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Long-term effects of dupilumab on chronic rhinosinusitis with nasal polyps: A step towards clinical remission

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ABSTRACT

Background and objectives: Clinical remission, defined as the absence of disease activity and symptoms, is an emerging goal in the management of chronic rhinosinusitis with nasal polyps (CRSwNP). This study aimed to evaluate the long-term effects of dupilumab on patients with CRSwNP, with or without asthma, and explore the potential for achieving clinical remission.

Methods: A two-year prospective study was conducted on 109 patients with CRSwNP, with or without asthma, who were eligible for dupilumab as an add-on therapy. Comprehensive assessments, including clinical, laboratory, and radiological evaluations, were performed before and after treatment. Clinical remission of CRSwNP was defined as 12 months of dupilumab treatment, no exacerbations requiring oral corticosteroids (OCS), no need for nasal sinus operation, no anosmia or hyposmia, a Sino-Nasal Outcome Test (SNOT-22) score under 20, and a Lund-Mackay score (LMS) below 10. For those with comorbid asthma, clinical remission was defined as an asthma control test (ACT) score of 19 or higher, no asthma exacerbations, and no need for OCS.

Results: Dupilumab significantly improved CRSwNP outcomes in both groups, including SNOT-22 scores, nasal polyp size (LMS), and anosmia/hyposmia. Comorbid asthma was highly prevalent (79.8%), and patients with asthma had significantly larger nasal polyps, both before and after dupilumab therapy, despite similar symptom improvement. Higher fractional exhaled nitric oxide (FeNO) and blood eosinophil count (BEC) levels, along with anosmia/hyposmia, predicted larger polyp size. Dupilumab also significantly improved asthma outcomes, increasing forced expiratory volume in 1 s (FEV1) and decreasing FeNO. Clinical remission was achieved in 11% of patients, with a slightly lower rate in those with asthma (7.3%).

Conclusion: Dupilumab treatment can achieve clinical remission in CRSwNP. However, comorbid asthma appears to reduce the likelihood of remission and is associated with larger nasal polyps, even with similar symptom improvement. Asthma may independently influence polyp development, potentially impacting long-term outcomes in CRSwNP.

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INTRODUCTION

Chronic rhinosinusitis (CRS), a prevalent condition affecting a significant portion of the global population, poses a substantial burden on healthcare systems and leads to productivity losses.[1,2] Characterized by inflammation of the nose and paranasal sinuses, CRS manifests with persistent symptoms such as nasal congestion, nasal discharge, facial pain, and a diminished sense of smell.[3,4] Diagnosis relies on endoscopic or computed tomography (CT) scan evidence, revealing abnormalities like nasal polyps, mucosal changes, or sinus involvement.[5]

CRS is traditionally classified into 2 categories: chronic rhinosinusitis with nasal polyps (CRSwNP) and without nasal polyps (CRSsNP).[6] However, going beyond the traditional classification, Tomassen et al identified 10 distinct inflammatory clusters in CRS patients, revealing diverse immune profiles.[7] Clusters with negative or low T2 markers were mostly CRS without nasal polyps and lower asthma rates, while clusters with high markers, particularly IgE and *Staphylococcus aureus* association, were predominantly CRSwNP and higher asthma prevalence. CRSwNP, identified by the presence of bilateral polyps in the middle meatus visible via endoscopy, affects approximately 1–2.5% of the population.[1] The progression of CRSwNP is influenced by various factors, including age of onset, smoking, allergies, asthma, and disease severity.[8] Particularly, there is a significant overlap between CRSwNP and asthma, with 30–70% of CRSwNP patients also experiencing asthma.[9] The prevalence of nasal polyps increases with asthma severity, ranging from 10–30% in mild asthma to 70–90% in severe cases.[10]

Despite optimal medical treatment and surgical interventions, many CRSwNP patients continue to experience uncontrolled symptoms, emphasizing the need for innovative therapeutic approaches.[10] Biologic therapies, originally approved for severe asthma, have shown promise in managing CRSwNP by targeting the type 2 inflammatory pathway.[8,11–14] Among these, dupilumab, a monoclonal antibody that inhibits IL-4 and IL-13 signaling, has emerged as the first biologic for treating CRSwNP in adults to be approved by the United States Food and Drug Administration (FDA).[15–18]

The concept of remission, defined as the absence of symptoms and disease activity, is increasingly being recognized as a primary goal in managing chronic conditions.[19] While established in fields like rheumatology and gastroenterology, this concept is gaining traction in the management of asthma and other airway diseases.[19–21] The Global Initiative for Asthma (GINA) has outlined criteria for clinical and complete remission in asthma, emphasizing the importance of sustained symptom improvement and reduced medication use.[22,23]

Given the potential of biologic therapies like dupilumab to impact polyp size and disease activity, this study aims to investigate the long-term effects of dupilumab on patients with CRSwNP, with or without asthma. By assessing clinical parameters such as quality of life, olfactory function, and asthma symptom control, alongside radiological changes in nasal polyp size, this study seeks to evaluate the potential of achieving clinical remission in this patient population.

METHODS

Study design, patient inclusion, and exclusion criteria

This prospective study was conducted from January 2022 to January 2024 and included 109 adult patients (≥18 years) with a confirmed diagnosis of CRSwNP, based on the EPOS 2020 guidelines criteria for biologic eligibility.[24] Diagnosis confirmation involved endoscopic assessment for nasal polyps and sinus CT scans to detect polypoidal nasal mucosal thickening. Patients with

a substantial disease burden not fully controlled by conventional therapies, those unsuitable for nasal sinus surgery, and those with severe CRSwNP were evaluated for biologic therapy eligibility according to EPOS 2020 guidelines.[24] Only those who had been receiving dupilumab treatment for at least 3 months prior to the start of the 12-month observation period were included. Comorbid asthma was diagnosed based on symptom variability and FEV1% reversibility, with additional tests like peak expiratory flow (PEF) variability and fractional exhaled nitric oxide (FeNO) measurements used to confirm inconclusive initial spirometry results.[25] Moreover, the asthma symptom control has been measured using the Asthma Control Test (ACT) score as recommended in GINA 2024.[26] Patients under 18 years old, those who declined participation, or those unable to complete the study were excluded.

