ORIGINAL ARTICLE

Very Rapid Improvement in Extended Nitric Oxide Parameters Is Associated With Clinical and Functional Improvement in Patients With Chronic Rhinosinusitis With Nasal Polyps Treated With Dupilumab

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J Investig Allergol Clin Immunol 2023; Vol. 33(6): 457-463
doi: 10.18176/jiaci.0851

Abstract

Background: Dupilumab, an anti–IL-4 receptor α monoclonal antibody, was recently approved for the treatment of chronic rhinosinusitis with nasal polyps (CRSwNP) and moderate-to-severe asthma. Onset of its clinical effects is rapid. CRSwNP is characterized by extended type 2 inflammatory involvement that can be assessed using extended nitric oxide analysis.
Objectives: We investigated whether dupilumab was 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 an indication for dupilumab were evaluated for extended nitric oxide analysis (exhaled, FeNO; bronchial, JawNO; alveolar, CalvNO; nasal, nNO) and lung function 15 and 30 days after initiation of treatment and for clinical outcomes (nasal polyps score [NPS], quality of life questionnaires, visual analog scale [VAS] for the main symptoms, and the Asthma Control Test [ACT]) 30 days after initiation of treatment.
Results: We enrolled 33 patients. All extended nitric oxide and lung function parameters improved significantly after 15 days of treatment, remaining stable at 30 days. Scores on the NPS, VAS for the main CRSwNP symptoms, quality of life questionnaires, and the ACT improved significantly 30 days after initiation of treatment.
Conclusions: Dupilumab is associated with very rapid improvement in type 2 inflammation in all airway areas. This is associated with improved lung function and clinical parameters in patients with CRSwNP.

Key words: 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.

Summary box

- **What do we know about this topic?**

  Dupilumab proved to be effective in patients with moderate-to-severe asthma and in those affected by chronic rhinosinusitis with nasal polyps (CRSwNP).

- **How does this study impact our current understanding and/or clinical management of this topic?**

  We showed that administering dupilumab for CRSwNP leads to a very rapid improvement in airway inflammation (at the nasal, alveolar, and bronchial levels), together with a rapid improvement in polyps, symptoms, and quality of life, suggesting extended nitric oxide analysis as an early marker of response to dupilumab.

Introduction

Chronic rhinosinusitis (CRS) is an inflammatory disorder of the nose and the paranasal sinuses that lasts 12 weeks or longer [1]. 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 2 or more of these symptoms, the diagnosis is confirmed upon the presence of consistent signs on endoscopy, computed tomography scan, or both [1].

CRS occurs in 2 distinct phenotypes: CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP). CRSwNP is usually associated with high morbidity and has an impact on lower airway disease [3]. In fact, several studies suggest that CRSwNP is strongly associated with asthma, which is found in 30%-70% of CRSwNP patients [4]. Inflammation in the nasal mucosa and inflammation 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 than with childhood-onset asthma, 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 asthma patients may be a risk factor for severity of asthma [4,9].

In Europe and the United States, type 2 inflammation is the most dominant endotype of both CRSwNP and severe asthma. It is characterized by elevated levels of type 2 proinflammatory cytokines, such as interleukin (IL) 4, IL-13, and IL-5, which are produced by type 2 proinflammatory cells, mainly type 2 helper T cells and group 2 innate lymphoid cells [10,11]. Type 2 inflammation elicited by the effect of IL-4 and IL-13 on production of immunoglobulin E (IgE) and an increase in IL-5, with concomitant activation and proliferation of eosinophils, leads to mucus production and tissue remodeling consisting in polyp formation, goblet cell hyperplasia, and epithelial barrier abnormalities, which account for the symptoms, persistence, and recurrence of CRS [10]. Interestingly, in Asian CRSwNP patients, other endotypes are predominant (mainly type 1 and type 3, characterized by neutrophilic inflammation) [12], although the type 2 endotype has become more frequent in the last 20 years [13]. These have been recorded 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.

