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ORIGINAL ARTICLE

Use of intraoperative frontal sinus mometasone-eluting stents decreased interleukin 5 and interleukin 13 in patients with chronic rhinosinusitis with nasal polyps

Alexander L. Schneider MD[1] | **Samuel D. Racette MD**[1] | **Anthony K. Kang BA**[1] | **Abhita T. Reddy MD**[1] | **Julia H. Huang DDSMS**[1] | **David S. Lehmann MD**[1] | **Caroline P.E. Price BA**[1] | **Jacob G. Eide MD**[1] | **Samuel R. Rodeghiero BS**[1] | **David B. Conley MD**[1] | **Kevin C. Welch MD**[1] | **Robert C. Kern MD**[1] | **Stephanie Shintani-Smith MDMS**[1] | **Anju T. Peters MDMS**[1,2] | **Atsushi Kato PhD**[1,2] | **Whitney S. Stevens MDPhD**[1,2] | **Robert P. Schleimer PhD**[1,2] | **Bruce K. Tan MDMS**[1,2]

[1]Department of Otolaryngology, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA

[2]Division of Allergy and Immunology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA

Correspondence
Bruce K. Tan, MD, MS, Department of Otolaryngology – Head and Neck Surgery, Northwestern University Feinberg School of Medicine, 676 North St. Clair Street, Suite 1325, Chicago, IL 60611, USA.
Email: b-tan@northwestern.edu

Abstract

Background: Mometasone-eluting stents (MES) have demonstrated improvement in short-term endoscopic outcomes and reduce short- to medium-term rescue interventions. Their effect on the local inflammatory environment, longer-term patient-reported outcomes, and radiographic severity have not been studied.

Methods: Middle meatal mucus and validated measures of disease severity were collected before and 6 to 12 months after endoscopic surgery in 52 patients with chronic rhinosinusitis with nasal polyps (CRSwNPs). Operative findings, type 2 mediator concentrations, intraoperative variables, and disease severity measures were compared between those who did and those who did not receive intraoperative frontal MES.

Results: A total of 52 patients with CRSwNPs were studied; 33 received frontal MES and were compared with 19 who did not. Pre–endoscopic sinus surgery (ESS) middle meatus (MM) interleukin (IL) 13 and eosinophil cationic protein (ECP) were higher in the stented group ($p < 0.05$), but pre-ESS clinical measures of disease severity were similar as were surgical extent and post-ESS medical management. Intraoperative eosinophilic mucin was more frequent in the stented group (58% vs 11%, $p = 0.001$). IL-5 ($p < 0.05$) and IL-13 ($p < 0.001$) decreased post-ESS in the stented group, but this was not observed in the nonstented group. Post-ESS IL-4 and IL-13 were higher in the nonstented vs stented group ($p < 0.05$ for both).

Conclusion: Although patients who received intraoperative frontal MES had significantly higher pre-ESS MM IL-13 and ECP, patients who received frontal MES had lower concentrations of IL-4 and IL-13 than those who did not at a median of 8 months post-ESS. However, these changes did not correspond to significantly different measures of symptomatic or radiographic disease severity.

KEYWORDS

CRSwNP, endotype, mometasone, nasal polyps, patient-reported outcome measures, sinus stent

1 | INTRODUCTION

The treatment of chronic rhinosinusitis (CRS) generally begins with medical therapy, with functional endoscopic sinus surgery (ESS) reserved for recalcitrant disease.[1] Post-ESS endoscopic findings of ostial stenosis and synechiae make up two of the most common complications following ESS and are often thought to represent treatment failure.[2–4] CRS with nasal polyps (CRSwNPs) represents a particularly challenging CRS subtype known to be characterized by local elevation of type 2 (T2) inflammatory mediators and high rates of post-ESS symptom recurrence or revision surgery. Elevated T2 inflammation at the time of surgery has been associated with poor surgical outcomes, and it is thought that post-ESS inflammation of the sinonasal cavities may lead to the aforementioned complications of synechiae and ostial stenosis.[5,6] Additionally, the major medical therapies for CRSwNPs including intranasal corticosteroids (INCs) and systemic oral corticosteroids (OCS), as well as recently approved biologics, all revolve around inhibiting T2 inflammatory mediators such as interleukin (IL) 4, IL-5, and IL-13.[7]

Given the importance of combating T2 inflammation as well as preventing synechiae and ostial stenosis, drug-eluting implants that mechanically maintain sinus patency and locally release a lipophilic corticosteroid have been approved for intraoperative placement following ESS.[8] The Propel family of bioabsorbable mometasone-eluting stents (MES) (Intersect ENT, Palo Alto CA) were approved for intraoperative placement into the post-ESS ethmoid, maxillary, and frontal sinuses and have been shown to result in improved postendoscopic and patient-reported outcome measures (PROMs) in short to medium time-frames up to 6 months post-ESS.[8–11]

The effects of intraoperative MES in CRS without nasal polyps (CRSsNPs) and CRSwNP have been well-studied in terms of their effect on endoscopic severity, need for rescue OCS or intervention, and symptomatic severity, primarily within 30- to 90-day postoperative periods in randomized controlled trials.[10,12,13] Although T2 inflammation is thought to play an important role in the pathogenesis and post-ESS recalcitrance of CRSwNPs,[14–16] to our knowledge there have been no published studies on the effects of MES on T2 mediators or their relationship with post-ESS disease severity. Here, we compare T2 middle meatus (MM) inflammation in patients with CRSwNPs before and after ESS after stratifying by placement of intraoperative MES. We also explore the relationship of these effects with post-ESS disease severity on an intermediate- to long-term time frame.

