

Systematic Review

Use of dupilumab as adjuvant therapy in patients with previous sinus surgery for uncontrolled chronic rhinosinusitis with nasal polyps: a systematic review

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ABSTRACT

Chronic rhinosinusitis with nasal polyps (CRSwNP) is an inflammatory disease of the nose and sinuses where most patients undergo surgery, however, postoperative recurrence of nasal polyps is common resulting in multiple re-interventions. Biological therapies such as dupilumab have been developed to suppress the inflammatory pathways involved in this disease. The aim of the present review is to evaluate the impact of the use of dupilumab in patients with uncontrolled CRSwNP, and its effect on the frequency of revision surgeries. A bibliographic search was performed in PubMed, Cochrane and Google Scholar. included articles published between 2019 and 2024, meta-analyses, systematic reviews, randomized controlled trials, studies in adult population, and the use of dupilumab in patients with previous sinus surgery. The quality of evidence was assessed using GRADE. Seven studies were included, totaling 1603 patients with uncontrolled CRSwNP, 84.6% of the total patients had a history of having undergone at least one surgery, after completion of follow-up, dupilumab demonstrated a reduction in the frequency of revision surgeries in addition to an improvement in sinonasal symptoms. Existing evidence supports the benefit of the use of dupilumab as an adjuvant therapy in patients with uncontrolled CRSwNP due to the reduction in the frequency of revision surgeries. Further studies addressing the effect of dupilumab in the short-term postoperative period are needed to compare the results obtained.

Keywords: Chronic rhinosinusitis, Sinus surgery, Nasal polyps, Dupilumab

INTRODUCTION

Chronic rhinosinusitis (CRS) is an inflammatory disease of the nose and paranasal sinuses with an overall prevalence of 3% to 6%.¹ It is characterized by nasal obstruction, rhinorrhea, smell dysfunction and persistent facial pain for at least 3 months. Also, CRS can be classified into CRS with or without nasal polyps.²

Chronic rhinosinusitis with nasal polyps (CRSwNP), accounts for 25% to 30% of CRS cases and significantly impacts patient's quality of life.³ CRSwNP is

characterized by the presence of polyps in both nostrils confirmed by endoscopy or computed tomography (CT) scan. Type 2 inflammation is also observed, characterized by high levels of IL-4, IL-5, IL-13, increased immunoglobulin E (IgE) in tissues and the presence of eosinophils and mast cells in the mucosa.⁴

Asthma and non-steroidal anti-inflammatory drug exacerbated respiratory disease (N-ERD) are common type 2 inflammatory comorbidities, present in 65% and 16% of patients with CRSwNP, respectively.⁵ Patients with concomitant bronchial asthma have more intense

inflammation in the sinuses. In the case of N-ERD, both upper and lower airways are sensitive to NSAIDs, which may unfavorably influence the course of the disease.^{6,7} Both comorbidities worsen nasal obstruction and loss of smell, and increase costs and use of medical resources.^{8,9} Patients with CRSwNP and asthma have higher rates of polyp recurrence and revision surgery (28.8%) compared to those without asthma (15.2%).^{10,11}

First-line management of CRSwNP includes nasal irrigation with saline solution and intra-nasal corticosteroids (INCS) as mometasone fuorate administered twice daily; short courses of oral corticosteroids (OCS) may be included.^{12,13} If medical therapy is insufficient, endoscopic sinus surgery (ESS) is considered an option to reduce nasal obstruction, improve ventilation and allow better access to subsequent local treatments. It is estimated that 46% to 79% of patients with CRSwNP undergo at least one surgery.^{14,15}

Even so, a large proportion of patients do not experience improvement after surgery, showing recurrence of the disease.^{16,17} These cases are categorized as “uncontrolled CRSwNP”. EUFOREA in 2020 defined it as inflammation that persists despite the use of INCS or after receiving at least one course of OCS in the past 2 years and/or previous surgery.¹⁸ About 40% of patients suffer recurrence of nasal polyps within 18 months postoperatively, 60% within 7 years, and 80% within 12 years.¹⁹⁻²¹

In recent decades, biologic agents, such as monoclonal antibodies, have been developed that are specifically designed to target key components of the type 2 inflammatory pathway. In late 2019, the FDA cleared dupilumab to treat adults with uncontrolled CRSwNP. EPOS in 2020 suggested the use of dupilumab in patients with CRSwNP who did not respond to surgical treatment.²²

Dupilumab is a monoclonal antibody that prevents IL-4 and IL-13 signaling by binding to the alpha subunit of its receptor (IL-4R α), which blocks the type 2 inflammatory pathway involved in CRSwNP.^{23,24} Dupilumab modulates mast cell activity, IgE synthesis and inhibits the inflammation cascade leading to eosinophilia.²⁵⁻²⁷

The aim of the present review is to evaluate, based on current evidence, the impact of the use of dupilumab as an adjunct to standard therapy in patients with uncontrolled CRSwNP, and its effect on the frequency of revision surgeries.

