Characteristics of macrolide responders in persistent post-surgical rhinosinusitis*,#

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Introduction: The anti-inflammatory effects of long term low dose macrolide therapy have shown benefit in the management of diffuse panbronchiolitis. Dramatic responses to macrolide in the upper airway are seen but our understanding of the patient phenotype predisposing to macrolide response in chronic rhinosinusitis (CRS) is poor.

Methods: A case control study was performed in a tertiary level rhinology practice of consecutive chronic rhinosinusitis patients placed on a 3-month low dose macrolide therapy after failing at least 3 months of corticosteroid irrigation therapy post-endoscopic sinus surgery. Patients were defined as a "macrolide responder" when having near normal endoscopy after a 3-month period of clarithromycin treatment. Patient characteristics of smoking, asthma, atopy status, revision surgery, symptom severity (SNOT-22) along with biomarkers from serum and tissue histopathology results were compared between groups.

Results: Of twenty-eight consecutive macrolide treated patients, 19 responders were compared to 9 non-responders. The groups were similar in age, female gender, non-smoking, asthma, and atopy. Macrolide response was associated with a lack of tissue eosinophilia (>10/HPF) and lower serum eosinophilia. Neutrophil expression was similar in tissue and serum. Squamous metaplasia was overexpressed in non-responders.

Conclusion: Low tissue and serum eosinophilia, and absence of tissue squamous metaplasia may predict a CRS phenotype suitable to a trial of long-term macrolide therapy when surgery and topical therapy has failed.

Key words: chronic rhinosinusitis, sinusitis, neutrophilic, macrolide, medical management

Introduction

Macrolide antibiotics, as anti-inflammatory or immunomodulatory agents, first demonstrated great success in managing diffuse panbronchiolitis [(1)], a non-eosinophilic lower airway disease common in the Japanese population, before being applied to inflammatory upper airway conditions and chronic rhinosinusitis (CRS). The 14- and 15-member ring macrolides (clarithromycin, erythromycin, azithromycin, and roxithromycin) are used for their immunomodulatory properties, which includes the blockage of pro-inflammatory cytokines, such as interleukin (IL)-8 and tumor necrosis factor-α (TNF-α), inhibition of neutrophil adhesion and migration, and changes to mucus synthesis and secretion [(2,3)]. There may be other quorum sensing disruption properties and other effects on mucus rheology exhibited by these macrolides, but it is their anti-neutrophilic IL-8 blocking effects that are thought to contribute to their success in diffuse panbronchiolitis [(4)].

A cornerstone of CRS medical management is anti-inflammatory medication. Corticosteroids are the workhorse of many treatment regimens and are commonly utilized and recommended in postoperative care based on evidence-based reviews [(5,6)].

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Many patients notice a large improvement with systemic corticosteroid use and the majority of patients with Th2-mediated, eosinophilic CRS will likely respond favorably to local corticosteroid therapy post-surgery. However, there is a subset of patients with CRS who are corticosteroid resistant, often with poor response to either oral or topical corticosteroid. Poor response to corticosteroid has been investigated in CRS with an eosinophilic patient group responding to oral corticosteroid with significantly greater reduction in polyp size, nasal congestion, total nasal symptom scores, and nasal resistance than a neutrophilic patient group [7]. Research into recalcitrant CRS patients who respond poorly to first line anti-inflammatory treatments suggests that these patients may benefit from long term, low dose macrolide treatment [8-10]. Findings are not universal, with two randomized, placebo-controlled studies assessing outcomes following macrolide therapy having conflicting results [10,11]. There are clearly macrolide sensitive CRS patients within these trial populations but defining the phenotype of a macrolide 'responder' is not clear. Our ability to define the appropriate patient to select for macrolide therapy is poor and limits the use of macrolides to simply patients that do not respond to initial therapy or are recalcitrant. The objective of this study was to identify patient and disease characteristics that may define a CRS phenotype suitable to macrolide therapy. Such data might assist the clinician to weigh the risk-benefit of long term macrolide therapy and better define an appropriate CRS population for future research.

Methods

A case control study was performed in a tertiary level rhinology practice of consecutive chronic rhinosinusitis patients placed on a 3-month low dose macrolide therapy after failing at least 3 months of corticosteroid irrigation therapy post-endoscopic sinus surgery. Both patient characteristics and disease biomarkers were collected prospectively as part of routine assessments conducted in all chronic rhinosinusitis patients by the surgeon, and were retrospectively reviewed to determine the phenotypical difference between patients who demonstrated a dramatic macrolide response compared to a macrolide non-responder. The study was approved by the local human research ethics committee (HREC – SVH09/083). Informed consent was obtained from the participants.