2 | METHODS

2.1 | Patient enrollment

This study was a prospective recruitment of patients with CRSwNPs who had undergone ESS at Northwestern Memorial Hospital and had previously consented to collection of MM secretions for our biorepository between 2017 and 2020 (institutional review board number STU00016917). Patients with an established pregnancy, immunodeficiency or coagulation disorder, or diagnosis of classic allergic fungal sinusitis, eosinophilic granulomatous polyangiitis (or Churg-Strauss syndrome), or cystic fibrosis were excluded. All patients were prospectively recruited and enrolled in the postoperative period (Northwestern University Feinberg School of Medicine institutional review board STU00202510-CR0004), to include review of their medical record and access to their samples in the biorepository from the time of ESS, as well as specific study-related procedures including nasal endoscopy, placement of middle meatal sponge, a research-related sinus CT, and completion of PROMs.

2.2 | Study overview

Standard clinical and demographic information was collected from patients pre-ESS. This included the patients' pre-ESS noncontrast computed tomography (CT) scans

that were scored using the Lund–Mackay (LM) and modified Lund–Mackay (MLM) scoring systems.[17–19] The MLM score is a variation of the traditional LM score that allows for gradations within each sinus ranging from 0 to 4 giving a scoring range of 0 to 44, and this scale was used to examine frontal sinus–specific radiographic severity. Pre-ESS patient-reported severity data were also solicited and obtained within 1 week before ESS, comprising Chronic Rhinosinusitis Patient-Reported Outcomes (CRS-PRO) and 22-item Sinonasal Outcomes Test (SNOT-22) measures.[20] These instruments are validated PROMs utilized in CRS, with scores ranging from 0 to 110 and 0 to 48, respectively, and higher scores designating worse symptoms. The CRS-PRO is a recently developed and validated CRS-specific PROM that was developed in concordance with Food and Drug Administration guidelines regarding PROM development appropriate for use in clinical trials. It differs from the SNOT-22 primarily in that it was developed with extensive input from patients who had CRS defined using current definitions of CRS including its two major phenotypes. At 12 items, it is also more concise than the SNOT-22.[21–23] Pre-ESS CRS-PRO was completed for 36 (69%) patients and pre-ESS SNOT-22 was completed for 42 (81%) patients.

After ESS, at an interval between 6 and 12 months post-ESS, patients were invited back to the ear, nose, and throat clinic for dedicated research visits during which a CT scan was obtained for post-ESS LM and MLM ascertainment, as well as PROM assessment with both the CRS-PRO and SNOT-22. Patients also underwent an endoscopic assessment by a rhinologist with endoscopic severity graded according to modified Lund-Kennedy (MLK) score, which has a scoring range of 0 to 12, with 12 being the most severe.[24] Polyp recurrence was defined by any patient who had a score of > 0 on the MLK polyp score.

At the time of ESS and at the post-ESS research visit, prepunched 3/8-inch hydroxylated polyvinyl acetate (Medtronic, Inc) sponges were placed in the MM for 10 minutes to collect MM mucus. Intravenous (IV) steroids and antibiotics were held for 98% of patients before sample collection. One patient received perioperative IV corticosteroids and one patient received perioperative IV antibiotics, both in the MES group. Samples were kept at −80°C before and after processing. The polyvinyl alcohol sponges were then centrifuged at 14,000 rpm for 10 minutes and extracted with a further 100 μL of phosphate-buffered saline and 1% protease inhibitor cocktail (Sigma, St Louis, MO) to collect nasal secretions. The resultant analytes were stored at −80°C before analysis. The concentration of eosinophil cationic protein (ECP) in MM mucus was determined by a commercial ELISA kit (MBL, Woburn, MA) following manufacturer's instructions. The minimal detection limit for this kit is 0.125 ng/mL. The concentrations of IL-4, IL-5, and IL-13 in the middle meatal mucus were measured using EMD Millipore MILLIPLEX MAP Human Luminex (Burlington, MA) kits following the manufacturer's recommended protocols. The minimal detection limits for IL-4, IL-5, and IL-13 using this kit are 1.83 pg/mL, 0.48 pg/mL, and 0.24 pg/mL, respectively. Values read as below the minimal detection limit were replaced with a value that was half of the lowest detectable threshold for each cytokine. There were no values that were above detectable limits for the cytokines.

Intraoperative and postoperative management, including degree of surgery and placement of MES, was left to the discretion of the five treating surgeons. When performed, the endoscopic modified Lothrop (Draf 3) was uniformly done in the "inside-out" manner according to the discretion of the operating attending rhinologist.[25] All treating surgeons utilized frontal sinus MES in some instances. All patients also received a resorbable chitosan or nasopore pack (nontreated) placed into the MM postoperatively as a mechanical spacer that is routinely removed in postoperative debridement. If utilized, all MES were of the Propel family (Intersect ENT, Palo Alto CA), with Propel Mini and Propel Contour accounting for 8 (24%) and 25 (76%) of the stents; 3 (9%) were unilateral. Criteria for MES placement were not prespecified and left to the discretion of the 4 treating rhinologists; however, all surgeons utilized MES at least once. The endoscopic presence of purulence or eosinophilic mucin[26] was based on endoscopic visualization as dictated by the operating rhinologist in the operative note. We retrospectively analyzed the patients after stratification into two groups: those who did receive frontal sinus MES and those who did not receive frontal sinus MES.

