Dupilumab improves symptoms and reduces rescue treatments in patients with CRSwNP and recalcitrant frontal sinusitis

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Abstract

**Background.** Recalcitrant frontal sinusitis in patients with chronic rhinosinusitis with nasal polyps (CRSwNP) have a negative impact on quality of life due to frontal pain and a high risk of sinus occlusion, thus necessitating repeated courses of antibiotics, systemic corticosteroids, and multiple surgeries. **Objective.** The aim of this study was to investigate if the use of biologics can improve symptoms including facial pain and reduce use of rescue treatments in patients with severe uncontrolled CRSwNP and concomitant recurrent frontal sinusitis. **Materials and Methods.** This is a real-life, observational, no-profit case series. Between November 2022 and December 2023, we enrolled cohort of 10 patients with severe uncontrolled CRSwNP and concomitant recurrent frontal sinusitis associated to invalidating facial pain measured by MIDAS score and that were treated with dupilumab 300 mg every 2 week and followed for at least 12 months. **Results.** The mean MIDAS score decreased from 45.6±10.7 at baseline to 1.3±2.3 at 6 months (p<0.05). The same trend was observed for VAS craniofacial pain: from 7.3±1.6 at baseline to 1.2±1.5 at 6 months (p<0.05). The use of systemic corticosteroids and analgesics was significantly reduced. No patient needed oral corticosteroids during treatment with dupilumab (p<0.05), and the use of analgesics decreased from 9.6±3.1 mean brief cycles of NSAIDs at baseline to 0.6±1.3 at 1 year of follow-up (p<0.05). **Discussion.** Our results demonstrated that use of an anti-type-2 inflammatory pathway biologic can improve symptom control including recurrent craniofacial pain and reduce the need for rescue medical treatments in patients with severe uncontrolled CRSwNP and concomitant recurrent frontal sinusitis.

ABSTRACT

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**Keywords:** Chronic Rhinosinusitis; nasal polyps; biologics; Endoscopic Sinus Surgery; frontal sinusitis; headache; oral corticosteroids.

**INTRODUCTION**

Severe uncontrolled chronic rhinosinusitis with nasal polyps (CRSwNP) has a significant impact on the quality of life of patients. In the majority of cases clinical manifestations are caused and sustained by a predominant type 2 inflammatory profile, whose inflammatory mediators contribute to the pathogenesis of the disease, including excessive tissue remodeling. In particular IL-13 is thought to be a key driver of airway epithelial remodeling and cell-type compositional changes. Recalcitrant frontal sinusitis may be associated with severe uncontrolled CRSwNP and lead to an extra burden of the disease on the quality of life, which in some patients may be debilitating. Indeed, recurrent frontal sinusitis may worsen symptoms, especially frontal pain, increasing the need for courses of systemic corticosteroids and multiple surgeries to avoid sinus occlusion and complications. Unfortunately, even though the surgery performed was effective and radical, re-stenosis of the frontal ostium occurs often and represents a persistent problem. This increases the risk of recurrent frontal sinusitis due to bacterial superinfections, which requires the prolonged use of antibiotics and, in some cases, a new surgery to prevent major complications.

Therefore, in cases of severe uncontrolled CRSwNP and concomitant recurrent frontal sinusitis, it may be possible to obtain some benefits with biologics, especially considering that dupilumab has been demonstrated to be very effective on both the inflammatory response and tissue remodeling by inhibiting the signaling of IL-4 and IL-13. Indeed, its efficacy in severe uncontrolled CRSwNP has been demonstrated in both clinical trials and real-life studies, reducing the need for surgery and/or oral corticosteroids (OCS).

The objective of the present study was to evaluate benefits that may be obtained in the management of patients with CRSwNP and concomitant recalcitrant frontal sinusitis. In particular we aimed to verify its efficacy in reducing significant sinonasal symptoms including frontal pain and in reducing the need for rescue treatments.