METHODS

Data sources

The present review was conducted following the PRISMA 2020 guidelines.²⁸ The search was conducted in December 2024 in the following databases: PubMed, Cochrane Library, and Google Scholar.

Eligibility criteria

The requirements for inclusion were: articles published between 2019 and 2024, clinical trials, meta-analyses, systematic reviews, randomized controlled trials (RCTs) and cohort studies, investigations involving uncontrolled CRSwNP patients and age older than 18 years, and use of dupilumab in patients with previous sinus surgery for CRSwNP. Exclusion criteria involved: commentaries, narrative reviews, expert opinion articles or letters to the editor, and studies using biologic agents other than dupilumab.

Search strategy

The search strategy used was as follows: “dupilumab OR postoperative AND chronic rhinosinusitis AND nasal polyps”. A basic search strategy was performed because the amount of literature specific to the use of dupilumab in post-surgical CRSwNP is limited and a broad search was prioritized so as not to exclude relevant studies.

Assessment of research quality

The quality of the evidence was examined using the GRADE evaluation system; each study was classified as high (high confidence that the estimated effect is close to the true effect), moderate (moderate confidence in the estimated effect, with the possibility that the true effect is far from the observed effect) and low (limited confidence in the estimated effect; the true effect could differ considerably from the observed effect) according to the certainty of the evidence presented. Table 1 shows the design and quality of the evidence for each study.

Table 1: Characteristics and quality of evidence of the studies.

Author (s) and year	Study design	Quality of the evidence (GRADE)
Alicandri-Ciuffelli et al (2024) ²⁹	Retrospective cohort	Low ^a
De Corso et al (2023) ³⁰	Retrospective cohort	Moderate ^b
Jansen et al (2023) ³¹	Retrospective cohort	Moderate ^b
van der Lans et al (2023) ³²	Prospective cohort	Moderate ^b
Ottaviano et al (2022) ³³	Prospective cohort	Moderate ^b
De Corso et al (2022) ³⁴	Prospective cohort	Moderate ^b
Bachert et al (2019) ³⁵	Multicenter RCT	High

^aBecause it did not present a strong predictive association or robust consistency, ^bdue to the robustness of the findings and the consistency of the results

Institutional review board statement

The study was approved by the research committee of the Hospital Regional de Alta Especialidad Dr. Ignacio Morones Prieto (COFEPRIS 17 CI 24 028 093) on 18 December 2024, with registration number 09-24.

RESULTS

The initial search yielded 475 articles. Two independent reviewers (GJRR and VRSB) were in charge of the evaluation and selection of studies through the title and abstract, as well as the exclusion of duplicate studies. No language restriction was applied. After preliminary review, 22 articles were considered eligible in the title and abstract phase. They were retrieved to read the full text and evaluate their definitive inclusion in the review. Of the articles for reading, 3 were discarded because the full text was not available. The remaining 19 articles were then read, and 12 more were excluded because they did not fully address the use of dupilumab in patients with previous sinus surgery for CRSwNP. In the end, 7 articles (1RCT and 6 cohort studies) were included. The PRISMA flow chart summarizes the search process (Figure 1).

Seven articles were included in the present review, totaling 1603 patients who received dupilumab as adjunctive therapy to INCS. Table 2 summarizes the demographic information and characteristics of each study, including dupilumab dose, number of patients, mean age, and surgical history. All articles included patients with uncontrolled CRSwNP, most used a dupilumab dose of 300 mg applied subcutaneously (SC) every 2 weeks.

Regarding asthma, 63% of the total patients had this comorbidity. The average age of the population included was 52.5 years. 84.6% of the total patients had a history of having undergone at least one surgery.