2.3 | Statistical analysis

Prospectively collected data were retrospectively reviewed. Statistical analysis was performed using Prism GraphPad software version 9 (GraphPad Software; La Jolla, CA) and SPSS 24 (IBM; Armonk, NY). We assessed variables for normality using Kolmogorov–Smirnov and Shapiro–Wilk tests. Descriptive categorical data are presented as frequency counts and percentages. Descriptive continuous data are presented as median and interquartile range (IQR) when non-normally distributed and mean and standard deviation (SD) when normally distributed. Mann–Whitney U test and independent t tests were used to analyze differences between the medians and means of two groups, respectively. Wilcoxon matched pairs was used to compare repeated measures of inflammatory mediators from the same patients at different time points. Pearson chi-square was

TABLE 1 Baseline demographics and pre-ESS disease severity

	No frontal MES ($n = 19$)	Any frontal MES ($n = 33$)	p value
Age, years	46.26 (16.01)	46.67 (13.33)	0.92
Men, *n* (%)	11 (58)	16 (49)	0.51
Atopic, *n* (%)	8 (42)	19 (58)	0.28
Tobacco, *n* (%)	6 (32)	8 (24)	0.57
Asthma, *n* (%)	11 (58)	20 (61)	0.85
AERD, *n* (%)	1 (5)	6 (18)	0.24 (FE)
Revision ESS, *n* (%)	11 (58)	15 (46)	0.39
INCs, *n* (%)	7 (37)	11 (33)	0.79
OCS, *n* (%)	1 (5)	9 (27)	0.07 (FE)
Pre-ESS patient-reported and radiographic severity			
Pre-ESS CRS-PRO	26.15 (9.94)	25.47 (11.37)	0.86
Pre-ESS SNOT-22	39.93 (18.12)	47.50 (20.87)	0.26
Pre-ESS total MLM	27.0 (18.0)	31.5 (14.5)	0.30
Pre-ESS frontal MLM	4.0 (6.0)	7.0 (4.0)	0.15

Intranasal corticosteroids (INCs; either fluticasone propionate 50 μg nasal spray [flonase] or triamcinolone acetonide 55 μg nasal spray [nasocort]) and oral corticosteroids (OCS) are reported from the 2 weeks before surgery. Continuous variables are presented as mean and standard deviation with the exception of modified Lund–Mackay (MLM), which is presented as median and interquartile range. Categorical variables are presented as frequency count (percentages). Continuous variables were compared using independent *t* tests and Mann–Whitney *U* tests; categorical variables were compared using chi-square or Fischer exact where appropriate. AERD, aspirin-exacerbated respiratory disease; CRS-PRO, Chronic Rhinosinusitis Patient-Reported Outcomes; ESS, endoscopic sinus surgery; FE, Fisher's Exact test; MES, mometasone-eluting stent; SNOT-22, 22-item Sinonasal Outcomes Test.

used to compare differences in categorical data between groups.

3 | RESULTS

Fifty-two patients with CRSwNPs were recruited to the study. Thirty-three patients received frontal MES during ESS (63%) and 19 did not receive frontal MES (37%). Of 33 patients with stents, 8 (24%) had Propel Mini and 24 (76%) had Propel contour stents. The median time from ESS to research evaluation was 8 months. Patient demographics and baseline characteristics before surgery are outlined in **Table 1**. No differences were observed in pre-ESS demographics, PROM severity, or radiographic severity between patients who did and did not receive frontal MES, although patients who had intraoperative frontal MES placed exhibited nonsignificantly greater frontal sinus–specific radiographic severity when examining the bilateral frontal sinus scores on the MLM (4.0 vs 7.0, $p = 0.15$.).

Operative technique, intraoperative findings, and post-ESS medical care were compared and are shown in **Table 2**. Operative technique was comparable between the

TABLE 2 Operative findings, operative technique, and postoperative disease severity between the MES and non-MES groups

	No frontal MES ($n = 19$)	Frontal MES ($n = 33$)	p value
Intraoperative findings and extent of surgery, *n* (%)			
Maxillary antrostomy	19 (100)	33 (100)	N/A
Total ethmoidectomy	19 (100)	33 (100)	N/A
Sphenoidotomy	19 (100)	32 (97)	>0.99 (FE)
Frontal sinusotomy	19 (100)	33 (100)	N/A
Lothrop	2 (11)	9 (27)	0.29 (FE)
Purulence	2 (11)	15 (46)	**0.01**
Eosinophilic mucin	2 (11)	19 (58)	**0.001**
Post-ESS medical management and disease severity			
Enhanced topical steroid, *n* (%)	16 (84)	29 (85)	>0.99 (FE)
Budesonide rinse/drop, *n* (%)	12 (63)	15 (47)	0.22
X-hance, *n* (%)	1 (5)	2 (6)	>0.99 (FE)
Mometasone rinse/drop, *n* (%)	3 (16)	13 (39)	0.08
Biologic past month	1 (5)[#]	3 (9)[##]	>0.99 (FE)
Oral corticosteroids 3 months prior, *n* (%)	3 (16)	8 (24)	0.73 (FE)
Systemic antibiotics 3 months prior, *n* (%)	4 (21)	5 (15)	0.71
Post-ESS CRS-PRO	7.50 (22.25)	6.0 (14.0)	0.37
Post-ESS SNOT-22	14.0 (25.0)	8.0 (24.50)	0.48
Post-ESS total MLM score	9.0 (13.0)	5.5 (17.0)	0.77
Post-ESS frontal MLM score	2.0 (5.0)	1.5 (5.0)	0.98
Post-ESS MLK score	2.0 (4.25)	2.0 (4.0)	0.36
Polyp recurrence, *n* (%)	4 (21)	6 (18)	>0.99 (FE)