Data collection and outcomes

Demographic information (age, sex) and disease-related data (number of nasal polyp surgeries, frequency of oral corticosteroids (OCS) courses in the year preceding dupilumab initiation) were collected from patient records. Patient outcomes were assessed at baseline and study end, comparing the following parameters:

1. **Olfactory Symptoms:** Olfactory function was assessed using a combination of subjective methods, including one-on-one structured interviews and a Visual Analogue Scale (VAS).[27] Structured interviews were conducted with all participants to gather qualitative information about their sense of smell, including questions on their perception of smell function, any changes noted, and how it affects their daily life. Additionally, patients rated their subjective sense of smell on a 100-mm VAS, where 0 represented complete loss of smell and 100 represented normal smell function. Based on these assessments, olfactory function was categorized as Normosmia (VAS score $\geq$70 and no reported smell difficulties in the interview), Hyposmia (VAS score between 30 and 69 and/or reported partial loss of smell in the interview), or Anosmia (VAS score $<$30 and/or reported complete loss of smell in the interview).[28]
2. **Quality of Life Assessment:** The verified Arabic version of the Sino-Nasal Outcome Test (SNOT-22) was used, with scores ranging from 0 to 110.[29] A score below 20 indicated normal values.[30]
3. **Exacerbation Frequency:** The frequency of exacerbations requiring a short OCS course of (20 mg prednisolone for 5 days) was recorded alongside the use of 1 of the following topical steroid sprays: fluticasone propionate (standard: 100–200 mcg/nostril, max: 400 mcg/day), mometasone furoate (standard: 100 mcg/nostril, max: 200 mcg/day), budesonide (standard: 64–256 mcg/nostril, max: 512 mcg/day), beclomethasone dipropionate (standard: 100–200 mcg/nostril, max: 400 mcg/day), and ciclesonide (standard: 50 mcg/nostril, max: 200 mcg/day).
4. **Asthma Symptoms:** The ACT score was used to assess asthma control, with scores ranging from 5 (poor control) to 25 (complete control).[31] A score above 19 indicated well-controlled asthma.
5. **Spirometry:** Post-bronchodilator parameters, including FEV1% predicted, FVC% predicted, and FEV1/FVC% predicted, were collected.
6. **Type 2 Inflammatory Markers:** Blood eosinophil count (BEC) was measured from blood samples, and fractional exhaled nitric oxide (FeNO) levels were measured from exhaled breath.
7. **Radiological Assessment:** Paranasal sinus (PNS) CT scans were performed using a 64-multislice scanner and interpreted using the Lund-Mackay Score (LMS) to assess nasal polyp size.[32]
8. **Clinical Remission Criteria for CRSwNP:** Clinical remission was defined as fulfilling all the following criteria after at least 12 months of dupilumab treatment (600 mg as an initial dose for patients with comorbid asthma, and 300 mg for patients with CRSwNP only, administered subcutaneously, followed by a maintenance dose of 300 mg every two weeks, as per EPOS 2020[24]): no exacerbations requiring OCS, no need for nasal sinus surgery, no anosmia or hyposmia, SNOT-22 score $<$20,[30] and LMS $<$10.[33] For patients with comorbid asthma, remission also required an ACT score $\geq$19, no asthma exacerbations, and no need for OCS.

Statistical analysis

Data were collected in Excel and analyzed using Minitab 17.1.0.0. Median and interquartile range (Q1-Q3) were used for numerical data, and categorical data were presented as numbers and percentages. Paired t-tests or Mann-Whitney tests were used to compare pre- and post-treatment differences, and the chi-square test was used for categorical data. Receiver Operating Characteristic (ROC) curves were used to determine the discrimination utility of LMS, with an area under the curve above 0.6 considered significant. Trend analysis with linear and quadratic models was used to fit changes in LMS over time, and multiple linear regression analysis was used to identify factors independently influencing LMS. All tests were two-sided, and significance was set at $p < 0.05$.

RESULTS

Characteristics of patients with CRSwNP

Table 1 shows that, of the 109 patients recruited, 79.81% (87) had comorbid asthma. Nearly two-thirds of these patients (60 out of 87) had adult-onset asthma. Additionally, almost half of the patients (45.87%) reported having allergic rhinitis (AR), while atopic dermatitis was observed in only 6.42% of cases. The median age was 44 years (IQR 37.5–56.5), and most patients were male (62.39%). However, only 22.93% of patients were current smokers. Prior to dupilumab treatment, 84.4% had undergone nasal sinus surgery, 65.14% had used OCS, and 95.41% reported anosmia or hyposmia (VAS score <70). The median SNOT-22 score was 63 (IQR 51–79), FeNO level was 38 ppb (IQR 18–51), BEC was 460 cells/μL (IQR 250–660), and total IgE was 325 IU/L (IQR 127–689). The total median nasal polyp score was 5 (IQR 4–7), and total LMS was 20 (IQR 14–23). Among patients with comorbid asthma, the median ACT score was 19 (IQR 13–22), and the median percentages of predicted FEV1, FVC, and FEV1/FVC were 75.5%, 80.8%, and 81.6%, respectively (Supplementary Table 1). Supplementary Table 2 presents follow-up data collected before the 12-month follow-up period.

Impact of comorbid asthma on CRSwNP

In Table 2, CRSwNP patients with and without asthma were matched for age and sex ($p = 0.13$ and 0.14). However, the proportion of current smokers was significantly higher in the CRSwNP group without asthma ($p = 0.04$). Despite the high asthma prevalence, there were no significant differences between groups in symptomatic status (SNOT-22, anosmia/hyposmia), type 2 inflammatory markers (FeNO, BEC), or history of nasal sinus surgery/OCS use ($p > 0.05$ for all). However, patients with asthma had significantly higher total IgE levels ($p = 0.01$), total nasal polyp scores, and individual scores for the right and left sides ($p = 0.01$, 0.03, and 0.004, respectively). Additionally, the total LMS and certain sub-scores (anterior/posterior ethmoidal sinuses, right frontal sinus, maxillary sinus, osteomeatal sinuses) were significantly higher in the group with comorbid asthma ($p < 0.05$). Total LMS effectively discriminated asthma groups (AUC 74%, $p = 0.001$), with a sensitivity of 74% and specificity of 63% for values above 16.5 (Fig. 1).

Effect of dupilumab on CRSwNP

Fig. 2 showed the changes in SNOT-22 scores and various inflammatory markers following dupilumab treatment. Significant decreases were observed in SNOT-22, FeNO, and total IgE levels ($p < 0.01$), while BEC remained unchanged ($p = 0.49$). Additionally, as shown in Fig. 3, there was a significant reduction in the frequency of anosmia/hyposmia and the need for OCS ($p < 0.001$ for both), with no patients requiring further sinus surgery.

Fig. 4 showed the significant reductions in all LMS and sub-scores ($p < 0.01$). The analysis of LMS trends using both linear and quadratic models revealed a clear reduction in nasal polyp size over 24 months, demonstrating the effectiveness of dupilumab therapy. While the linear model highlights a consistent rate of improvement, the quadratic model provides a more nuanced perspective, capturing the initial rapid decline followed by a potential plateauing of LMS values. This non-linear pattern may reflect the dynamics of treatment response or disease progression. Although accuracy measures vary slightly between the models, the quadratic model's ability to represent both the initial steep improvement and subsequent stabilization offers valuable insights into the treatment's impact on polyp size. Moreover, CT for PNS (Fig. 5) provided further

	Total (n = 109)		
	Median	Q1	Q3
Age (Year)	44	37.5	56.5
Sex	**N**	**%**	
Male	68	62.39	
Female	41	37.61	
Smoking status	**N**	**%**	
Current smoker	25	22.93	
Non-smoker	84	77.06	
Nasal sinus surgery (Yes)	92	84.4	
	Median	**Q1**	**Q3**
Nasal sinus surgery number	2	1	3
	N	**%**	
OCS in 1 year before (Yes)	71	65.14	
	Median	**Q1**	**Q3**
OCS course number	1	0	3
	N	**%**	
Anosmia/hyposmia (VAS < 70)	104	95.41	
NP score	**Median**	**Q1**	**Q3**
RT-NP	2	2	3
LT-NP	2	2	3
Total NPS	5	4	7
	Median	**Q1**	**Q3**
SNOT-22	63	51	79
Associated comorbid asthma	**N**	**%**	
	87	79.81	
Asthma onset	**N**	**%**	
Childhood onset	27	24.77	
Adulthood onset	60	55.04	
Associated allergies	N	%	