Table 3 shows the clinical parameters evaluated in each study, comparing the results obtained for each parameter at the beginning and end of the follow-up period after the use of dupilumab. The study by Ottaviano et al is not included because it does not present the results of the sinonasal parameters during the follow-up period.³³

Nasal polyp size

Polyp size was assessed with the nasal polyp score (NPS), which is based on a scale of 0-8, the highest values corresponding to large polyps in both nostrils. Most of the studies obtained a significant reduction of the NPS during their follow-up periods. Bachert et al indicated that patients treated with dupilumab experienced significant improvement in NPS compared to those receiving placebo ($p < 0.0001$).³⁵

Nasal symptoms and quality of life

Quality of life was assessed using the sinonasal outcome test-22 (SNOT-22) with a score of 0-110; higher values correspond to worse outcomes. A score of less than 20 indicates mild symptoms.³⁶ Similarly, most studies obtained significant reductions during follow-up. Bachert et al reported that SNOT-22 scores improved significantly with dupilumab compared to placebo ($p < 0.0001$).³⁵

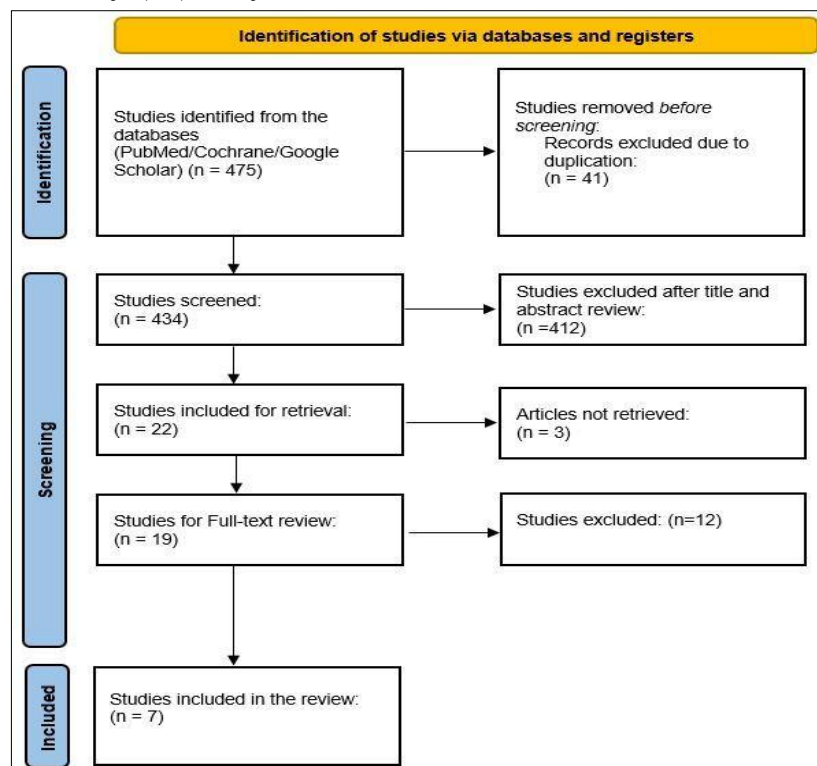


Figure 1: PRISMA flow chart.

Olfactory function

Most studies used the Sniffin' Sticks-16 identification test (SSIT-16) to assess this parameter. In this test, 16 odors are exposed to the patient, who must recognize each one. Depending on the number of substances identified, the result varies between 0 (none identified) and 16 (all identified). Thus, patients are grouped into anosmic (0-5), hyposmic (6-10) or normosmic (11-16).³⁴ van der Lans et al reported that 43.4% of their patients who completed follow-up went from anosmia to hyposmia; on the other hand, De Corso et al reported that 66.7% of patients obtained normosmia.^{32,34}

Bachert et al evaluated olfactory function through the University of Pennsylvania Smell Identification Test

(UPSIT).³⁵ It is reported that about 75% of patients suffered from anosmia at the beginning of the study, while only 24% to 30% continued with anosmia after dupilumab treatment.

Nasal obstruction

Nasal obstruction was evaluated through the nasal congestion score (NCS) with a scale of 0-3, where a score of 0 refers to the absence of symptoms and 3 to the presence of severe symptoms that are difficult to tolerate. In general, significant results were obtained in the studies that evaluated this parameter. Bachert et al indicated that treatment with dupilumab significantly improved NCS scores compared to placebo until the end of treatment in both studies ($p<0.0001$).³⁵

Table 2: Demographic information and study characteristics.