Enhanced topical steroid: spray or rinsed budesonide or mometasone, X-hance (fluticasone proprionate 93 μg nasal via exhalation delivery system).Purulence is defined as endoscopic presence of purulent secretions-Budesonide or mometasone rinses were high-volume, low-pressure nasal saline irrigations that were mixed with corticosteroid before administration.# $n = 1$ taking dupilumab 300 mg every 2 weeks for 5 months.## $n = 2$ taking dupilumab 300 mg every 2 weeks, 2 months and 7.5 months. Dupilumab was used in patients who had benefit for both lower and upper airway disease.$n = 1$ taking benralizumab 30 mg every month for 4 months (given for lower airway disease, not chronic rhinosinusitis with nasal polyps).Continuous variables are presented as median with interquartile range and compared using Mann–Whitney *U* test. Categorical variables are presented as frequency count (percentage) and compared with chi-square or Fischer exact tests where appropriate.

CRS-PRO, chronic rhinosinusitis patient-reported outcomes; FE, _____; ESS, endoscopic sinus surgery; MES, mometasone-eluting stent; MLK, modified Lund-Kennedy; MLM, modified Lund–Mackay; N/A, not available; SNOT-22, 22-item Sinonasal Outcomes Test.

frontal MES and nonfrontal MES groups, with nearly all patients undergoing full bilateral ESS and 27% of MES vs 11% of nonfrontal MES patients undergoing an endoscopic modified Lothrop procedure ($p = 0.30$). Purulence was more frequently observed in the MES group at the time of surgery (46% MES compared with 11% non-MES, $p = 0.01$), as well as presence of eosinophilic mucin (58% MES compared with 11% non-MES, $p = 0.001$). Post-ESS medical management was similar between the MES and non-MES groups, as can be seen in Table 2, showing no differences in the use of topical steroids, monoclonal antibodies (biologics), oral corticosteroids, and systemic antibiotics, between the non-MES and MES groups.

The post-ESS total MLM, CRS-PRO, SNOT-22, and endoscopic severity (polyp recurrence, MLK endoscopic severity) scores were similar between groups, with frontal MLM decreasing in the MES group to a level below that of the non-MES group. (**Table 2**). The decrease in total and frontal MLM scores after surgery relative to pre-ESS scores were significant in both groups, with a decrease of 50% ($p < 0.05$) frontal MLM in the non-MES group and >75% in the MES group ($p < 0.0001$) (**Figure 1**). Both groups showed significantly improved total MLM (**Figure 1**).

In terms of pre-ESS T2 mediator concentrations, pre-ESS MM IL-13 was significantly higher in the frontal MES group, with a median concentration of 10.06 pg/mL compared with 2.90 pg/mL in the nonfrontal MES group ($p < 0.05$) (**Figure 2**). Likewise, pre-ESS MM ECP concentrations were higher in the MES group, with a concentration of 1143.0 ng/mL compared with 272.8 ng/mL in the nonfrontal MES group ($p < 0.05$). IL-4 and IL-5 were nonsignificantly higher in MES-receiving patients (**Figure 2**).

After ESS, T2 MM mediators were lower in the MES group relative to the nonfrontal MES group (**Figure 3**). Specifically, post-ESS IL-4 and IL-13 were higher in the nonfrontal MES group compared with the MES group ($p < 0.05$ for both), while IL-5 and ECP were nonsignificantly higher in the non-MES group compared with the MES-receiving group. When comparing the change in T2 MM inflammatory mediators before and after ESS, T2 MM mediators broadly decreased in the MES group but increased in the nonfrontal MES group. IL-5 and IL-13 significantly decreased in the MES group (IL-5, $p < 0.05$; IL-13, $p < 0.001$) (**Figure 4**) and IL-4 significantly decreased in the non-MES group ($p < 0.05$), while IL-5, IL-13, and ECP increased in the nonfrontal MES group, although this change was nonsignificant (**Figure 5**).