(continued)

	Total (n = 109)		
	Median	Q1	Q3
AR	50	45.87	
AD	7	6.42	
Total IgE (IU/mL)	325	127	689
FeNO (ppb)	38	18	51
BEC (cells/microL)	460	250	660
CT for PNS-LMS	**Median**	**Q1**	**Q3**
FS1	2	1	2
FS2	2	1	2
AE1	2	2	2
AE2	2	1	2
PE1	2	1	2
PE2	2	1	2
MS1	1	1	2
MS2	1	1	2
SS1	1	1	2
SS2	2	1	2
OMC1	2	2	2
OMC2	2	0	2
Total LMS	20	14	23

Table 1. (Continued) Basic characteristic of CRSwNP patients before starting biologics. *N: number, Q1: quartile 1, Q3: quartile 3, OCS: oral corticosteroid, SNOT-22: Sino-Nasal Outcome Test, AR: allergic rhinitis, AD: atopic dermatitis, FeNO: fractional exhaled nitric oxide, ppb: part per million, BEC: blood eosinophil count, IgE: Immune globulin E, NP: nasal polyp, RT-NPS: Right nasal polyp score, LT-NPS: left nasal polyp score, VAS: visual analogue score, CT: computerized tomography, PNS: paranasal sinus, FS: frontal sinus, AE: anterior ethmoidal, PE: posterior ethmoidal, MS: maxillary sinus, SS: sphenoidal sinus, OMC: ostiomeatal complex, 1 for right side and 2 for left side, LMS: Lund Macke score. The numerical data presented as median and interquartile range (Q1-Q3), and categorical data as number and percentage*

illustration of the changes in sinus opacity before and after dupilumab.

There were no reported adverse events with the treatment of dupilumab in all CRSwNP patients.

Difference in dupilumab effect on CRSwNP with and without asthma

In Table 3, there were no significant differences observed between both groups regarding the improvement of symptoms (SNOT-22 scores and frequency of anosmia and hyposmia, p = 0.52 and 0.68, respectively), as well as exacerbations requiring OCS use (p = 0.99). However, BEC was significantly higher in patients with comorbid asthma (p = 0.05), despite the insignificant difference in the level of FeNO and total IgE, p = 0.14 and 0.08, respectively. Additionally, some LM sub-scores remained higher in those with asthma (right frontal, anterior ethmoidal, and maxillary sinuses), although the difference in total LMS was not significant (p = 0.09). Additionally, dupilumab significantly improved asthma control and airway obstruction, with increased ACT scores,

	NP without asthma (n = 22)			NP with asthma (n = 87)			p
	Median	Q1	Q3	Median	Q1	Q3	
Age (Year)	40	30	53.25	44	40	60	0.13†
Sex	**N**	**%**		**N**	**%**		
Male	17	77.27		51	58.62		0.14*
Female	5	22.73		36	41.38		
Smoking status	**N**	**%**		**N**	**%**		
Current smoker	10	45.45		15	17.24		0.04*
Non-smoker	12	54.54		72	82.76		
Nasal sinus surgery (Yes)	18	81.82		74	85.06		0.71*
	Median	**Q1**	**Q3**	**Median**	**Q1**	**Q3**	
Nasal sinus surgery number	2	1	2	2	1	3	0.77†
	N	**%**		**N**	**%**		
OCS in 1 year before (Yes)	16	72.73		55	63.22		0.39*
	Median	**Q1**	**Q3**	**Median**	**Q1**	**Q3**	
OCS course number	2	0	3	1	0	4	0.79†
	N	**%**		**N**	**%**		
Anosmia/hyposmia (VAS < 70)	22	100		82	94.25		0.12*
NP score	**Median**	**Q1**	**Q3**	**Median**	**Q1**	**Q3**	
RT-NP	2	1	3	3	2	3	0.03†
LT-NP	2	2	2	3	2	3	0.004†
Total NPS	4	4	5	5	4	7	0.01†
	Median	**Q1**	**Q3**	**Median**	**Q1**	**Q3**	
SNOT-22	64	49.5	82	61.5	51	78.25	0.81†
Type 2 inflammatory markers	**Median**	**Q1**	**Q3**	**Median**	**Q1**	**Q3**	
Total IgE (IU/mL)	203	113	511	298	140	789	0.01†
FeNO (ppb)	32	18	50	39	17.75	51.75	0.91†
BEC (cells/microL)	350	168	605	500	257.5	670	0.12†
CT for PNS-LMS	**Median**	**Q1**	**Q3**	**Median**	**Q1**	**Q3**	

(continued)

	NP without asthma (n = 22)			NP with asthma (n = 87)			p
	Median	Q1	Q3	Median	Q1	Q3	
FS1	0	0	2	2	1	2	**0.001†**
FS2	1	1	2	2	1	2	0.12†
AE1	1	0	2	2	2	2	**0.003†**
AE2	1	1	2	2	2	2	**0.03†**
PE1	1	1	2	2	1	2	**0.04†**
PE2	1	1	2	2	1	2	**0.03†**
MS1	1	1	1	2	1	2	**0.001†**
MS2	1	1	1	1	1	2	0.07†
SS1	1	0	2	2	1	2	**0.01†**
SS2	1	1	2	2	1	2	0.19†
OMC1	2	0	2	2	2	2	**0.04†**
OMC2	2	0	2	2	1	2	0.18†
Total LMS	13	8	19	21	14.25	23	**0.001†**

Table 2. (Continued) Impact of comorbid asthma on CRSwNP patients before starting biologics. *N: number, Q1: quartile 1, Q3: quartile 3, OCS: oral corticosteroid, SNOT-22: Sino-Nasal Outcome Test, FeNO: fractional exhaled nitric oxide, ppb: part per million, BEC: blood eosinophil count, IgE: Immune globulin E, NP: nasal polyp, RT-NPS: Right nasal polyp score, LT-NPS: left nasal polyp score, VAS: visual analogue score, CT: computerized tomography, PNS: paranasal sinus, FS: frontal sinus, AE: anterior ethmoidal, PE: posterior ethmoidal, MS: maxillary sinus, SS: sphenoidal sinus, OMC: ostiomeatal complex, 1 for right side and 2 for left side, LMS: Lund Macke score. The numerical data presented as median and interquartile range (Q1-Q3), and categorical data as number and percentage, †: Mann Whitney test, *: Chi square test, p < 0.05 considered significant*

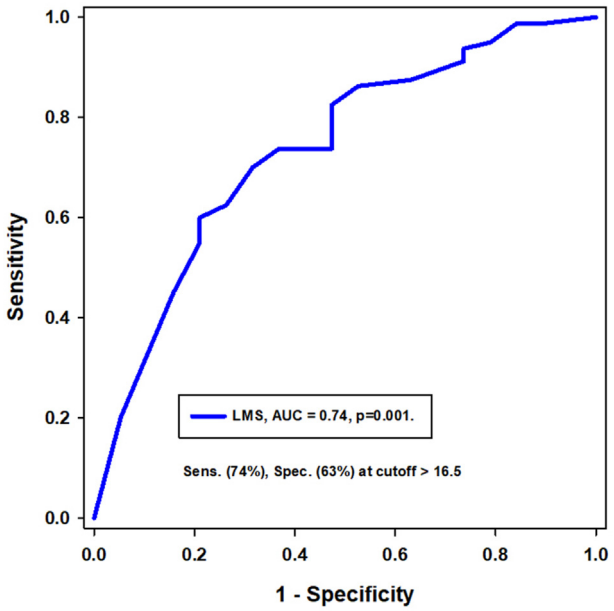

Fig. 1 ROC curve of LMS to detect the associate comorbid asthma in CRSwNP patients. AUC: area under curve, Sens.: sensitivity, Spec.: specificity, p < 0.05 considered significant.