**MATERIALS AND METHODS**

**Study population, inclusion and exclusion criteria.**

This was a real-life, observational, no-profit case series. We enrolled consecutive 10 adult patients with severe uncontrolled CRSwNP and concomitant recurrent frontal sinusitis on treatment with dupilumab between November 2022 and December 2023. We specifically enrolled patients complaining of significant craniofacial pain due to recalcitrant frontal sinusitis with at least one sinus completely opacified at computed tomography (CT) and who were candidates for revision frontal sinusotomy.

Inclusion criteria were: age > 18 years; severe uncontrolled diffuse CRSwNP and prescribed dupilumab based on the indications of Italian Agency of Drugs (AIFA) [confirmed diagnosis of diffuse CRSwNP by endoscopy and CT who met the following criteria: severe disease stage (NPS ≥5 and/or SNOT-22 ≥50; inadequate symptom control with intranasal corticosteroids (INCS; normal regimen: mometasone furoate 200mcg per nostril per day) in the previous 3 months; failure of previous medical treatments (at least 2 cycles of systemic corticosteroids over the last year) and/or of previous endoscopic sinus surgery (ESS)]; significant frontal facial pain measured by VAS (VAS >5), severe disability measured by MIDAS score >20; need for brief cycles of NSAIDs in the last 6 months (>2 per day at least 5 days); complete opacification of at least one frontal sinus at baseline CT scan.
Exclusion criteria: localized CRS; secondary CRS (cystic fibrosis, sinonasal tumor, primary ciliary dyskinesia, or autoimmune disease); continuous systemic steroid treatment; sino-nasal granulomatous disease/tumor; previous radiotherapy for head and neck cancer; complication of frontal sinusitis for which surgery is necessary.

Dupilumab 300 mg was self-administered subcutaneously every two weeks as add-on therapy to INCS.

Study design and outcomes

Data were analysed at baseline, and at 3, 6, and 12 months of follow-up. We took into consideration clinical data such as patient demographics, use of previous biologics, number, type and extension of previous surgeries, previous use of anti-inflammatory drugs or analgesics, and use of oral corticosteroids in the previous year. We analysed the response to treatment during the first year of follow-up time, by means of:

- Sino Nasal Outcome Test (SNOT)-22: we utilized the validated Italian version of SNOT-22 questionnaire for the evaluation of quality of life.\textsuperscript{10}

- Nasal endoscopy with Nasal Polyps Score (NPS). Each side of the nasal cavity was separately evaluated and scored according to the last EAACI position paper.\textsuperscript{11}

- Nasal Congestion Score (NCS): patients evaluated their symptoms of congestion/obstruction from the previous day using the NC scale.\textsuperscript{12}

- VAS for nasal symptoms: the intensity of symptoms (nasal obstruction, rhinorrhea, smell, cranio-facial pain) was assessed using a horizontal 10 cm line with points from 0 (no symptom at all) to 10 (symptom completely debilitating).\textsuperscript{11}

- EQ-5D-5L: we specifically used the EQ-VAS, which records the respondent’s overall current health on in a vertical visual analog scale from 0 to 100 points.\textsuperscript{13}

- Sniffin’ Sticks 16-identification test to assess the olfactory function: this test is performed administering 16 odors at supra-threshold intensity to the patient.\textsuperscript{14,15}

- Migraine Disability Assessment Score (MIDAS): this is a self-administered questionnaire that provides a quantitative measure of headache-related disability, assessing the amount of time lost for schoolwork or work, household work or chores, and family, social, and leisure activities. The scoring system for the MIDAS questionnaire is as follows: 5 to 10 indicates little or no disability; 10 to 20 indicates moderate disability; a score higher than 20 denotes severe disability.\textsuperscript{16}

- Nasal cytology was used to evaluate the presence of local eosinophilic inflammation: the examination was carried out on the material taken from the lower and middle turbinate bilaterally, by “scraping” the mucosa with a Rhino-probe (Farmark SNC, Milan, Italy). Eosinophilic inflammation was measured by the eosinophil count per high power field (Ec-hpf).\textsuperscript{17,18}

Statistical Analysis

All data were analyzed using \textit{SPSS} 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). Continuous data were tested for normality using the Kolmogorov-Smirnov test. Normally distributed data were described as mean ± standard deviation (SD) and compared using Student t-test for two independent samples. Non-normal data were described as median (interquartile range, IQR, and 25\textsuperscript{th} and 75\textsuperscript{th} percentiles) and comparisons between groups were assessed using the Mann-Whitney U test. Significance threshold was set at $p<0.05$.