Patient population

Patients diagnosed with CRS had radiologic evidence of mucosal inflammation and associated symptomatology consistent with Clinical Practice Guideline criteria or met the current European Position Paper of Rhinosinusitis and Nasal Polyps (EPOS) classification [12,13]. All patients had received a defined minimum prior treatment.

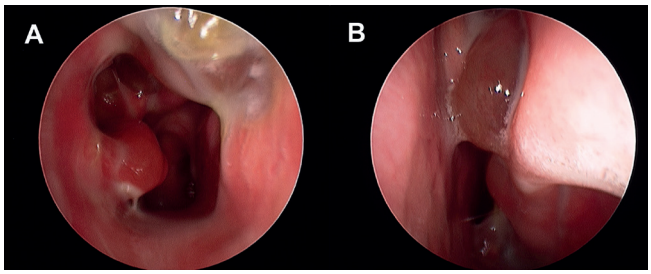

Figure 1. Endoscopic images from a 54 year old female who had ongoing disease despite prior surgery and treatment (right [A] and left nasal cavities [B]). Following this exam she underwent revision endoscopic sinus surgery and corticosteroid based treatment.

'Responder' (cases) and 'non-responder' (controls) populations were assessed after 3 months of macrolide therapy where the endoscopy demonstrated normal mucosa or near normal mucosa. Near-normal was defined as occasional areas of minor edema amongst normal mucosa. This equated to a mucosal score of 0 or 1 on the modified Lund-Mackay Endoscopy with a 0 score for secretions and purulence [14].

Endoscopic appearance was used to define a responder, but symptom scores also confirmed this. Nasal Symptom Scores following at least 3 months of macrolide therapy were significantly decreased in responders (from 14.0±4.0 to 8.5±5.0, p=0.01), compared to no change in non-responders (from 10.0±8.0 to 11.5±5.0, p=0.5). SNOT-22 scores in responders showed a significant decrease (from 48.4±17.6 to 37.4±22.0, p=0.04 compared to increased symptoms in non-responders (from 30.8±26.4 to 48.4±17.6, p=0.05).

The typical patient pre-operatively is demonstrated in Figure 1. This 54 year old female had prior therapy and surgery without benefit and underwent complete revision sinus surgery and corticosteroid based treatment as described above. The pre-macrolide cavity is demonstrated in Figure 2a, with severe persistent disease that is both evident symptomatically and on endoscopy. There is complete normalization of her mucosa 3 months post-macrolide therapy (Figure 2b). This was the appearance to define a "responder".

Prior treatment

All patients had undergone ESS after failing previous maximal medical therapy. The initial post-operative care included amoxicillin 875mg/clavulanic acid 125mg for 10 days for an antibiotic course appropriate based on culture obtained at the time of surgery. Patients were started on a 1mg budesonide or betamethasone in 240ml nasal irrigation once daily. Perioperative corticosteroids were given for a 21 day period (25mg for one week, 12.5mg for 1 week and then 5mg for 1 week). All patients