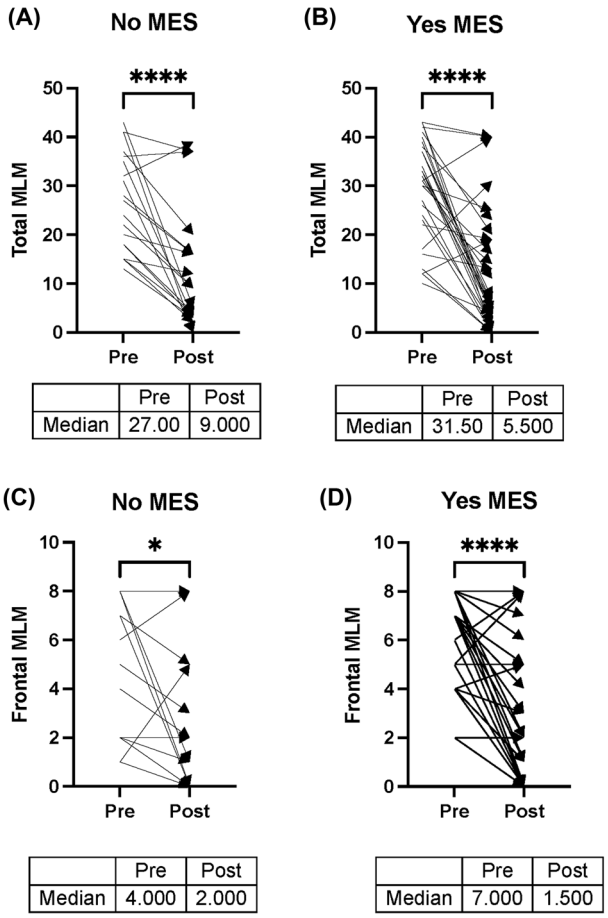

FIGURE 1 Post–endoscopic sinus surgery (ESS) total modified Lund–Mackay (MLM) (A, B) and frontal MLM (C, D) scores compared between mometasone-eluting stent (MES; yes MES) and non-MES (no MES) groups. Total MLM improved significantly between pre-ESS to post-ESS in both the non-MES and MES groups (A and B). Frontal-specific MLM improved significantly among both groups, but demonstrated greater improvement in the MES group. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$, by Wilcoxon matched pairs analysis

4 | DISCUSSION

This is the first study to analyze intermediate-term effects of an intraoperative frontal sinus MES on the local T2 inflammatory environment. We also compared radiologic and patient-reported disease severity between MES and nonfrontal MES groups at an intermediate term after ESS, which is unlike published studies that have primarily used shorter-term end points. Although MES placement was not randomized and performed at the operating surgeons' discretion, there were no differences between groups with regards to pre-ESS disease severity, demographics, or presence of comorbidities including asthma or atopy. When comparing these two otherwise fairly homogenous groups, we found that those who were implanted with frontal MES had higher pre-ESS MM T2 inflammation and some features of more severe intraoperative endoscopic findings. Post-ESS, we found that radiographic changes were similar, as were endoscopic and symptomatic outcomes between the two groups. However, T2 MM mediators