Author (s) and year	CRSwNP type	Dupilumab dosage	No. of participants	Asthma (%)	Mean age (years)	No. of participants with prior surgery	No. of past surgeries	Mean of previous surgeries	Years since last surgery, mean
Alicandri-Ciuffelli et al (2024) ²⁹	Uncontrolled CRSwNP	Dupilumab 300 mg SC every 2 weeks	145	110 (75.8)	55.1 (27-86)	145	Not specified	2.2 (1-13)	5.7
De Corso et al (2023) ³⁰	Uncontrolled CRSwNP	Dupilumab 300 mg SC every 2 weeks	648	366 (56.5)	54 (45-63)	592	1-244, 2-171 >3-177	2	4.8 (2.5-8.4)
Jansen et al (2023) ³¹	Uncontrolled CRSwNP	Dupilumab 300 mg SC every 2 weeks	40	35 (88)	52.7 (20-84)	40	Not specified	3.7±1.9	Not specified
van der Lans et al (2023) ³²	Uncontrolled CRSwNP	Dupilumab 300 mg SC every 2 weeks	228	184 (80.7)	51 (18-90)	227	>1-227, >3-117, >5-39	Not specified	4.5
Ottaviano et al (2022) ³³	Uncontrolled CRSwNP	Dupilumab 300 mg SC every 2 weeks	47	25 (53.2)	51.8 (21-74)	33	Not specified	2.3±1.5	6.1±4.3
De Corso et al (2022) ³⁴	Uncontrolled CRSwNP	Dupilumab 300 mg SC every 2 weeks	57	38 (67)	51.9 (23-75)	48	1-16, >1-32	Not specified	
Bachert et al (2019) ³⁵	Uncontrolled CRSwNP	SINUS-24 Dupilumab 300 mg SC every 2 weeks	143	82 (57)	52 (39-61)	99	>1-99, >3-33	2	5.9
		SINUS-52 Dupilumab 300 mg SC every 2 weeks	150	85 (57)	51 (42-61)	88	>1-88, >3-22	2	7.5

Continued.

Author (s) and year	CRSwNP type	Dupilumab dosage	No. of participants	Asthma (%)	Mean age (years)	No. of participants with prior surgery	No. of past surgeries	Mean of previous surgeries	Years since last surgery, mean
		weeks for 52 weeks (q2w)							
		SINUS-52 Dupilumab 300 mg SC every 2 weeks for 24 weeks then every 4 weeks for 28 weeks (q2w-q4w)	145	91 (63)	53 (42-63)	85	>1-85, >3-9	2	8.4

CRSwNP-Chronic rhinosinusitis with nasal polyps; SC-subcutaneous.

Table 3: Results of nasosinusal parameters after the use of dupilumab.

Author (s) and year	Follow-up period (months)	Moment of evaluation	NPS (0-8)	P value	SNOT-22 (0-110)	P value	SSTI	P value	NCS (0-3)	P value	ACT (5-25)	P value
Alicandri-Ciuffelli et al (2024) ²⁹	12	Baseline	5.6±1.3	0.000	56.1±18.4	0.000	5.7±2.7	0.0005	Not specified	Not specified	Not specified	Not specified
		End of follow-up	1.4±1.6	5	12.5±9.4	5	11.1±2.4					
De Corso et al (2023) ³⁰	12	Baseline	6	<0.00	58	<0.00	4	<0.001	Not specified	Not specified	Not specified	Not specified
		End of follow-up	1	1	12	1	12					
Jansen et al (2023) ³¹	13	Baseline	4.3±1.5	<0.00	60±22.2	<0.00	3.2±3.7	<0.0001	Not specified	Not specified	Not specified	Not specified
		End of follow-up	1.4±1.1	1	20.8±17.7	1	7.8±3.5					
van der Lans et al (2023) ³²	24	Baseline	5.3	Not specified	53.6	Not specified	3.7	Not specified	Not specified	Not specified	18.5	Not specified
		End of follow-up	1.3	Not specified	21.2	Not specified	7.3				21.4	Not specified
De Corso et al (2022) ³⁴	12	Baseline	5.7±1.5	<0.05	59.5±19.5	<0.05	3.83±3.2	<0.05	2.38±0.8	<0.05	17.4±5.5	<0.05
		End of follow-up	1.81±1.7		10.8±9.2		11.12±1.6		0.6±0.6		23.7±2.1	
Bachert et al (2019) ³⁵	SINUS-24 6	Baseline	5.6	<0.00	48	<0.00	14.6*	<0.0001	2.26	<0.00	Not specified	Not specified
		End of follow-up	3.75	01	18.5	01	25.3*		0.94			
	SINUS-52 13	Baseline	6.1	<0.00	51.02	<0.00	Not specified		2.46	<0.00	Not specified	Not specified
		End of follow-up	3.7	01	21.67	01			1.1			

NPS-Nasal polyp score; SNOT-22-sinonasal outcomes test-22; SSTI-Sniffin Sticks identification test; NCS-nasal congestion score; ACT-asthma control test; *values according to the University of Pennsylvania Smell Identification Test (UPSIT) (score 0-40)