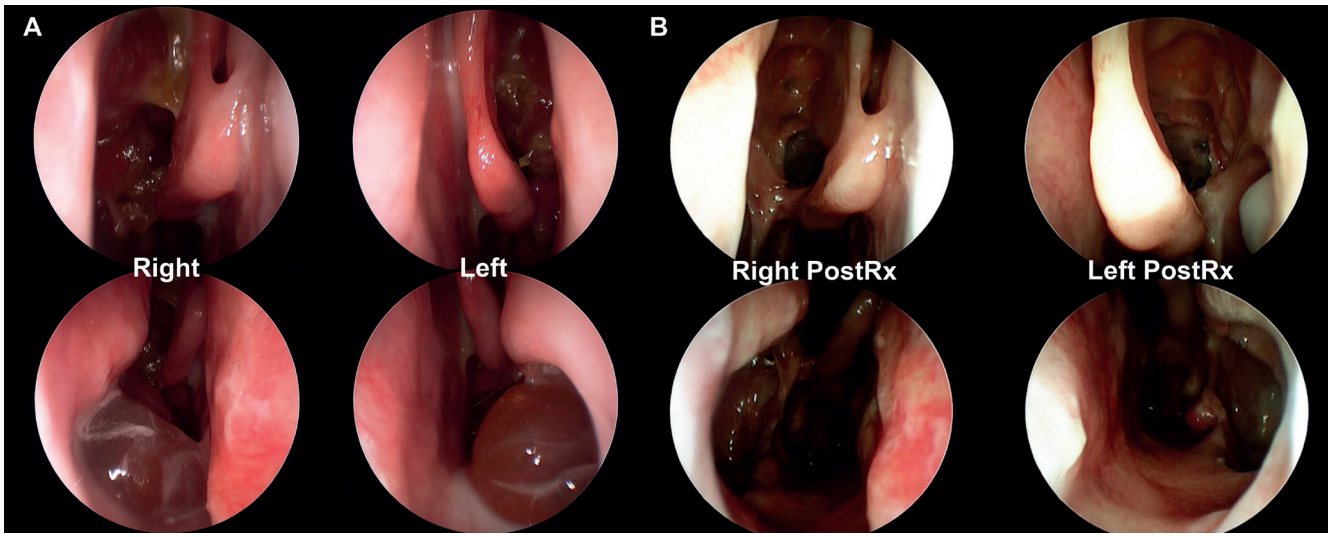

Figure 2. Three month postoperative endoscopy following revision ESS and corticosteroid based treatment. She continues to have severe persistent disease both symptomatically and on endoscopy (A). She was then started on long term low dose macrolide therapy. After 3 months of this therapy, her endoscopic exam reveals complete normalization of mucosa (B).

remained on a daily corticosteroid irrigation and were reviewed at least 3 months post-surgery. If significant and symptomatic inflammation on post-operative endoscopy persist, that included both severe edema and discharge, macrolide therapy was considered.

Macrolide therapy

Macrolide therapy was low dose and consisted of once daily clarithromycin 250mg for 3 months. If no response was seen clinically and endoscopically at 3 or more months then the course was ceased. Patients with prior cardiac disease and arrhythmias were excluded. No patient ceased therapy based on presumed side effects. Once daily corticosteroid irrigations (described above) continued during the macrolide therapy but no other systemic corticosteroids were given. Consecutive patients prescribed macrolides were included for the review.

Exclusion criteria

Exclusion criteria consisted of patients under 18 years of age; patients who had been treated with oral corticosteroids during the 4 weeks prior to their original surgery when the serum and tissue biomarkers were collected; patients with systemic illnesses affecting nasal mucosa such as immunodeficiencies, cystic fibrosis, granulomatous conditions or vasculitis.

Patient characteristics

Asthma status was determined by either a positive spirometry result on challenge testing or β-agonist use, or if currently using regular inhaled bronchodilator or corticosteroid therapy. Smokers were defined as any patient currently smoking or had ceased within the last 12 months. Polyp status was determined by clinical assessment, including endoscopic examination and computed tomography.

As an assessment of baseline disease, a preoperative 22-item Sinonasal Outcome Test (SNOT-22) and nasal symptom score (NSS) was used to assess disease severity. The SNOT-22 is a validated 22-question survey with four domains: psychological function, sleep function, rhinological symptoms, and ear and/or facial symptoms [15]. The SNOT-22 is reported as a mean of the 22 questions, each ranging from 0 to 5, with a total score of 110. Nasal symptom score (NSS) is the result of a 5 question survey regarding 'nasal obstruction', 'thick nasal discharge', 'facial pain/pressure', 'smell disturbance' and 'need to blow nose', with a total score of 25. A global rating of sinonasal function on an ordinal scale from -6 (terrible) to 0 (neither good nor bad) to +6 (excellent) was also obtained.

Atopy status

Atopy status, or aeroallergen sensitization, was defined by serological assessment at the time of surgery. Serum specific IgE to four allergen mixes was evaluated (Dust mite, mould, animal and grass). House dust allergen mix tested for *Dermatophagoides pteronyssinus, Dermatophagoides farinae, Blatella germanica*, mould mix for *Penicillium chrysogenum, Cladosporium herbarum, Aspergillus fumigatus, Alternaria alternata*, epithelial mix for Cat dander, Horse dander, Cow dander, Dog dander and grass mix for *Cynodon dactylon, Lolium perenne, Phleum pratense, Poa pratensis, Sorghum halepense* and *Paspalum notatum*. Serum specific IgE (>0.35mU/mL) for any four of the mixed airborne antigens was considered positive.

Table 1. Allocation table. The baseline characteristics between macrolide responders and non-responders is shown.