Given its predominance in both CRSwNP and asthma, type 2 inflammation became a "treatable trait" for both upper and lower airway disease [14,15] from a precision medicine 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 α, the shared receptor component of IL-4 and IL-13, thus inhibiting the signaling pathways of both cytokines [19]. Dupilumab proved its efficacy in improving the most relevant outcomes of moderate-to-severe asthma [20,21] and severe uncontrolled CRSwNP [22]. In a recent post hoc analysis of phase 3 trials including patients affected by moderate-to-severe asthma and severe CRSwNP, the authors demonstrated that treatment with dupilumab provides rapid, significant, and clinically meaningful improvements in the most relevant outcomes, which are sustained for the duration of treatment [23].

Fractional exhaled nitric oxide (FeNO) is an easy, noninvasive, and rapid method for assessment of airway inflammation [24]. It reflects type 2 inflammation [25] and has been shown to be particularly elevated not only in asthma patients, but also in patients with CRSwNP, irrespective of whether asthma is a comorbidity [26]. Measuring FeNO at different exhaled flow rates enables us to differentiate nitric oxide production at the bronchial and alveolar levels. This approach is known as extended nitric oxide analysis [27],

and by combining it 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 the alveolar, bronchial, and nasal levels and when asthma is not a comorbidity [5].

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

Methods

Study Design and Patients

The study population comprised all consecutive adult patients (≥18 years) evaluated by our Allergy Department or ENT Department from March 2021 to January 2022 for severe uncontrolled CRSwNP and for which dupilumab was prescribed. 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), they meet the following criteria: nasal polyp score (NPS) ≥5 and/or Sinonasal Outcome Test (SNOT) 22 score ≥50.

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

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

The study was approved by the local ethics committee (Approval no. 59/20). Signed informed consent was obtained from all enrolled participants. The study was performed in accordance with the ethical standards laid down in the Declaration of Helsinki and its subsequent revisions.

Demographic and clinical data were collected from all patients at baseline.

Data were collected at baseline and 30 days after initiation of dupilumab using a visual analog scale (VAS) for nasal obstruction, hyposmia, hypogeusia, postnasal drip, facial pain, headache, anterior rhinorrhea, and sneezing [29]. We also recorded the SNOT-22 score [30], Nasal Polyposis Quality of Life (NPQ) questionnaire score [31], Nasal Obstruction and Septoplasty Effectiveness Scale (NOSE) score [32], and Asthma Control Test (ACT) score [33]. The images of the last sinus CT scan performed (in the previous 6 months) were viewed, and the Lund-MacKay score [34] was calculated.

All patients underwent an ENT evaluation including nasal endoscopy at baseline and 30 days after initiation of dupilumab, and the NPS [35] was collected.

Patients were evaluated using extended nitric oxide analysis and lung function assessment at the baseline visit, 15 days, and 1 month after initiation of dupilumab.

Airway Inflammation and Lung Function Assessment

All patients underwent assessment of extended nitric oxide analysis, including FeNO, nitric oxide alveolar concentration (CalvNO), bronchial output (JawNO), and nNO measurement at baseline and 15 and 30 days after the initiation of dupilumab. FeNO was measured at exhaled flow rates of 50, 100, 150, and 350 mL/sec using an electrochemical analyzer (FEN0+, MediSoft), following the most recent recommendations [24,36]. JawNO and CalvNO were calculated using the linear model proposed by Tsoukias and George [37] based on 3 flow rates of at least 100 mL/sec and corrected according to Condorelli et al [38]. nNO was assessed using the same electrochemical analyzer by asking patients to insert a nasal olive into one nostril and to inhale to total lung capacity for more than 2-3 seconds through an 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 and 15 and 30 days after initiation of treatment, lung function was assessed using a portable spirometer (CareFusion), regardless of the presence or absence of asthma as a known comorbidity, and a series of parameters were collected, as follows: forced expiratory volume in the first second (FEV_1, absolute value and percent predicted), forced vital capacity (FVC, percent predicted), Tiffeneau index (FEV_1/FVC), and forced expiratory flow at 25%-75% of forced vital capacity (FEF_{25-75}, percent predicted). Patients had to fast for 12 hours before assessments of airway inflammation and lung function, stop any intranasal or oral corticosteroid treatment at least 10 days before enrollment, and stop maintenance asthma treatment 48 hours before the measurements.

Statistical Analysis

The statistical analysis was performed using SPSS for Windows, Version 20.0 (IBM Corp.). The Kolmogorov-Smirnov test was used to evaluate the normality of the distribution of each continuous variable, and the paired *t* test was used to compare continuous variables. Values were presented as mean (SD). A P value <.05 was considered statistically significant.