FEV1, and FEV1/FVC, p < 0.001, 0.02, and 0.04, respectively, as shown in Fig. 6.

Factors influencing nasal polyp size: LMS

In Table 4, the multiple linear regression models showed that the higher level of FeNO and blood eosinophil count (BEC) as well as presence of anosmia/hyposmia were independently predict the higher value of Lund Macke score (LMS) and pointed to possibility of significant nasal obstruction with large polyposis despite the duration of treatment with dupilumab. The equation of LMS prediction in case of positive anosmia/hyposmia was (LMS = 6.22 + 0.1252 FENO + 0.00354 BEC - 0.1626 dupilumab duration).

Prevalence of CRSwNP remission

Based on the defined criteria, 11% (12/109) of patients achieved clinical remission, with a slightly lower rate in those with asthma (7.3%, 8/109).

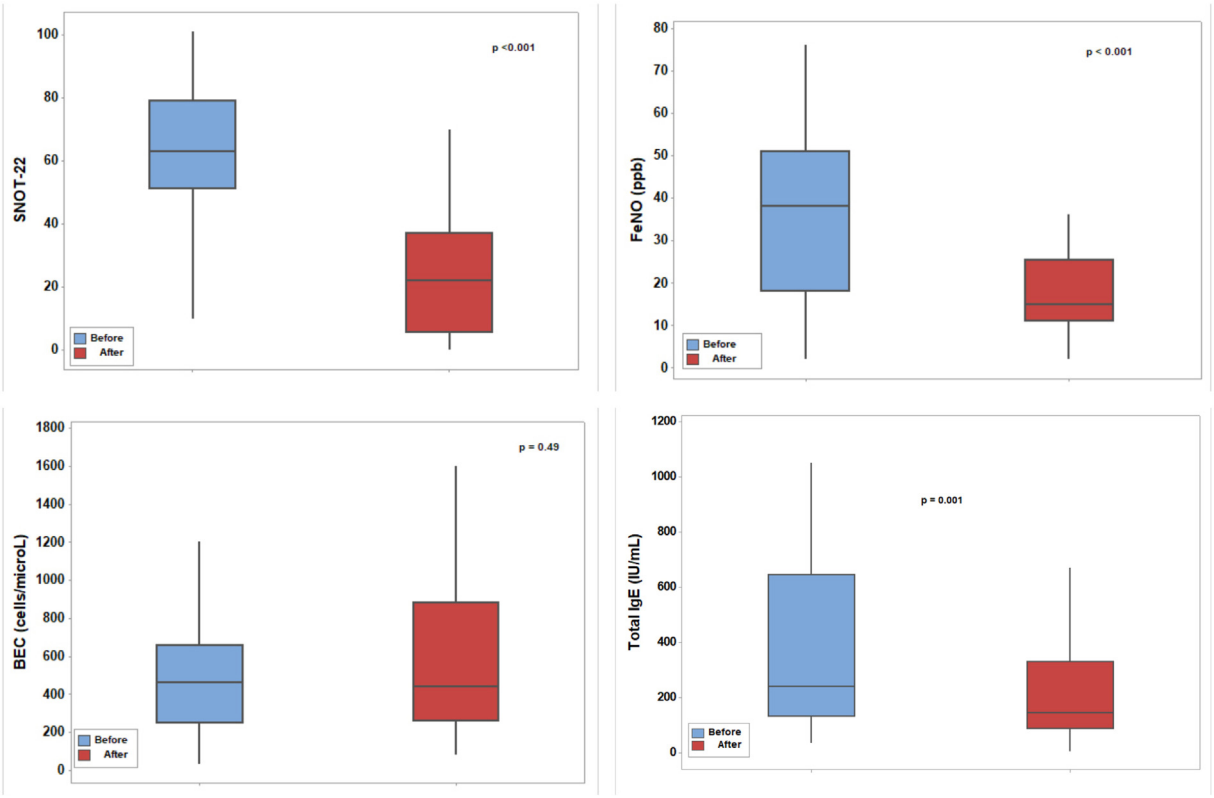

Fig. 2 Effect of dupilumab on SNOT-22, FeNO, BEC and total IgE in patients with CRSwNP SNOT-22: Sino-Nasal Outcome Test, FeNO: fractional exhaled nitric oxide, ppb: part per million, BEC: blood eosinophil count, IgE: Immune globulin E, the test of significant: Mann Whitney test, $p < 0.05$ considered significant. Recruitment period (0–12 months), and follow-up period (12–24 months).

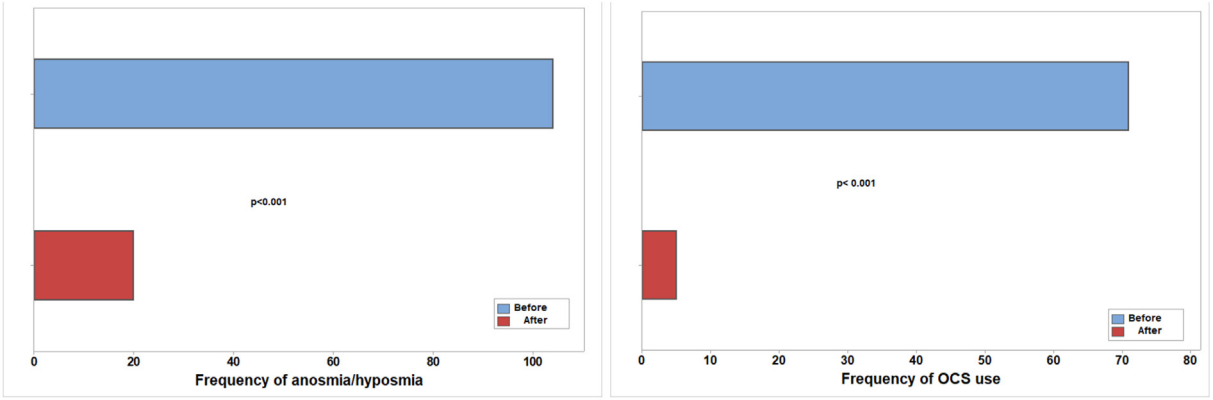

Fig. 3 Effect of dupilumab on the frequency of anosmia/hyposmia and OCS use in patients with CRSwNP OCS: oral corticosteroid, the test of significant: Chi square test, $p < 0.05$ considered significant. Recruitment period (0–12 months), and follow-up period (12–24 months).