	Macrolide responder	Macrolide non-responder	P-value
N	19	9	
Age at surgery (years), mean ± SD	53.4 ± 10.4	56.0 ± 22.2	0.68
Gender (female)	57.9	22.2	0.11
Smoking	0%	0%	n/a
Asthma	31.6%	22.2%	1.0
Allergy	46.7%	50.0%	1.0
Nasal polyps	15.8%	33.3%	0.35
Revision	57.9%	100%	0.03
Time of endoscopy since macrolide start (months)	11.2 ± 7.1	10.8 ± 5.0	0.87
Pre-SNOT-22 (mean ± SD)	48.4 ± 17.6	30.8 ± 26.4	0.04
Pre-NSS (mean ± SD)	14.0 ± 4.0	10.0 ± 8.0	0.08
Pre-Global nasal function (%"bad" or worse (≤-4))	53.0	85.8	0.03
Post-SNOT-22 (mean ± SD)	37.4 ± 22.0	48.4 ± 17.6	0.2
Post-NSS (mean ± SD)	8.5 ± 5.0	11.5 ± 5.0	0.1

SNOTT-22 = sinonasal outcome test 22; NSS = Nasal Symptom Score; Revision = surgery performed prior to the surgical intervention described in the inclusion criteria; SD = standard deviation; HPF = high power field.

Biomarkers

Disease defining characteristics from serum and tissue were assessed. No patients received oral corticosteroids for 4 weeks prior to surgery when the serum and tissue was taken for assessment.

Serologic assessment

At the time of surgery, the patient had a 10ml EDTA blood collection, which was analyzed for total IgE (IU/mL), eosinophils (10^9/L) and neutrophils (10^9/L). No patients received oral corticosteroids for 4 weeks prior to surgery when the serum and tissue was taken for assessment.

Histopathology assessment

Mucosal samples were obtained intra-operatively from the maxillary or ethmoid sinus and underwent standard haematoxylin and eosin (H&E) staining, using standard laboratory techniques. Histopathological scoring followed the system previously described by Snidvongs, et al. [16]. Tissue eosinophilia was categorized as <10 eosinophils per high power field (HPF), 10-100 eosinophils per HPF, and >100 eosinophils per HPF. Tissue eosinophilia was defined by tissue eosinophil count (>10 per HPF) and recorded if seen at HPF in 2 or more fields. Neutrophilic infiltrate was either absent, focal, or diffuse. Remodeling changes were defined by: basement membrane thickening (BMT) (<7.5µm, 7.5-15µm, >15µm); fibrosis (either absent, partial, or extensive using polarized light to identify areas of excess collagen deposition); and squamous metaplasia (absent, present). The severity of subepithelial edema was considered as absent, mild (focal or perivascular only), moderate (distortion of mucosal structure) or severe (diffuse/polypoid change). The reporting pathologists were blinded to other data.

Statistical analysis

Statistical analyses were performed using SPSS v22 (IBM SPSS Statistics for Windows, Version 22, Armonk, NY, USA). Descriptive data is represented as percentages and means ± standard deviations (SD). Chi-squared analysis was used for the analysis of nominal values. Student's t-test (2-tailed) was for comparison of parametric data. Ordinal values were analyzed with Kendall's tau-b. Results with a p value of <0.05 were considered significant. Multivariate logistic regression was performed with gender, revision surgery, tissue remodelling, and eosinophilic disease as factors and increasing age as a covariate. The Model fit was assessed with the chi-squared statistic and the R^2 coefficient of determination was reported by Nagelkerke and McFadden for proportion of variance. Factors were reported as Odds Ratios (OR) and 95% confidence intervals (CI).

To reiterate, the design and aim of this study was to assess patients who had received macrolides for at least 3 months and then divide them into two groups (responders and non-respon-

Table 2. Comparison of disease factors, serology and histopathology, between macrolide responder and non-responder groups.

	Macrolide responder	Macrolide non-responder	P-value
Serum eosinophilia (109/L)	0.16 ± 0.11	0.39 ± 0.36	0.03
Serum neutrophilia (109/L)	4.3 ± 2.4	3.8 ± 2.2	0.67
Preoperative IgE (IU/mL)	79.4 ± 82.3	90.0 ± 96.3	0.79
Tissue eosinophil count % >10/HPF (n)	17.6 (3/17)	62.5 (5/8)	0.02
Tissue neutrophil infiltrate % focal/diffuse (n)	58.8 (10/17)	37.5 (3/8)	1.0
Squamous metaplasia	0 (0/17)	37.5 (3/8)	0.02
Basement membrane thickening % with >7.5µm (n)	56.3 (9/16)	37.5 (3/8)	0.71
Fibrosis % with extensive (n)	5.9 (1/17)	25.0 (2/8)	0.42
Subepithelial edema % with severe (n)	18.8 (3/16)	12.5 (1/8)	0.43

HPF = high power field; IU = international units.

ders) based on their endoscopy findings at that point, then look back at their disease biomarkers and other patient characteristics to see which correlated with a response to macrolides or lack thereof.

