 ± 22.2	<0.001	63.3 ± 23.4	0.427

Table II – Change of clinical outcomes after 30 days of Dupilumab treatment.

ACT: Asthma Control Test; NPS: Nasal Polyps Score; NOSE: Nasal Obstruction and Septoplasty Effectiveness Scale; SNOT-22: Sinonasal Outcome Test 22; NPQ: Nasal Polyposis Quality of Life questionnaire; VAS: Visual Analogue Scale.

	Baseline	After 30 days	p-value (Baseline vs 30 days)
ACT (mean ± SD)	16.6 ± 4.2	20.9 ± 3.2	<0.001
NPS (mean ± SD)	6.5 ± 1.4	4.3 ± 2.1	<0.001
NOSE score (mean ± SD)	14.5 ± 5.3	8.1 ± 4.9	<0.001
SNOT-22 (mean ± SD)	66.8 ± 15.1	38.4 ± 18.4	<0.001
NPQ (mean ± SD)	73.5 ± 25.9	40.0 ± 22.2	<0.001
VAS nasal obstruction (mean ± SD)	7.8 ± 1.9	3.8 ± 2.4	<0.001
VAS hyposmia (mean ± SD)	9.8 ± 0.8	5.6 ± 3.5	<0.001
VAS hypogeusia (mean ± SD)	7.5 ± 3.2	4.4 ± 3.3	<0.001
VAS post-nasal drip (mean ± SD)	7.1 ± 2.8	3.0 ± 2.8	<0.001
VAS facial pain (mean ± SD)	5.5 ± 3.7	3.1 ± 3.4	<0.001
VAS headache (mean ± SD)	2.7 ± 3.8	2.8 ± 3.2	0.814
VAS anterior rhinorrhea (mean ± SD)	6.5 ± 3.0	3.2 ± 2.8	<0.001
VAS sneezing (mean ± SD)	3.3 ± 3.3	2.3 ± 2.3	0.155

Figure 1 – Fractional Exhaled Nitric Oxide (FENO), its bronchial (JawNO) and alveolar (CalvNO) components, nasal Nitric Oxide (nNO), and lung function parameters, before and 15 and 30 days after Dupilumab initiation.