Results

A total of 33 patients were enrolled. Mean age was 54.2 (11.2) years. Twenty patients (60.6%) were female, 20 (60.6%) were atopic, 29 (87.9%) had asthma as a comorbidity (10 [30.3%] with severe asthma), and 20 (60.6%) had experienced hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs) and were therefore affected by NSAIDs-exacerbated respiratory disease (N-ERD) [36]. All patients were nonsmokers (45.4% ex-smokers, all of whom had stopped over 5 years previously). Twenty-six patients (78.8%) had a clinical history of at least 1 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/µL. The mean baseline NPS, NOSE, SNOT-22, NPQ, and Lund-MacKay scores 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 FeNO, JawNO, CalvNO, 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 used to compare ex-smokers and never smokers, patients with and without asthma or with severe asthma, or those with and without a previous history of surgery for CRSwNP.

All airway inflammatory parameters derived from the extended nitric oxide analysis (FeNO, JawNO, CalvNO, nNO) and lung function parameters (FEV_1, FVC, FEV_1/FVC, FEF_{25-75}) improved significantly at 15 days after initiation of dupilumab, while no further improvement was seen between 15 and 30 days of treatment (Table 1 and Figure). FEV_1 as an absolute value improved to a mean of 260 mL after 15 days (P<.001) and by a further 100 mL after day 30 (P=.083) (Table 1).

When baseline values were compared with those obtained after 30 days of dupilumab, statistically significant improvements were recorded for the NPS, NOSE, SNOT-22, NPQ, and VAS (nasal obstruction) scores, as well as for hyposmia, hypogeusia, postnasal drip, facial pain, headache, anterior rhinorrhea, and ACT score (Table 2).

Nine patients (27.3%) had a mean baseline FeNO lower than 20 ppb (15.1 [4.4] ppb). Seven of the 9 patients had asthma (2 with severe asthma). In this subgroup of patients, no

Table 1. Change in Extended Nitric Oxide and Lung Function Parameters 15 and 30 Days After Initiation of Dupilumab.[a]

	Baseline	After 15 d	*P* Value (baseline vs after 15 d)	After 30 d	*P* Value (15 d vs 30 d)
FeNO, ppb	40.5 (30.6)	26.6 (23.3)	.001	25.5 (16.4)	.749
JawNO, nL/sec	2.25 (1.73)	1.33 (1.37)	.014	1.48 (1.26)	.412
CalvNO, ppb	8.7 (4.6)	5.3 (5.3)	.026	5.8 (5.0)	.874
nNO, ppb	455.8 (360.4)	656.5 (329.8)	.020	677.0 (343.0)	.759
FEV_1, L	2.60 (0.90)	2.86 (0.79)	<.001	2.96 (0.74)	.083
FEV_1, %	82.4 (21.1)	93.1 (19.1)	.001	95.3 (17.0)	.635
FVC, %	97.4 (17.1)	104.0 (17.1)	.003	102.7 (24.9)	.682
FEV_1/FVC	69.2 (10.7)	73.3 (9.7)	.002	74.2(16.8)	.737
FEF_{25-75}, %	52.0 (24.5)	64.2 (22.2)	<.001	63.3 (23.4)	.427

Abbreviations: FeNO, fractional exhaled nitric oxide; JawNO, bronchial output of nitric oxide; CalvNO, alveolar concentration of nitric oxide; nNO, nasal nitric oxide; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; FEF_{25-75}, forced expiratory flow at 25%-75% of forced vital capacity.
[a]Values shown as mean (SD).

