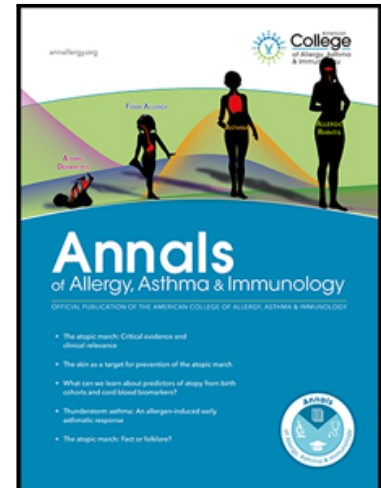


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Title: Dupilumab as an adjunct to surgery in patients with aspirin-exacerbated respiratory disease: a case series

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Abbreviations/Acronyms: AEC – absolute eosinophil count, AERD – aspirin-exacerbated respiratory disease, CRSwNP – chronic rhinosinusitis with nasal polyps, ESS- endoscopic sinus surgery, SNOT-22 - Sino-Nasal Outcome Test 22 Questions, ACT – Asthma Control Test

Aspirin-exacerbated respiratory disease (AERD) is characterized by the triad of asthma, chronic rhinosinusitis with nasal polyps (CRSwNP), and respiratory reactions to cyclooxygenase-1 inhibitors.¹ Patients with AERD have severe CRSwNP that is often refractory to standard therapies including intranasal corticosteroids² and is associated with high utilization of healthcare resources.³ Following endoscopic sinus surgery (ESS), nasal polyp regrowth occurs within two years for 85% of patients with AERD,⁴ and for many patients, surgery does not provide complete resolution of symptoms.⁵ While aspirin desensitization followed by high-dose daily aspirin can delay nasal polyp recurrence in many patients with AERD,⁶ not all patients respond to this therapy, and some cannot tolerate high-dose daily aspirin due to side effects.⁷ Given the significant burden of recurrent nasal polyposis following ESS in AERD, targeted respiratory biologics are promising.⁸

Dupilumab, a monoclonal antibody targeting the interleukin 4 receptor α subunit, is approved for inadequately controlled CRSwNP, and has demonstrated efficacy in reducing endoscopic nasal polyp size, decreasing congestion and mucus production, and improving sense of smell.^{5,9} In a *post hoc* analysis of a Phase 2a proof-of-concept study of dupilumab for CRSwNP, patients with AERD had robust improvements in endoscopic nasal polyp score and sinonasal symptoms.¹⁰ Prior studies of dupilumab for CRSwNP have targeted patients with substantial nasal polyp burden, but its effectiveness when used perioperatively in combination with ESS has not been reported. In this study, we assess the effects of perioperative dupilumab treatment in patients with AERD who had rapid nasal polyp recurrence after previous ESS and did not tolerate or benefit from high-dose daily aspirin therapy.

We performed a retrospective chart review of eight patients enrolled in the Brigham and Women's Hospital AERD patient registry with physician-diagnosed AERD. All eight patients had rapid recurrence of CRSwNP after a previous ESS and subsequently underwent a revision surgery with peri-operative dupilumab initiation. The study was approved by the Mass General Brigham Institutional Review Board. Demographic information, medications, ESS history and surgical outcomes, Sino-Nasal Outcome Test (SNOT-22) and Asthma Control Test (ACT) scores, pulmonary function testing, and radiologic and laboratory data were extracted from the electronic medical records (Epic Systems, Verona, WI) and analyzed with paired t-test or McNemar's test as appropriate, with GraphPad Prism v7.0d (GraphPad, La Jolla, CA).

Patients were prescribed dupilumab 300 mg every 14 days between 1/2018 and 8/2020 and underwent revision ESS within 6 months of being prescribed dupilumab with the indication listed in **Table 1**. Only the most recent prior ESS (which we refer to as "initial ESS") was compared as data was not available for all prior sinus surgeries. Time to polyp recurrence was compared for initial ESS and revision ESS with perioperative dupilumab. Nasal polyp regrowth after initial ESS was measured via rhinoscopy by patients' otolaryngologist in 7/8 cases, and in 1 case by an allergist's examination. With revision ESS, nasal polyp regrowth was assessed by rhinoscopy by the patient's otolaryngologist in all 8 cases. Symptom scores and lung function were available only before and after the revision ESS, and pre-dupilumab and post-dupilumab scores were compared.

Patients had a mean of 3.1 lifetime ESSs (range 2-5) and a mean Lund-Mackay score before the revision ESS of 18.3 (range 12 – 22). Five out of 8 patients had history of physician-dianosed

atopy. Following the initial ESS, all patients underwent aspirin desensitization with plan for daily aspirin therapy. One patient did not tolerate the desensitization due to severe aspirin-induced reaction, four patients did not find daily aspirin therapy to be effective (which could indicate a more severe phenotype of AERD) and three patients discontinued aspirin therapy due to gastrointestinal side effects. Ultimately all eight patients had nasal polyp recurrence requiring revision ESS. At the end of the study period, all eight patients remained on dupilumab. Total follow-up time from dupilumab initiation to the end of the study period was 21.1 months (range 11-36 months).