DISCUSSION

The rise of powerful biologic treatments has shifted the goal of managing chronic inflammatory diseases toward achieving disease remission. Initially seen in rheumatology and gastroenterology,[19] this concept was extended to asthma in 2020, where "clinical remission" is defined by criteria such as no need for systemic steroids, stable lung function, minimal symptoms (eg, ACT score), and agreement between patient and physician.[20-23] In CRSwNP, remission may involve symptom control, normalized inflammation, and a healthy nasal lining.[34] Although not yet fully defined, achieving remission in CRSwNP could revolutionize treatment, offering shorter therapies and possibly a "cure" in some cases, especially with biologic

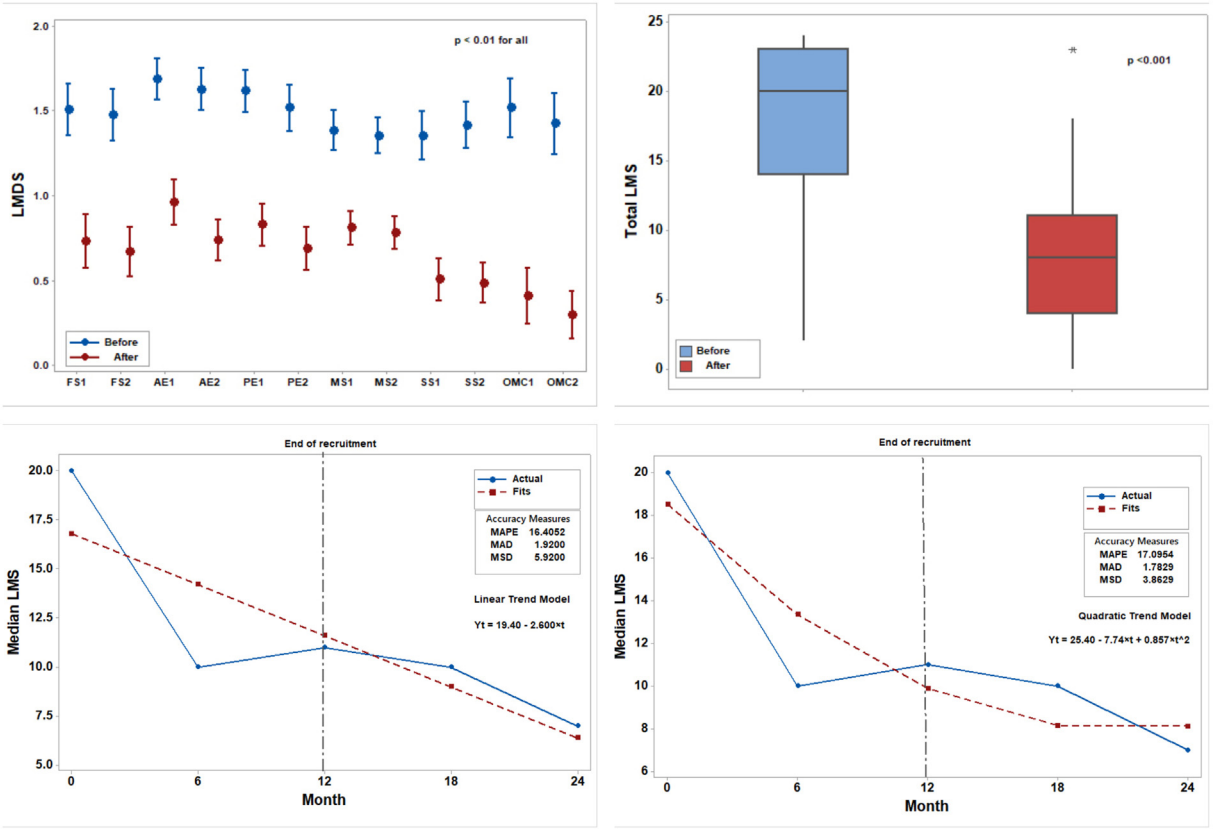

Fig. 4 Impact of dupilumab on LMS and its trend of reduction with treatment duration LMS: Lund Macke score, the test of significant: Mann Whitney test, $p < 0.05$ considered significant. Recruitment period (0–12 months), and follow-up period (12–24 months).

therapies showing promising results in symptom resolution and endoscopic improvements.[35,36] To date, no study has explored the correlation among the 3 aspects of CRSwNP remission, encompassing clinical, laboratory, and radiological remission. The current study exhibited the potential of clinical remission of patients with CRSwNP with and without comorbid asthma who were treated with dupilumab for at least 12 months and fulfilled our clinical remission criteria. The data showed that 12 out of 109 patients with CRSwNP (11%) achieved clinical remission within the studied cohort. However, the prevalence of clinical remission was slightly lower among patients with associated comorbid asthma, with 8 out of 109 patients (7.3%) achieving remission. Unlike the broader definition of Fokkens et al[37] which allowed more flexibility in the treatment options. Our study agreed with the beforementioned report in the exclusion of systemic corticosteroids and nasal sinus surgery as well as the need for sustained disease control. Additionally, while Fokkens et al[37] suggests nasal endoscopy for evaluating the absence of active disease, our criteria were based on using the LMS. Clinical trials of biologic therapies have utilized various endpoints, such as changes in nasal polyp score (NPS), nasal congestion severity, and patient-reported outcomes like the SNOT-22 score.[38–40] Real-world studies and guidelines from organizations like EUFOREA have attempted to define "adequate response" using multiple parameters, including NPS, symptom severity scores, and the need for surgery or systemic therapy after a certain duration of treatment.[41–43] Although the remission prevalence in our cohort was lower than the rates reported in other studies, this likely reflects the differences in patient populations, remission definitions, and follow-up durations. Stringent remission criteria, such as those used in our study, are necessary for rigorous evaluation but may underestimate the broader benefits of therapy. However, restricting clinical remission criteria may lead to premature discontinuation of effective treatment. Therefore, a balanced approach that considers both objective measures and patient-reported outcomes is essential for evaluating treatment success and