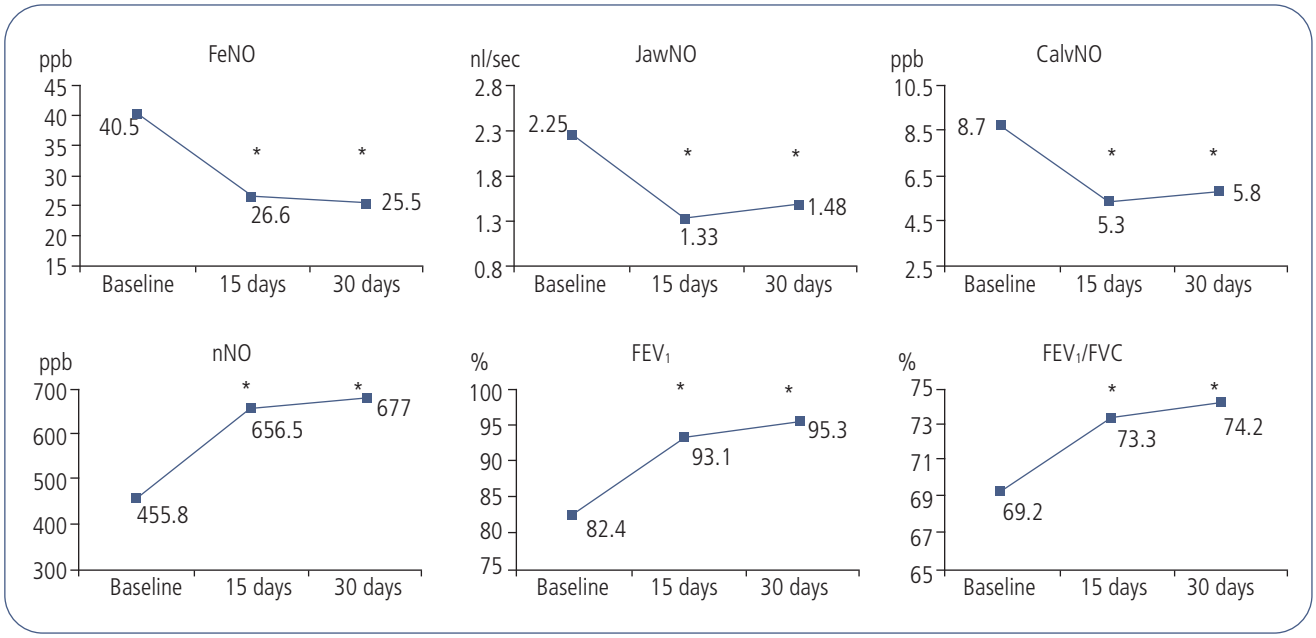

Figure. Fractional exhaled nitric oxide (FeNO), its bronchial component (JawNO) and alveolar component (CalvNO), nasal nitric oxide (nNO), and lung function parameters before and 15 and 30 days after initiation of dupilumab.

Table 2. Change in Clinical Outcomes After 30 Days of Dupilumab Treatment.

	Baseline	After 30 d	*P* Value (baseline vs 30 d)
ACT	16.6 (4.2)	20.9 (3.2)	<.001
NPS	6.5 (1.4)	4.3 (2.1)	<.001
NOSE score	14.5 (5.3)	8.1 (4.9)	<.001
SNOT-22	66.8 (15.1)	38.4 (18.4)	<.001
NPQ	73.5 (25.9)	40.0 (22.2)	<.001
VAS nasal obstruction	7.8 (1.9)	3.8 (2.4)	<.001
VAS hyposmia	9.8 (0.8)	5.6 (3.5)	<.001
VAS hypogeusia	7.5 (3.2)	4.4 (3.3)	<.001
VAS post-nasal drip	7.1 (2.8)	3.0 (2.8)	<.001
VAS facial pain	5.5 (3.7)	3.1 (3.4)	<.001
VAS headache	2.7 (3.8)	2.8 (3.2)	.814
VAS anterior rhinorrhea	6.5 (3.0)	3.2 (2.8)	<.001
VAS sneezing	3.3 (3.3)	2.3 (2.3)	.155

Abbreviations: 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 analog scale.
[a]Values shown as mean (SD).

statistically significant improvement was seen in any extended nitric oxide analysis or in lung function parameters at 15 and 30 days of treatment, while after 30 days of treatment, a significant improvement was seen in the NPS (6.43 [1.72] vs 3.57 [2.57], *P*=.04), NOSE (15.7 [3.5] vs 6.7 [3.5], *P*<.001), SNOT-22 (71.4 [12.1] vs 34.6 [19.1], *P*<.001), NPQ (67.8 [28.7] vs 36.7 [22.1], *P*=.001), and VAS (nasal obstruction) (8.1 [1.5] vs 2.8 [1.5], *P*<.001). A significant improvement was also recorded for hyposmia (9.9 [0.3] vs 3.1 [3.0], *P*<.001), hypogeusia (7.4 [4.0] vs 2.7 [2.7], *P*=.007), postnasal drip (6.2 [3.3] vs 2.4 [2.0], *P*=.03), and facial pain (6.8 [3.2] vs 2.9 [3.0], *P*=.03). Moreover, these 9 patients did not differ significantly from patients with FeNO greater than 20 ppb in any baseline parameters, including blood eosinophils or smoking status (ex-smokers vs never smokers).