RESULTS

Baseline characteristics of the cohort.

We enrolled a cohort of 10 consecutive patients (6 females and 4 males; mean age: 51.4± 12.0 years; range 29-60). The mean number of previous endoscopic sinus surgery for CRSwNP before starting with dupilumab
The NPS decreased from a mean of 3.1 ± 0.6 at baseline to 1.9 ± 0.8 at 3 months (p < 0.05), to 1.3 ± 0.7 at 6 months (p < 0.05), and to 0.2 ± 0.4 at 12 months (p < 0.05). Mean NCS values decreased from 2.6 ± 0.5 at baseline to 1.3 ± 0.8 at 3 months (p < 0.05), and to 1.1 ± 0.7 and 0.4 ± 0.5 at 6 and 12 months, respectively (p < 0.05).

Regarding quality of life, the mean SNOT-22 total score significantly decreased from 66.9 ± 9.6 at baseline to 77.0 ± 11.3 after 3 months of therapy (p < 0.05). This trend was sustained at 6 and 12 months, with values that decreased to 35.6 ± 7.4 and 20.6 ± 6.2, respectively (p < 0.05). The mean VAS score for nasal obstruction decreased from 7.0 ± 1.3 at baseline to 3.6 ± 1.8 at 3 months (p < 0.05), to 2.4 ± 2.0 at 6 months (p < 0.05), and to 1.3 ± 1.1 at 12 months (p < 0.05); Mean VAS rhinorrhea values decreased from 6.7 ± 1.4 at baseline to 2.9 ± 2.1 at 3 months (p < 0.05), to 2.6 ± 1.9 at 6 months (p < 0.05), and to 1.0 ± 1.1 at 12 months (p < 0.05).

For olfaction, mean VAS smell values decreased from 7.1 ± 2.3 at baseline to 4.0 ± 1.8 at 3 months with no statistically significant difference; however, mean values significantly decreased to 2.4 ± 1.6 at 6 months (p < 0.05) and to 1.4 ± 2.5 at 12 months (p < 0.05). Moreover, Sniffin’ Sticks Identification test total score increased from a mean of 5.3 ± 3.0 at baseline to 7.1 ± 1.1 at 3 months (p < 0.05), to 9.3 ± 1.6 at 6 months (p < 0.05), and 10.6 ± 1.5 at 12 months (p < 0.05).

Finally, a significant difference between local eosinophilia at nasal cytology before and after treatment was observed in all patients and specifically the mean eosinophil count for high power field (Ec-hpf) decreased from a mean value of 30.9 ± 10.2 to 5.5 ± 3.5 (p < 0.05) after 12 months.

**Efficacy on cranio-facial algia and need for analgesics**

With regard to cranio-frontal pain, we analyzed the trend of MIDAS score and VAS craniofacial algias. The mean MIDAS score decreased from 45.6 ± 10.7 at baseline to 10.4 ± 2.57 at 3 months (p < 0.05), to 1.3 ± 2.3 at 6 months (p < 0.05), and 0.9 ± 0.6 at 12 months (p < 0.05). The same trend was observed for VAS craniofacial pain: this decreased from 7.3 ± 1.6 at baseline to 2.5 ± 3.2 at 3 months (p < 0.05), to 1.2 ± 1.5 and 1.0 ± 1.4 at 6 and 12 months, respectively (p < 0.05).