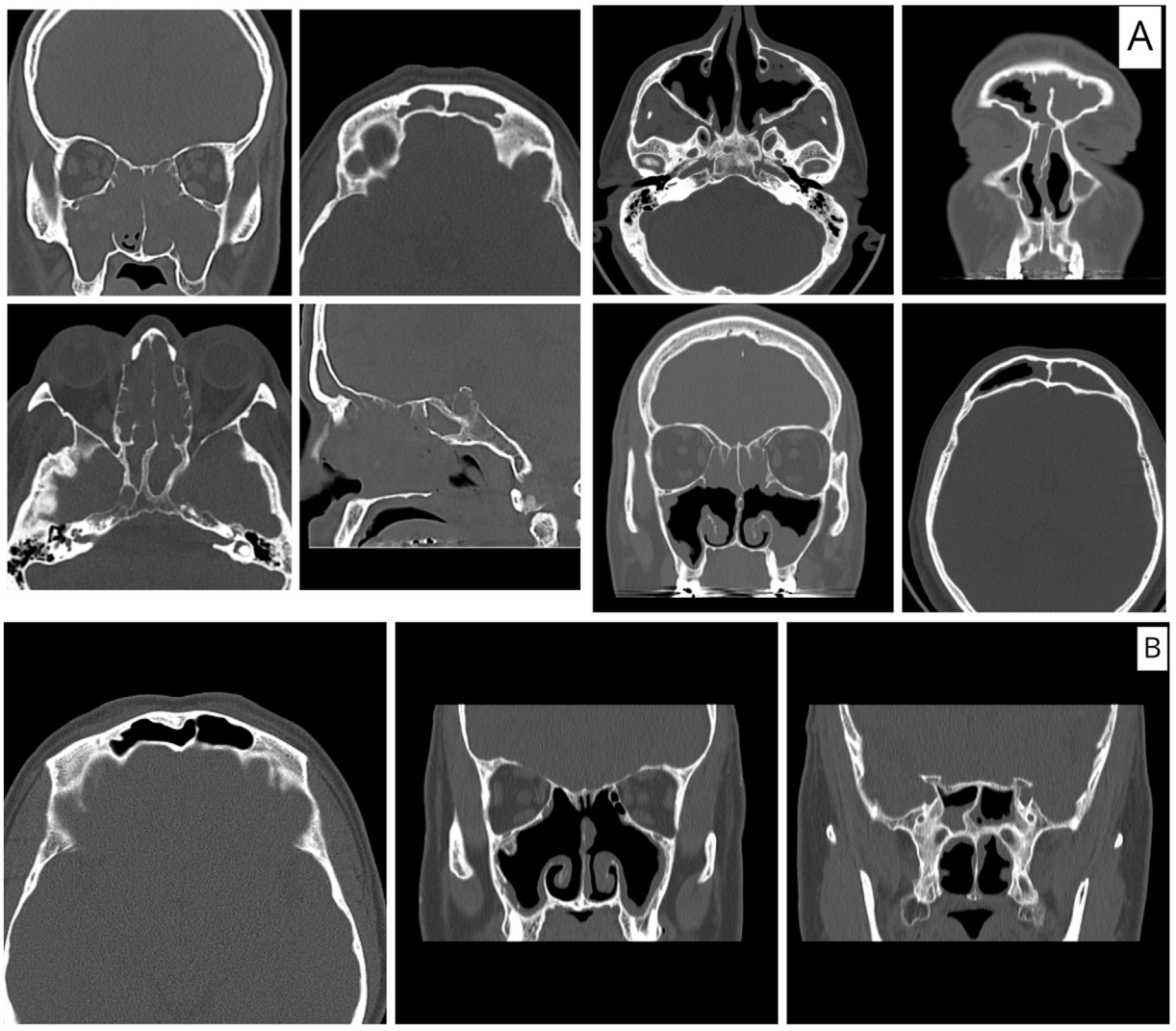

Fig. 5 Changes in CT-PNS before and after dupilumab In the (A) collection, the figure showed complete and partial opacification of PNS, the LMS was above 10, however, in the (B) collection, the effect of dupilumab was obvious; the figure showed absence or even mild opacification of both maxillary and both sphenoid sinuses with clear frontal, anterior ethmoid, posterior ethmoid with non-obstructed ostiomeatal complexes, with a score of less than 10 of 24 according to LMS. Recruitment period (0–12 months), and follow-up period (12–24 months).

determining when to consider discontinuing therapy in CRSwNP patients. Chan et al,[34] reported that remission rates in CRSwNP patients vary significantly based on comorbid conditions, with rates as low as 23% for those with asthma and aspirin-exacerbated respiratory disease (AERD). These findings align with our results, as our cohort had a high prevalence of asthma and other risk factors for severe disease. Even without achieving strict remission, dupilumab therapy yielded clinically meaningful improvements. In this study, dupilumab therapy offered both symptomatic relief and potential long-term benefits in reducing disease severity and the need for surgical interventions. Hence, patients experienced notable reductions in symptom severity, as evidenced by decreased SNOT-22 scores and frequency of anosmia and hyposmia. Additionally, there was a substantial decrease in type 2 inflammation, as indicated by reduced FeNO levels. The severity of nasal polyposis also significantly diminished, with marked reductions in LMS and subscores. Importantly, none of the patients required further nasal sinus surgery, and only a small fraction needed OCS for exacerbation. That came in consistence with Japanese study who followed 49 CRSwNP patients for up to a year. They looked at key measures like nasal polyp score, congestion score, and LMS at the 24-week mark. Compared to placebo, dupilumab treatment resulted in significant improvements in all these measures by week 24. This

	NP without asthma (n = 22)			NP with asthma (n = 87)			p
	N	**%**		**N**	**%**		
OCS for exacerbation (Yes)	1	4.55		4	4.6		0.99*
	Median	**Q1**	**Q3**	**Median**	**Q1**	**Q3**	
OCS course number	2	0	3	1	0	4	0.93†
	N	**%**		**N**	**%**		
Anosmia/hyposmia (VAS < 70)	3	13.64		17	19.54		0.52*
	Median	**Q1**	**Q3**	**Median**	**Q1**	**Q3**	
SNOT-22	14	4	37.5	22	8	37	0.68†
Type 2 inflammatory markers	**Median**	**Q1**	**Q3**	**Median**	**Q1**	**Q3**	
Total IgE (IU/mL)	112	88	185	139	77	210	0.08
FeNO (ppb)	7	5	23	15	11	26.25	0.14†
BEC (cells/microL)	240	88	450	450	270	900	**0.05**†
CT for PNS-LMS	**Median**	**Q1**	**Q3**	**Median**	**Q1**	**Q3**	
FS1	0	0	1	1	0	1	**0.04**†
FS2	0	0	2	1	0	1	0.96†
AE1	1	0	1	1	1	1	**0.03**†
AE2	0	0	1	1	0	1	0.04†
PE1	1	0	1	1	0	1	0.51†
PE2	0	0	1	1	0	1	0.11†
MS1	0	0	1	1	1	1	**0.02**†
MS2	1	0	1	1	1	1	0.42†
SS1	0	0	1	0	0	1	0.42†
SS2	0	0	1	0	0	1	0.74†
OMC1	0	0	0	0	0	0	0.95†
OMC2	0	0	2	0	0	0	0.34†
Total LMS	4	2	12	8	5	11	0.09†

Table 3. Comparison between the effect of dupilumab treatment on patients with CRSwNP with and without asthma. *N: number, Q1: quartile 1, Q3: quartile 3, OCS: oral corticosteroid, SNOT-22: Sino-nasal outcome test, FeNO: fractional exhaled nitric oxide, ppb: part per million, BEC: blood eosinophil count, IgE: Immune globulin E, VAS: visual analogue score, CT: computerized tomography, PNS: paranasal sinus, FS: frontal sinus, AE: anterior ethmoidal, PE: posterior ethmoidal, MS: maxillary sinus, SS: sphenoidal sinus, OMC: ostiomeatal complex, 1 for right side and 2 for left side, LMS: Lund Macke score. The numerical data presented as median and interquartile range (Q1-Q3), and categorical data as number and percentage, †: Mann Whitney test, *: Chi square test, p < 0.05 considered significant*