Discussion

The results of our study showed that treatment of CRSwNP with dupilumab in patients with or without associated asthma is associated with a very rapid reduction in airway inflammation at all levels (nasal, bronchial, alveolar), with an equally rapid improvement in lung function parameters, and a reduction in the extent of the disease, symptoms, and impact on quality of life.

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

According to data from the phase 3 studies of dupilumab for moderate-to-severe asthma, high levels of FeNO have been associated with a better clinical response to the drug [20,41]. In our study, mean FeNO values were approximately 40 ppb, ie, significantly higher than the 20-ppb cut-off used in phase 3 trials to stratify the level of clinical response [41]. In the 9 patients with FeNO 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 improved significantly, suggesting that, in contrast to what happens in moderate-to-severe asthma, baseline FeNO and its extended parameters cannot be used as a predictive biomarker of response for CRSwNP outcomes.

It is well known that FeNO is the first parameter to improve after initiation of corticosteroid therapy in asthma patients, even before symptoms and lung function [42]. In our study, this finding was also confirmed for dupilumab, although, surprisingly, lung function improved significantly after administration of a single drug, suggesting that bronchial obstruction in patients with CRSwNP and asthma is strictly dependent on type 2 airway inflammation. Notably, FEV_1 improved significantly to a mean of 260 mL at 15 days after initiation of dupilumab, and an additional 100 mL was gained after a further 15 days of therapy, although the difference was not statistically significant (probably owing to the small number of patients treated). The level recorded was far superior to the commonly considered minimal clinically important difference of 100 mL [43,44]. FVC also improved significantly as early as at 15 days of therapy, suggesting the presence of air trapping [45] that responded to dupilumab, probably owing to the presence of a relevant component of small airway dysfunction [46] associated with type 2 inflammation.

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

In conclusion, taken together, our results are in line with the finding of rapid improvement in CRSwNP outcomes and lung function parameters in patients treated with dupilumab in clinical trials [23,47]. However, we add information on the extremely rapid onset of action of the drug in the type 2 inflammatory component of both the upper and the lower airways. Furthermore, the results suggest that extended nitric oxide analysis, including measurement of nNO, may be an early marker of the rapid response to dupilumab observed in patients with CRSwNP, making it possible to define a potential role for 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, leading us to believe that they can be a starting point for larger studies—real-life and registry-

based [49,50]—to explore whether the rapid reduction in FeNO and its extended analysis apply only to patients who respond to dupilumab, thus making it a reliable, easy, noninvasive, 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 enable us to confirm or reject the persistence of the benefit obtained so quickly and described in our study.

Acknowledgments

The authors would like to thank Ms Laura Nasca and Ms Lina Spinello for nursing support and Ms Melissa Sansonna for her administrative and organizational work.

Funding

This work was supported by an unconditional grant from Chiesi Italia.

Conflicts of Interest

Giovanni Paoletti has received fees for speaking and/or advisory board participation from Novartis and Lusofarma outside the submitted work.

Luca Malvezzi has received fees for speaking and/or advisory board participation from Sanofi, AstraZeneca, and Novartis outside the submitted work.

Francesca Puggioni has received fees for speaking and/or advisory board participation from AstraZeneca, Sanofi, GSK, Menarini, Chiesi, Mundipharma, Valeas, Alk Abelló, Allergy Therapeutics, Boehringer Ingelheim, and Grifols outside the submitted work.

Giorgio Walter Canonica has received fees for speaking and advisory board participation from Menarini, Alk Abelló, 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, and Vibor Pharma outside the submitted work.

Enrico Heffler has received fees for speaking and/or advisory board participation from Sanofi, Regeneron, GSK, AstraZeneca, Novartis, Circassia, Stallergenes-Greer, Nestlè Purina, and Chiesi outside the submitted work.

The remaining authors declare that they have no conflicts of interest.

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Manuscript received April 30, 2022; accepted for publication August 3, 2022.

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