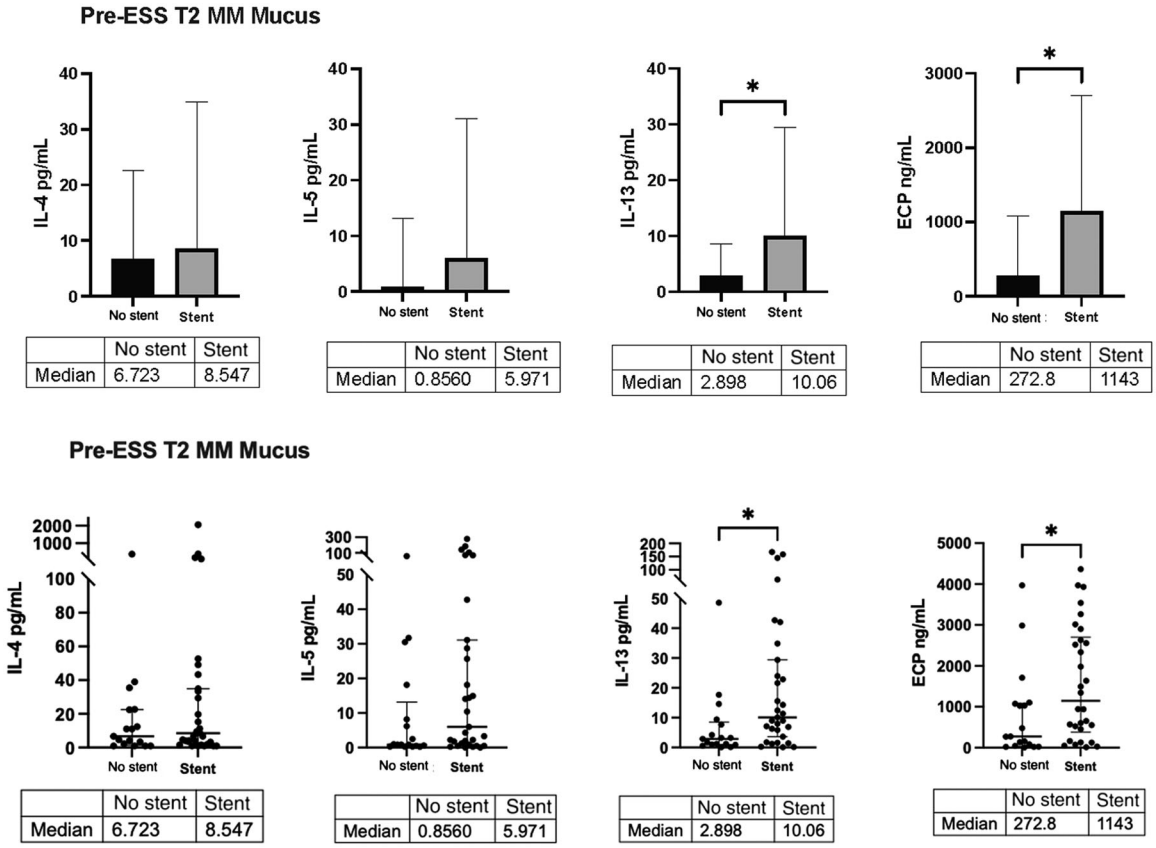

FIGURE 2 Type 2 (T2) middle meatal (MM) inflammatory mediators are elevated in the frontal mometasone-eluting stent (MES) group before endoscopic sinus surgery (ESS). Pre-ESS MM concentrations of interleukin (IL) 13 and eosinophil cationic protein (ECP) were significantly elevated in the no frontal MES group compared with the frontal MES group. Results are shown as median with interquartile range and expressed in pg/mL for IL-4, IL-5, and IL-13, and ng/mL for ECP. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$, by Mann-Whitney *U* analysis

decreased in the MES group but remained elevated in the non-MES group with higher levels as compared with the MES group.

Corticosteroids, whether delivered systemically or locally, are mainstays of CRSwNP medical management because of their broad inhibition of type 1 and T2 inflammation.[1,6,27,28] However, utilization of systemic corticosteroids is tempered by potential side effects, and topically applied steroids have inherent limitations in efficacy, patient adherence, and inability to access diseased mucosa.[7,29,30] The development of the MES, placed intraoperatively in dissected sinuses, largely circumvents many of these limitations of corticosteroids. High levels of evidence exist for their ability to improve post-ESS endoscopic appearance and decrease need for rescue intervention or OCS based on endoscopic appearance, particularly in the 30- to 90-day timeframe.[8,31] The aforementioned improvements may correlate with the 30-day period over which the implants are designed to elute steroid, and comparatively little has been published regarding longer-term post-ESS benefits of these devices. Post-ESS outcomes in CRSwNPs are often quantified in years, and the degree to which short-term endoscopic improvement associated with MES correlates with long-term outcome remains unclear. Despite their utility, there is also a dearth of knowledge on the exact effects that MES exert on the local sinonasal inflammatory environment after placement and there is also a relative dearth of information regarding how MES may relate to long-term validated measures of disease severity.

In our study, surgeons were unaware of T2 mediator MM concentrations at the time of surgery, yet pre-ESS levels of studied T2 mediators were higher in MES-implanted patients, with significant differences in pre-ESS concentrations of ECP and IL-13. At our research visit at a median of 8 months after surgery, concentrations had essentially reversed, with the MES-implanted concentrations of all T2 mediators measuring lower in the non-MES patients, with significantly higher levels of IL-4 and IL-13. Despite no differences in post-ESS usage of biologics, OCS, or enhanced topical nasal steroids, IL-5 and IL-13 had significantly decreased in the MES group, while, in the non-MES