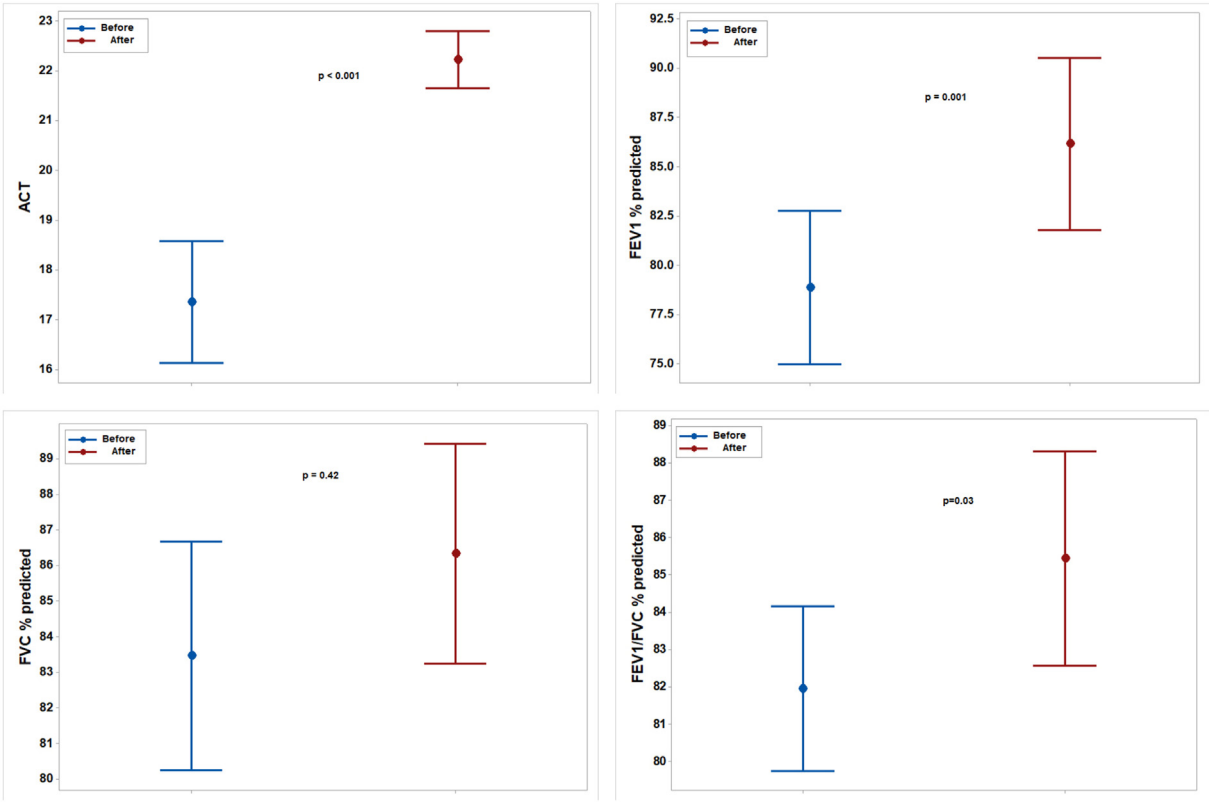

Fig. 6 Effect of dupilumab on asthma control and airway obstruction ACT: Asthma control test score, FEV1: Forced expiratory flow in 1 s, FVC: Forced expiratory capacity, the test of significant: Mann Whitney test, $p < 0.05$ considered significant. Recruitment period (0–12 months), and follow-up period (12–24 months).

Factors	Coefficient	SE	P*
FeNO (ppb)	0.125	0.051	**0.020**
BEC (cells/microL)	0.004	0.001	**0.014**
Dupilumab treatment duration (month)	−0.163	0.096	0.102
Anosmia/hyposmia (VAS <70)	5.380	1.770	**0.005**

Table 4. Factors influencing the LMS. *FeNO: fractional exhaled nitric oxide, ppb: part per million, BEC: blood eosinophil count, VAS: visual analogue score, SE: standard error of coefficient, the sign before coefficient denotes the direction of relationship, $p < 0.05$ considered significant, *: the test of significant: Multiple linear regression with stepwise model. In case of anosmia/hyposmia (LMS = 6.22 + 0.1252 FENO +0.00354 BEC - 0.1626 Dupilumab duration)*

study reinforces the rapid and substantial clinical benefits of dupilumab for Japanese CRSwNP patients, with consistent safety and effectiveness observed throughout the study.[44] Additionally, analyses of patients receiving dupilumab in the SINUS trials (both 24 and 52 weeks) suggest a link between treatment effectiveness (measured by reduced nasal polyp score) and a decrease in specific local biomarkers linked to nasal type 2 inflammation in severe CRSwNP.[38] While the beforementioned study didn't find strong connections with overall systemic measurements, it underscores the importance of further research to identify the specific biomarkers that best correlate with both objective disease severity measures and patient-reported outcomes.[38]

Given the association between asthma and nasal polyps, our data demonstrated dupilumab's remarkable effectiveness in treating CRSwNP regardless of comorbid asthma. Both groups with and without asthma experienced significant symptom improvement, including reduced SNOT-22 scores and decreased anosmia and hyposmia.

No notable differences were observed between the groups in symptom relief or oral corticosteroid-requiring exacerbations.

Although BEC were higher in asthma patients, FeNO levels did not significantly differ between groups. This may be due to the fact that BEC and FeNO reflect different aspects of type 2 inflammation; BEC indicates systemic eosinophilic inflammation, while FeNO is more specific to airway inflammation.[45,46] FeNO primarily reflects lower airway inflammation,[46] so in CRSwNP patients without asthma, upper airway inflammation could elevate FeNO to levels similar to those in asthma patients. Treatment differences may also contribute, as inhaled corticosteroids could lower FeNO levels without affecting BEC.[45,46] CRSwNP is heterogeneous, and some patients may have high eosinophilic inflammation without elevated FeNO. Additionally, FeNO is more sensitive to environmental factors,[46] and the relatively small sample size may have limited the ability to detect differences. Furthermore, our study found that dupilumab significantly improved asthma control, as reflected by increased ACT scores, FEV1, and FEV1/FVC ratios, suggesting a reduction in airway inflammation. These findings underscore dupilumab's broad efficacy in alleviating nasal and asthma-related symptoms while mitigating inflammation, making it a valuable treatment for CRSwNP, particularly in patients with concomitant asthma. This aligns with previous studies,[42,47,48] further showcasing dupilumab's potential as a versatile therapeutic option for patients with multiple comorbidities like asthma, CRSwNP, and atopic dermatitis.[49]