Finally, the frequency of administration of OCS and analgesics was significantly reduced. In fact, no patient needed a cycle of OCS during treatment with dupilumab (p < 0.05), and the use of analgesics decreased from 9.6 ± 3.1 brief cycles of NSAIDs in the last year to 0.6 ± 1.3 at 1 year of follow-up (p < 0.05). Finally, regarding globally evaluated quality of life, the EQ-VAS improved from 50 ± 12.9 at baseline to 69.3 ± 11.3 at 3 months (p < 0.05) to 77.0 ± 14.2 and 81.4 ± 9.4 at 6 and 12 months of follow-up, respectively (p < 0.05). The most representative results after 6 months of treatment are reported in Table 3, while Figures 1-3 show some of the most representative clinical cases and their outcome after therapy with dupilumab.

**DISCUSSION**

Endoscopic sinus surgery (ESS) is currently considered the standard surgical procedure for CRSwNP that is not controlled with medical treatment. Although surgery can improve the quality of life in the short term, a proportion of patients experience poor control of symptoms, especially in the long-term. Predictors of failure have been supposed to be type 2 inflammation, asthma, aspirin-exacerbated respiratory disease, lack of compliance with long-term post-operative local corticosteroids, and incomplete initial surgery. Recalcitrant frontal sinusitis can occur in patients with diffuse CRSwNP, especially after multiple surgeries and/or inadequate surgery, due to chronic inflammation and abnormal scarring. The anatomy of the frontal recess and frontal ostium, in fact, are quite complex and this is heightened in cases of revision...
frontal sinus surgery due to prior mucosal trauma, increasing the likelihood of additional complications. Moreover, in these patients it is often necessary to prescribe cycles of corticosteroids and antibiotics to manage exacerbations of symptoms including cranio-facial pain that could invalidating.

The advent of biologics can significantly change the approach to this condition. For the first time we preliminarily demonstrated that in patients with CRSwNP and recalcitrant frontal sinusitis dupilumab was effective not only in improving sino-nasal outcomes, but also in reducing severe pain and the use of rescue treatments. Furthermore, treatment with dupilumab can be a valuable alternative to surgery, especially when a revision of frontal surgery can be challenging for ENT surgeon and it may be associated with a higher risk of failure and/or complications.

The effectiveness of dupilumab in the treatment of recalcitrant frontal sinusitis could be explained on the one hand by its documented role in reducing the type 2 inflammation by blocking IL-4, and on the other hand in reducing remodeling/fibrotic processes by interfering with the IL-13 pathway. Certainly, the inhibition of excessive scarring and fibrosis in these cases would be a determining factor, as these phenomena are particularly common after frontal revision surgery. However, the evaluation of previous surgery cannot be disregarded before starting biological therapy, since the post-surgical anatomical features could preclude the effectiveness of the biologics. In this regard, all patients of our cohort at the time of the enrollment had a significant number of previous surgeries but with a low ACCESS score, thus indicating a complete or nearly complete surgery. In this context, the condition that could have led to a frontal recurrence is mainly attributable to the high load of type 2 inflammation.

Over the years a significant value to the surgical clearance of the frontal recess has been given by surgeons.

For that reasons frontal sinus surgery was extended especially when standard sinus surgery has failed, resulting in stenosis of the frontal ostium due to scar tissue or new bone formation. According to previous classification, the Draf 3 procedure, creates a common drainage pathway from the frontal sinus to the nasal cavity. This is achieved by removing the upper nasal septum, the inter-frontal sinus septum, the agger nasi regions, and the floor of each frontal sinus using a drill. Previous studies showed that the primary Draf 3 procedure in patients with CRSwNP has a failure rate of 8.9%, while the revision Draf 3 procedure has a failure rate of 21%; however, the success rates of the Draf 3 procedure may vary due to the surgical technique and patient population. In fact, Morrissey et al. observed that patients with intraoperative pus during their initial Draf 3 procedure, more than 5 previous sinus operations, or NSAID-ERD are at an increased risk of failure.