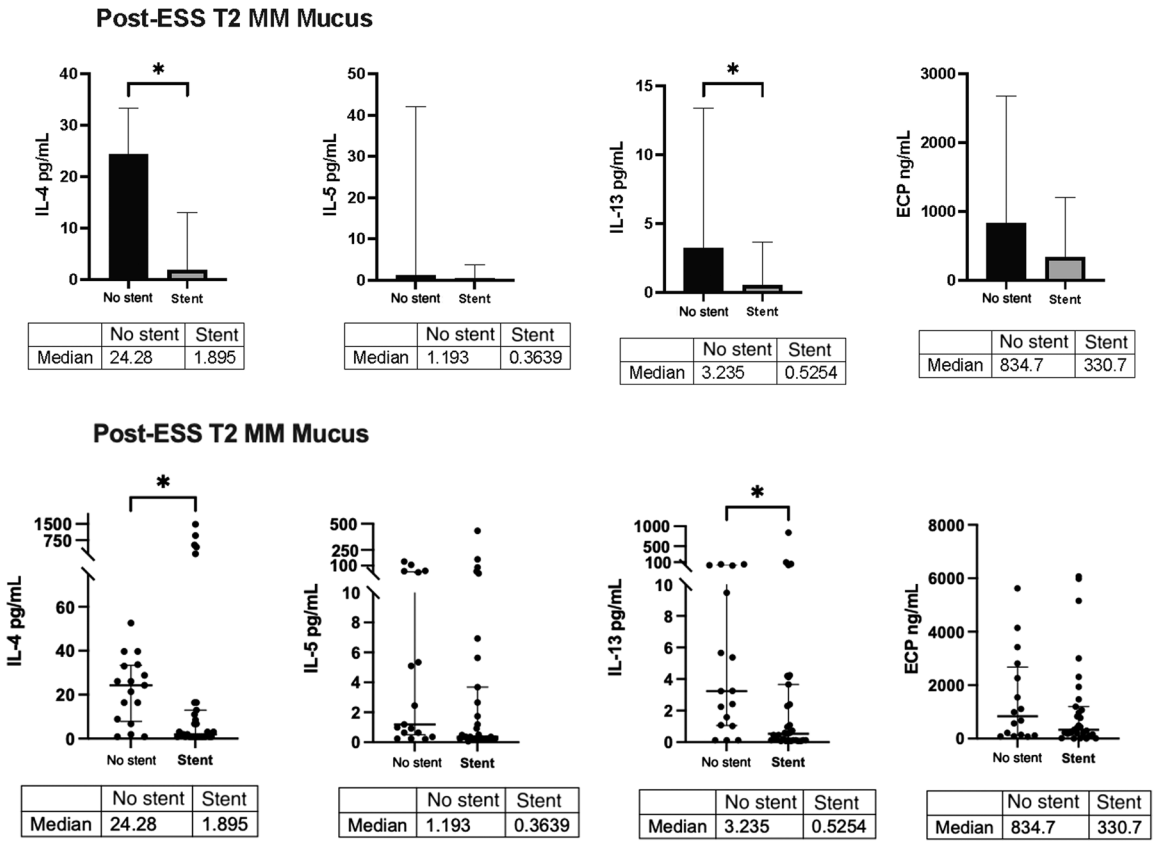

FIGURE 3 Post–endoscopic sinus surgery (ESS) type 2 (T2) middle meatal (MM) inflammatory mediators are higher in the no frontal mometasone-eluting stent (MES) group compared with the frontal MES group. Post-ESS MM concentrations of interleukin (IL) 4 and IL-13 were higher in patients who did not receive a frontal MES. Results are shown as median with interquartile range and expressed in pg/mL for IL-4, IL-5, and IL-13, and ng/mL for eosinophil cationic protein (ECP). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$, by Mann-Whitney U analysis

group, IL-4 significantly increased. IL-5 and IL-13 are known to be specifically produced primarily by group 2 innate lymphoid cells (ILC2s) unlike IL-4, which is made by both T-helper T2 cells and mast cells.[32,33] These changes may indicate that the release of mometasone for a short duration after surgery may affect ILC2-dependent production of IL-5 and IL-13 over a longer period than anticipated. A recent ex vivo study similarly found that nasal mucosal cells taken from patients pretreated with INCs exhibited decreased numbers of ILC2 as well as the allergen-induced production of IL-5 and IL-13.[34] The T2 endotype is classically associated with eosinophilia and nasal polyposis, while the type 3 endotype is classically associated with neutrophilia and the presence of purulence.[35]

Given the observed differences in concentrations of MM T2 mediators, we evaluated whether patients who did and did not receive MES at the pre-ESS and post-ESS time points were similar. Although the patient characteristics were relatively similar, we did find that intraoperative findings of eosinophilic mucin were more frequently associated with more frontal sinus MES placement (58% vs 11%, $p < 0.001$), suggesting that MES use may have been selected for patients with some endoscopic features of worse T2 inflammation (eosinophilic mucin). Figures 2 and 3, when shown as individual values, also demonstrate the potential contribution of outliers to drive median concentration differences and thereby decrease the biologic significance of these differences. However, biologic data are commonly non-normally distributed, and we accounted for non-normality by using nonparametric statistical analyses whenever data were nonparametric.[36] Further, all of the general trends appear to remain the same despite visualizable outliers. It is also possible that an 8-month follow-up period is not enough time for T2 severity to become clinically manifested. The detailed intraoperative variables as well focus on long-term patient-reported and radiographic severity measures distinguish this work from prior work on outcomes following frontal MES, which have had no longer than 90-day outcomes that largely revolved around standardized measures of endoscopic grading and need for rescue steroid or intervention, which may not necessarily have reflected real-world decision-making.[37,38] The

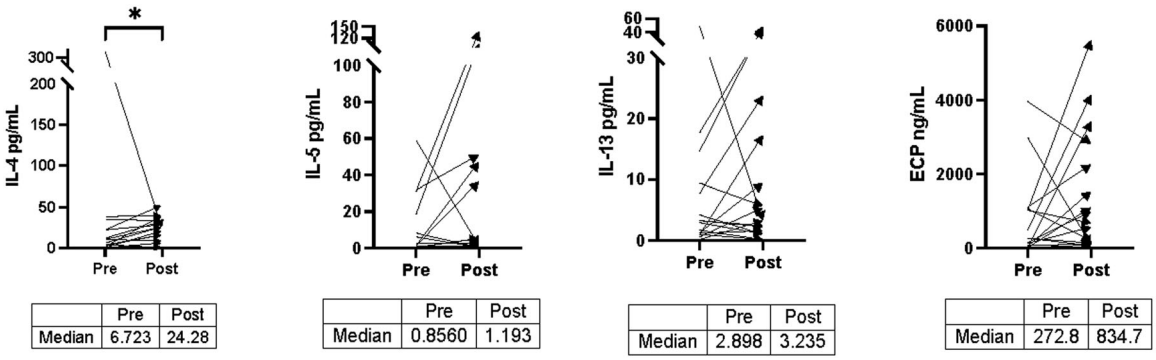

FIGURE 4 Concentration of middle meatal (MM) type 2 inflammatory mediators increased in patients who did not receive frontal mometasone-eluting stent (MES). MM interleukin (IL) 4 significantly increased in patients who did not receive a frontal MES, while other mediators nonsignificantly increased. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$, by Wilcoxon matched pairs analysis. ECP indicates eosinophil cationic protein