Several scoring systems exist for evaluating rhinosinusitis on CT scans, with the LMS being the most popular and recommended due to its ease of use.[50] This score has been linked to the extent of surgery required in CRS patients.[50] Nasoendoscopic examinations also utilize scoring systems, like the modified Lund Kennedy (MLK) score, which has shown good reliability and correlation with patient-reported outcomes.[51] Studies have compared the diagnostic accuracy of nasoendoscopy and CT scans in CRS, suggesting that while nasoendoscopy is useful for confirming diagnosis and assessing severity, CT scans are recommended for cases with high clinical suspicion, negative nasoendoscopy, and persistent symptoms.[52] Although we did not use a nasoendoscopic score in this study to correlate with the LMS, previous research has explored correlations between the LMS and Lund Kennedy scores on nasoendoscopy.[53] However, in our study, the LMS was significantly correlated with another finding: it was significantly higher in patients with comorbid asthma, and its utility in discriminating between groups with and without comorbid asthma was good. The sensitivity and specificity of a LMS value above 16.5 were 74% and 63%, respectively, suggesting that the LMS could reflect the impact of comorbid asthma in aggravating the severity of inflammation in CRS as reported by older study.[54] However, there is lack of association between atopy and CRS severity suggests that further research is needed to fully understand the complex relationship between these conditions. Moreover, a link between specific allergens and increased inflammation in specific sinus pockets has been reported, with the author finding that cockroach allergy affects the maxillary sinus, and attributing this to unique properties of cockroach allergens, allowing easier access to the sinus.[54] These findings could support the current observation; hence, we found that inflammation in the anterior and posterior ethmoidal sinuses, right frontal sinus, maxillary sinus, and osteomeatal sinuses were significantly higher in patients with comorbid asthma. However, this result could be due to chance and needs further investigation. Furthermore, the abovementioned study found that asthma, not allergies, is a key predictor of severe radiological disease and CRSwNP phenotype.[54] A possible mechanism for this link is the upregulation of inflammatory cells, which migrate to the airway mucosa and cause inflammation. Additionally, after dupilumab, the severity of nasal polyposis decreased, with marked reductions of LMS. Analysis of LMS trends using both linear and quadratic models showed a clear reduction in nasal polyp size over 24 months of dupilumab therapy. The quadratic model, capturing an initial rapid decline followed by potential stabilization, offers a more nuanced understanding of treatment response and disease progression compared to the linear model. Moreover, the multiple linear regression models showed that the higher level of FeNO and BEC as well as

presence of anosmia/hyposmia were independently predict the higher value of LMS and pointed to possibility of significant nasal obstruction with large polyposis despite the duration of treatment with dupilumab. FeNO is a marker of eosinophilic airway inflammation and reflects more severe type 2 inflammation in the airways,[46] which likely extends to the sinuses, causing increased mucosal thickening and obstruction, thus raising LMS. However, elevated BEC, indicative of systemic eosinophilic inflammation,[45] correlates with more severe local inflammation in the sinuses, contributing to higher LMS. Anosmia and hyposmia, often caused by mechanical obstruction or inflammation-induced damage to the olfactory epithelium,[55] suggest more extensive disease, which is also reflected in a higher LMS. Together, these factors represent different aspects of CRSwNP: FeNO indicates local airway inflammation, BEC points to systemic eosinophilic inflammation, and anosmia/hyposmia indicates the extent of tissue involvement. Their independent association with higher LMS suggests they each provide valuable insights into disease severity. As markers of type 2 inflammation, both elevated FeNO and BEC contribute to tissue remodeling,[56] polyp formation, and mucosal thickening, all of which drive higher LMS. Additionally, more severe sinus disease may exacerbate inflammation, creating a potential feedback loop that further elevates FeNO and BEC. *Zhang et al*.,[57] found that FeNO levels are significantly lower in patients with nasal inflammation, particularly in chronic rhinosinusitis, compared to healthy individuals, which came in contrast with our data, however, another study found that subclinical eosinophilic lower airway inflammation is prevalent in primary care patients with CRSwNP, even in the absence of asthma.[58] This suggests that lower airway involvement may be more widespread in CRSwNP than previously thought. Extendedly, the role of nasal nitric oxide (nNO) levels has been examined for differentiating between eosinophilic and non-eosinophilic CRSwNP,[59] and the result showed that combining nNO with peripheral BEC and VAS score will further improve the diagnostic accuracy for eosinophilic CRSwNP after considering the atopic status of patients, as it can influence nNO levels. These findings highlight the complex relationship between local and systemic inflammation in CRSwNP and suggest that using these biomarkers and clinical symptoms could help assess disease severity.

The strength of this study lies in its use of real-world data, offering valuable insights into dupilumab's effectiveness in a large cohort of CRSwNP patients, including those with comorbid asthma, a population often underrepresented in clinical trials. The comprehensive assessment encompassed SNOT-22, anosmia/hyposmia, biomarkers (FeNO, BEC), and imaging (LMS), providing a holistic view of disease severity and treatment response. The longitudinal 24-month follow-up allowed for a thorough evaluation of dupilumab's long-term effects on nasal polyp size and asthma control. Notably, the study revealed a potential association between comorbid asthma and higher LMS scores, suggesting a link between asthma and more severe nasal polyposis, and utilized a quadratic model analysis to offer a unique perspective on treatment response dynamics. However, the study has some limitations, first, its observational design, which hinders establishing causal relationships between dupilumab and outcomes. Second, the study population, recruited from a single centre, may not be fully representative of all CRSwNP patients. Additionally, the lack of a placebo-controlled group makes it difficult to isolate dupilumab's specific effects from confounding factors or natural disease progression. Moreover, Olfactory function was assessed through one-on-one interviews and a VAS questionnaire, which may not be as accurate as specialized testing for smell function. Our center was not equipped to perform more precise olfactory tests, which are typically conducted at ENT specialized centers. Finally, the study did not extensively assess other potential comorbidities that could influence CRSwNP outcomes, or routinely used tissue cytology for evaluating important markers like tissue eosinophils.

CONCLUSION

Dupilumab treatment can achieve clinical remission in CRSwNP. However, the presence of comorbid asthma appears to reduce the likelihood of remission. Notably, asthma is associated with larger nasal polyps, even in patients experiencing similar symptom improvement with dupilumab.

The higher LMS scores observed in patients with asthma suggest a potential link between asthma and more severe nasal polyposis. Although further research is needed to confirm these findings and explore the underlying mechanisms, this study supports the use of dupilumab as a valuable treatment option for CRSwNP, particularly in patients with concomitant asthma.

Abbreviations

ACT, Asthma control test; BEC, Blood eosinophil count; CRS, Chronic rhinosinusitis; CRSwNP, Chronic Rhinosinusitis with nasal polyp; CT, Computed tomography; FeNO, Fractional exhaled nitric oxide; FEV1, Forced expiratory volume in 1 s; FVC, Forced vital capacity; LMS, Lund-Mackay score; MLK, modified Lund Kennedy; nNO, Nasal nitric oxide; NP, Nasal polyp; NPS, nasal polyp score; OCS, Oral corticosteroids; PNS, para nasal sinus; SNOT-22, Sino-Nasal Outcome Test-22; VAS, Visual Analog Scale.

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Availability of data and materials

The datasets used during the current study available from the corresponding author on reasonable request.

Author's contribution

M.A. and A.A. have contributed equally to this study. W.T. worked on data collection and A.A. analyzed and interpreted the results and helped in writing up the paper. H.D. and O.I. read the radiological film and helped in writing up the paper. M.A. and A.A. were a major contributor in writing up the manuscript. All authors read and approved the final manuscript.

Authors' consent for publication

We declare that all authors have read and approved submission of the manuscript, and the manuscript has not been published and is not being considered for publication elsewhere, in whole or in part in any language. The authors listed on the title page have contributed to the concept and design, statistical analyses, drafting, revision, and interpretation of the data.

Ethics approval and consent to participate

All participants had provided written informed consent, indicating their complete understanding of the nature and objectives of the research. Participation was voluntary, and they willingly agreed to participate after being fully informed. The study was approved by Kuwait University and the Ministry of Health ethical committee office with approval number (2121/2022), which was aligned with local guideline as well the Helsinki Declaration protocol.

Declaration of competing interest

All authors declare no conflict of interest. Each author has revised and approved the final version of the manuscript independently.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2024.101024.

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