Basing on that data in analyzing reasons for frontal surgeries failures, we should taking into account not only the anatomical characteristics e the surgical details but also the characteristics of the endotype of the disease.

If from one side authors have suggested that an extended surgical approach may yield better results than traditional ESS in preventing recurrent frontal sinusitis, other authors proposed different approaches to avoid re-stenosis of the frontal sinus, such as the use of mucosal flaps or use of balloon dilation or local stents with slow release of drugs. In particular, recent advances in biomaterial technology have led to the development of corticosteroid-coated sinus stents, which can elute the drug in a controlled manner via a bioabsorbable core. The stenting action is crucial in achieving this goal to separate the raw edges of the mucosal wound surface and to prevent formation of an adhesion and stenosis. Two randomized controlled trials (RCTs) have shown that sinus stents that release steroids can maintain the patency of the frontal sinuses and improve mucosal wound healing after functional endoscopic sinus surgery by reducing inflammation, polyposis, and adhesions. However, very few studies have evaluated the use of bioabsorbable steroid-eluting sinus stents for the treatment of recalcitrant chronic frontal rhinosinusitis and we are especially missing study comparing the outcomes of eluting stents and biologics.

In conclusion, our results demonstrate that the use of dupilumab, as anti-type-2 inflammatory pathway biologic drug, in patients with recalcitrant frontal sinusitis, can improve control of symptoms including severe and debilitating pain, avoid exacerbations and reduce the need for rescue treatments such as OCS, antibiotics, and analgesics. The preliminary results of our study should be interpreted in light of some significant limitations, such as the limited number of patients; for that reason a real-life multicenter study
is needed to confirm our observations, in particular to confirm the long-term control of symptoms and the reduction of need for further revision surgeries.

REFERENCES


**FIGURE LEGENDS**

**Figure 1.** Fifty-six years old male patient with 2 previous endoscopic sinus surgery (1 ESS in the 2016 and ESS + Draft 3 in 2019). One major complication during the last surgery (skull base CSF Leak in ethmoid intraoperatively repaired). Recurrence of NP diagnosed in the march 2022 with re-stenosis of the left frontal sinus with severe facial pain. Complete remission of polyps after three months of Dupilumab.

Figure 2. Fifty-three years old male patient with medical history of multiple long-lasting cycles of oral corticosteroid in the last years (>60 cumulative days/year) and previous treatment with Mepolizumab. Six previous surgeries including bilateral Draft 2b. In April 2022 diagnosis of recurrence of NP associated to severe facial pain. Complete resolution of pain and remission of polyps after 6 months of treatment with Dupilumab. A. Recurrence of nasal polyps in left frontal recess. B. Left frontal recess view after 3 months of treatment. C. Left frontal recess view after 6 months of treatment. D. Left frontal recess view after 12 months of treatment. E. Recurrence of nasal polyps in right frontal recess. F. Right frontal recess view after 3 months of treatment. G. Right frontal recess view after 6 months of treatment. H. Right frontal recess view after 12 months of treatment.


TABLES.

**Demographics**

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**Table 1.** Baseline characteristics prior to treatment with dupilumab. Abbreviations, SD: Standard Deviation; NSAID-ERD: Non-steroidal antinflammatory drugs – exacerbated respiratory disease; OCS: oral corticosteroids.

**Table 2.** Clinical characteristic of the entire cohort at baseline, in detail. Abbreviations, FESS: Functional Endoscopic Sinus Surgery; OSAS: Obstructive Sleep Apnoea Syndrome; NSAID-ERD: Non-steroidal anti-inflammatory drugs – exacerbated respiratory disease.
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Table 3. Outcomes after 6 months of treatment with dupilumab. Abbreviations, SNOT-22: Sinonasal Outcome Test; NPS: Nasal Polyp Score; NSAID: Non-Steroidal Antiinflammatory Drugs; VAS: Visual Analogue Scale; MIDAS: Migraine Disability Assessment Score.
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