Asthma management

Asthma symptoms were assessed through the asthma control test (ACT) ratings range from 5 (insufficient asthma control) to 25 (total asthma control). A score greater than 19 indicates good asthma control.³⁷ Better asthma control is reported in studies after dupilumab use, and a significantly faster reduction in NPS ($p<0.001$) and SNOT-22 ($p=0.004$) was demonstrated in asthmatic patients.³⁰

DISCUSSION

Uncontrolled CRSwNP is a disease in which most patients, despite first-line management, will require surgical intervention, and even post-procedure recurrence of nasal polyps is highly likely, causing patients to undergo multiple revision surgeries. Treatment with dupilumab resulted in a reduction in the frequency of revision surgeries. Jansen et al mentioned that it was not necessary to re-intervene on their patients during the study.³¹ Bachert et al maintained that treatment with dupilumab decreased the number of re-interventions.³⁵

Derived from the NPS evaluation, a significant reduction in the scores at the end of the follow-up period was demonstrated, indicating a reduction in the size of the polyps in patients with previously high scores now with small polyps in the middle meatus, but which do not condition a severe nasal obstruction, in turn this finding is related to the decrease or no need to use revision surgery as rescue therapy to improve nasal obstruction.

The use of dupilumab also showed better results in the scores of nasosinus parameters, on the results of SNOT-22 there was an improvement in the quality of life of patients at the end of follow-up, in the evaluation of olfactory function most of the studies used SSIT-16 with changes from hyposmia to normosmia. In the study by Bachert et al, UPSIT was used, which also evidenced a recovery of olfaction, for nasal congestion and asthma control only 2 studies evaluated these parameters, even so dupilumab achieved good control of the symptomatology.³⁵

In a post hoc analysis, Hopkins et al reported that in terms of NPS, the results with dupilumab were better in patients with more recent surgery (<3 years) compared to those with more than 5 years since the last surgery ($p=0.01$).³⁸ This suggests that the time elapsed since the last sinus surgery could influence the magnitude of the response to dupilumab, with better results being obtained in those patients where dupilumab is used as adjuvant therapy in the short-term postoperative period.

Derived from the results obtained by Bachert et al, the need for continuous suppression of the inflammatory process to maintain disease control is emphasized.³⁵ There is currently no consensus standardizing the appropriate timing of the use of this therapy; most guidelines suggest

that its use should be maintained as long as it continues to provide clinical benefit.

From a practical perspective, the high cost of biologics compared to other therapies represents a major limitation, especially if the clinical benefit is not sustained without continuous treatment, which could significantly increase cumulative costs. A recent analysis showed that ESS was the most cost-effective option over 36 years, regardless of the frequency of revision surgery.³⁹ If this therapy decreases the need for salvage interventions, and with the emergence of new biologics, costs could be reduced. In addition, increasing the interval between doses of dupilumab could improve its cost-effectiveness. However, the high cost of these treatments requires careful evaluation of their long-term feasibility.

The most frequently reported adverse events in the studies following the use of dupilumab included: mild joint pain, myalgia, moderate headache, conjunctivitis, nasopharyngitis, epistaxis, transient increase in eosinophils and erythema at the injection site, despite the effects, it is mentioned that treatment with dupilumab was well tolerated in most patients.

Although surgical treatment options are generally considered safe, they are not without risk. They can present both minor (1.1% to 20.8% incidence) and major (1.5%) risks, such as severe bleeding, infection, or damage to the ocular orbit or skull.⁴⁰ Treatment with dupilumab may be an alternative to reduce the risk in patients who have undergone multiple revision surgeries.

Limitations

The limited number of studies included in this review is due to the recent approval of dupilumab for the treatment of CRSwNP in 2019. Given the nascent nature of the field, a comprehensive clinical evidence base is not yet available. However, this review allows us to systematize the available information, identify gaps in the literature, and guide future research on the use of biologic therapies in CRSwNP.

It was decided not to perform a meta-analysis due to the design of the studies and the results reported. The synthesis was performed in a narrative manner, comparing the significant results of each study. We did not use a formal tool to assess risk of bias, as most of the included studies were clinical cohorts. Instead, the GRADE system was used to assess the quality of evidence, providing an overview of the level of confidence in the findings.

CONCLUSION

The data presented support the benefit of using dupilumab as adjuvant therapy in postoperative patients with CRSwNP that has been refractory to surgery, leading to a reduction in the rate of revision surgeries along with an improvement in nasosinus symptoms. Further studies

addressing the effect of dupilumab in the short-term postoperative period are needed to compare the results obtained. Before initiating treatment with dupilumab, shared decision making is recommended throughout the process to determine patient preferences.

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