All eight patients had regrowth of nasal polyps ≤ 9 months after initial ESS (mean time to polyp recurrence 3.0 ± 2.6 months). With revision ESS and perioperative dupilumab, no patients had rhinoscopic evidence of nasal polyp recurrence within 9 months of ESS ($P=0.013$, McNemar's test). Throughout the follow-up period, only Patient #1 (**Table 1**) had a recurrence of polyps. After 11 months on dupilumab (approximately 12 months after revision ESS), he complained of hyposmia and congestion, and on rhinoscopy was found to have an endoscopic nasal polyp score of 1/8. He stopped all other maintenance medications after starting dupilumab including intranasal steroids and saline irrigations, which likely contributed to nasal polyp recurrence. All the other patients continued on intranasal corticosteroids throughout the study period.

There were no significant differences in FEV_1 % predicted, ACT score, or absolute eosinophil count pre-dupilumab versus post-dupilumab (measured at least 2 months after initiation of dupilumab). SNOT-22 scores significantly improved following ESS with

perioperative dupilumab (mean improvement, 15.7, $P=0.03$). However, baseline SNOT-22 data were not available for the initial ESS making it difficult to assess the contribution of dupilumab to SNOT-22 improvement versus the impact of the revision surgery on SNOT-22 improvement.

There are significant challenges to treating severe CRSwNP in patients with AERD due to inadequate response to standard therapies and high rates of polyp recurrence after ESS. Respiratory biologic medications, such as dupilumab, provide promising therapeutic options, and this study is one of the first to examine outcomes of perioperative dupilumab in AERD patients. Patients with rapidly recurring nasal polyps following historical ESS showed significant decreases in rate of polyp regrowth and sinonasal symptoms after ESS with perioperative dupilumab therapy.

Our study is limited given the small number of patients and retrospective nature. While we were able to provide a direct comparison of time to polyp regrowth between initial and subsequent ESS, there are multiple potential confounding variables that could influence nasal polyp recurrence. Nevertheless, given the challenge of treating these patients and the lack of literature on dupilumab as an adjunct to surgery in this patient population, this is an important initial study. Further prospective studies on polyp regrowth and upper and lower respiratory symptoms after perioperative treatment with dupilumab are needed to confirm its utility.

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Table 1: Patient characteristics

Patient	1	2	3	4	5	6	7	8	Mean (SD)	P-value*
Sex	M	M	M	F	M	M	F	F		
Age	48	54	36	57	25	74	18	69	47.6 (20.0)	
Lifetime ESS (number)	4	2	5	4	2	3	3	2	3.1 (1.1)	
Lund Mackay Score	22	15	22	21	12	21	20	13	18.3 (4.2)	
Baseline eosinophil (cells/ μ L)	620	540	250	30	-	0	1500	1140	582.8	
Baseline IgE (IU/mL)	1700	489	9	259	-	-	18	152	437.8 (643.4)	
Prior maintenance aspirin dose (mg)	650 BID	650 BID	650 BID	650 BID	650 BID	N/A	325 qAM, 650 qPM	650 BID		
Indication for dupilumab therapy	Severe persistent asthma	Atopic dermatitis [†]	CRS wNP	Severe persistent asthma	CRS wNP	Severe persistent asthma	Severe persistent asthma	Severe persistent asthma		
Revision ESS date	12/2018	3/2018	6/2019	5/2019	2/2019	5/2019	4/2020	12/2018		
Dupilumab start date	1/2019	1/2018	9/2019	5/2019	8/2019	5/2019	8/2020	6/2019		
Total follow-up time (mo) [‡]	24	36	16	20	19	22	11	21	21.1	

									(7.2)
Historical time to polyp regrowth after prior ESS (mo) [#]	2	2	3	3	9	3	1	1	3.0 (2.6)
Time to polyp regrowth after repeat ESS + dupilumab (mo)	11	No recurrence	No recurrence	No recurrence	No recurrence	No recurrence	No recurrence	No recurrence	
Change in ACT score [@]	-6	+1	-	+4	+4	-1	+12	+8	3.1 [*]
Change in SNOT-22 [@]	-4	-27	-37	-	-7	-18	+4	-21	0.15 [*]
Change in FEV ₁ (%) predicted pre- to post-dupilumab	+5%	-8%	+2%	+14%	-	-6%	-	+26%	0.03 [*]

*Paired t-test. [#] From dupilumab start to end of follow-up period. ^{*} Dupilumab was prescribed for atopic dermatitis prior to the dupilumab approval for asthma and CRSwNP, but patient also had severe persistent asthma and severe CRSwNP. [#] After initial endoscopic sinus surgery. [@] Comparison of pre- and post-dupilumab assessment (≥ 2 months after dupilumab initiation). ^{*} Mean change in pre- and post-dupilumab values. ESS – endoscopic sinus surgery, ACT – asthma control test, CRSwNP – chronic rhinosinusitis with nasal polyps, SNOT – Sinonasal Outcome Test, FEV₁ – forced expiratory volume in 1 second