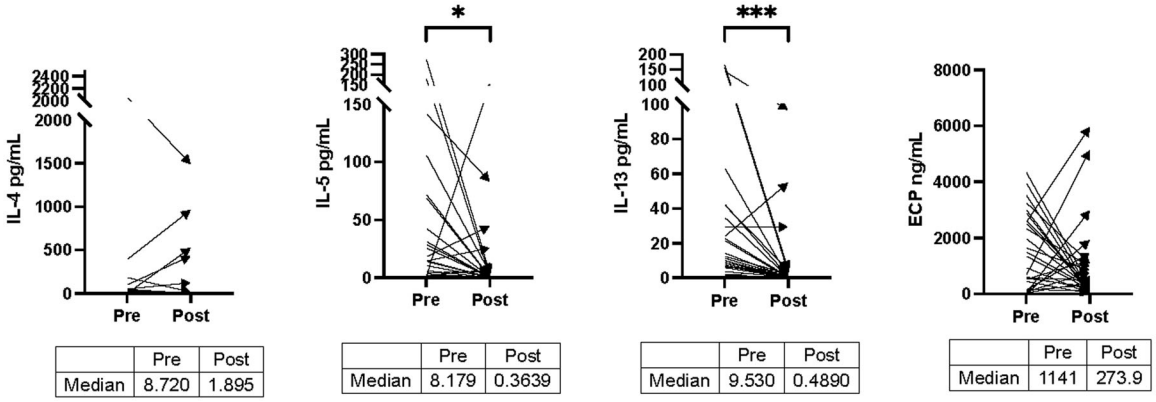

FIGURE 5 Concentration of middle meatal (MM) type 2 inflammatory mediators decreased in patients who received frontal mometasone-eluting stent (MES). MM interleukin (IL) 5 and IL-13 decreased significantly in patients who received a frontal MES, while IL-4 and eosinophil cationic protein (ECP) nonsignificantly decreased. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$, by Wilcoxon matched pairs analysis

longest post-ESS evaluation of the effects of MES was a 6-month evaluation of PROMs solely in patients with MES-implanted CRSsNPs and CRSwNPs which demonstrated that patient-reported severity decreased significantly out to 6 months following ESS, but this did not have a comparison group.[39]

This work is one of the longest-term post-MES outcomes evaluations solely in patients with CRSwNPs and is further strengthened by granular pre-ESS and post-ESS measures of disease severity and stented sinus-specific cross-sectional and longitudinal biologic data collected at the same time points. However, it is not without weaknesses. The group sizes were smaller in comparison to those of the most notable MES trials, there was not randomization between those who did and did not receive MES, and some differences were observed in intraoperative findings. Despite this lack of randomization, both groups were similar in terms of comorbidities, demographics, and pre-ESS patient-reported and radiographic diseases severity. Further, despite the lack of prespecified degree of surgery, there were no differences in the number of sinuses opened or Draf 3 procedure between groups. Our primary and secondary outcomes include biologic information, radiographic severity, and PROMs, which largely differ from the outcomes of larger MES publications. Furthermore, our inflammatory mediators were not measured in duplicate or triplicate because of low volumes of mucus. Additionally, our analysis did not include aspects of T2 inflammation such as IgE or chemokines, nor did this cohort of patients have systematically obtained bloodwork or structured histopathology results. Finally, even though there were no statistically significant differences in degree of surgery (postoperative management between those who did and did not receive MES), postoperative management

was left up to the treating surgeons, and this lack of control could be viewed as a confounding factor. Although not without weaknesses as outlined above, our results suggest that elevated T2 inflammation in MM mucus at the time of surgery may be associated with endoscopic disease severity and that frontal MES placement may result in longer-term changes in MM mucus inflammation.

5 | CONCLUSION

Patients who received intraoperative frontal MES had significantly worse pre-ESS MM T2 inflammation although radiographic severity, patient-reported symptoms, and comorbidities were similar between groups. After ESS, patients who had received frontal MES had reduced concentrations of MM T2 mediators, especially IL-5 and IL-13, than those who did not receive MES, but this did not correspond to significantly different measures of symptomatic or radiographic disease severity.

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CONFLICTS OF INTEREST

D.B.C. reports consulting fees from Intersect ENT and XORAN. K.C.W. reports consultant fees from Baxter, OptiNose, and Acclarent. A.T.P. reports personal fees from AstraZeneca and GlaxoSmithKline and personal fees and grants from Sanofi Regeneron, Merck, and OptiNose. A.K. reports a consultant fee from Astellas Pharma and a gift for his research from Lyra Therapeutics. W.W.S. has served on advisory boards for GlaxoSmithKline, Genentech, and Bristol Meyers Squibb. R.P.S. reports personal fees from Intersect ENT, Merck, GlaxoSmithKline, Sanofi, AstraZeneca/Medimmune, Genentech, Actobio Therapeutics, Lyra Therapeutics, Astellas Pharma Inc, and Otsuka Inc; and has Siglec-8– and Siglec-8 ligand–related patents licensed by Johns Hopkins to Allakos Inc. B.K.T. reports personal fees from Sanofi Regeneron/Genzyme.

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ORCID

Alexander L. Schneider MD https://orcid.org/0000-0001-9013-646X
Samuel D. Racette MD https://orcid.org/0000-0001-6731-2744
Anthony K. Kang BA https://orcid.org/0000-0002-6623-135X
David S. Lehmann MD https://orcid.org/0000-0002-8735-2847
Caroline P.E. Price BA https://orcid.org/0000-0002-9590-7419
Stephanie Shintani-Smith MDMS https://orcid.org/0000-0002-0605-3993
Whitney S. Stevens MDPhD https://orcid.org/0000-0002-2608-6610
Bruce K. Tan MDMS https://orcid.org/0000-0001-9210-5050

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