Results

Twenty-eight patients were identified who had been given macrolide therapy. Nineteen macrolide-responders (n=19) were compared to the nine non-responders (n=9). The patient factors and other biomarkers were assessed between the two groups to identify a potential phenotype that predicts response to macrolide.

Patient characteristics between groups

The responder and non-responder groups were similar in age, gender, and smoking, asthma, atopy, and polyp status (Table 1). The rate of previous surgery between responder and non-responder groups was 57.9% and 100% (p=0.03). Preoperative SNOT22 scores were 48.4±17.6 in responders and 30.8±26.4 in non-responders (p=0.04) and patients who rated their nasal function as "bad (-4)" or worse was 53.0% and 85.8% (p=0.03), but Nasal Symptom Score were similar between groups (14.0±4.0 v 10.0±8.0, p=0.08).

Disease biomarkers between groups

Tissue eosinophilia (>10/HPF) was inversely associated with macrolide response (17.7% v 62.5%, p=0.02). Tissue neutrophilia (presence of focal or diffuse neutrophilic infiltrate) was not significantly different between the groups (58.8% v 37.5%, p= 1.0). Serum eosinophil level (10^9/L) was lower in responders (0.16 ±0.11 v 0.39 ±0.36, p=0.03), whereas serum neutrophil level (10^9/L) was similar between groups (4.3 ±2.4 v 3.8 ±2.2, p=0.67), as was IgE level (79.4±82.3 IU/mL v 90.0±96.3 IU/mL, p=0.79).

Squamous metaplasia was overexpressed in non-responders (0% vs 37.5%, p=0.01). Basement membrane thickening, subepithelial edema, and fibrosis had no association with macrolide response (Table 2). Binary regression analysis revealed only tissue eosinophilia, defined at >10/HPF, was significant to predictive of a non-responder (OR 17.5 [CI 1.06-290.01], p=0.046) when a model was run with gender, revision surgery, tissue eosinophilia and squamous metaplasia (Nagelkerke R Squared = 0.718).

Discussion

Patients with a highly eosinophilic inflammation often have nasal polyposis, but only 76% of nasal polyposis demonstrates an eosinophilic phenotype [7]. It is understood that the greater the eosinophilic component, the better the response to corticosteroids. One study demonstrated a significantly greater reduction in bilateral polyp size, nasal congestion, total nasal symptom scores, and nasal resistance in the eosinophilic group treated with oral corticosteroids than the neutrophilic group [7]. Similarly, a study on high volume corticosteroid irrigation in the post-operative setting found better SNOT-22 and endoscopy outcomes in highly eosinophilic patients (>10/HPF) compared to those with low tissue eosinophilia (≤10/HPF) [17].

Long term low dose macrolide therapy has shown benefit in CRS patients who do not respond to first line anti-inflammatory therapies [8-10,18,19]. However, the key to effective implementation of this medical therapy is patient selection, especially when the anti-IL8 immunomodulation effects of macrolide are well described. Ideally, the goal should be early directed therapy to patients with identifiable characteristics known to be associated with macrolide therapy success, rather than blind use in all patients that fit into a difficult-to-treat category.

This study demonstrated that in a small group, both low serum eosinophilia and the absence of tissue eosinophilia were associated with responders. Prior studies also support macrolide therapy as most effective in non-atopic, non-eosinophilic patients. In a double-blind, randomized, placebo-controlled study, Wallwork et al. reported improvement in SNOT-20 score, nasal endoscopy, saccharine transit time, and IL-8 levels in lavage fluid in CRS patients treated with 3 months of roxithromycin therapy, but only significantly in the low IgE sub-group [10]. Suzuki et al. found a greater symptom improvement in patients with normal rather than high IgE. The same authors also report an inverse correlation between symptom response to macrolides and eosinophil counts in peripheral blood, nasal smear, and sinus mucosa [20]. In this study, baseline subjective measures were mixed between the responder and non-responder groups. Global nasal function scores were worse but SNOT-22 scores were better in the non-responder group, while there was no significant difference between the two with respect to nasal symptom scores (NSS). It is also noted that revision rate is significantly higher in the non-responder group. However, this reflects previous surgeries in these groups, not post-macrolide treatment surgeries, and is therefore consistent with what would be expected in a patient group that has been recalcitrant to previous standard CRS management. Patients who have been subjected to prior surgery may be prone to slower healing times and mucosal recovery due to such factors as prior scarring and challenged mucociliary clearance, which could act as a confounding variable when judging response to a new treatment modality. However, the authors feel that this imbalance between groups would have leveled out after more than 6 months postoperatively. Of note, there was no significant difference between the time each group spent on macrolides when they underwent endoscopy and determination of their response. Similarly, there was no significant difference with respect to when in the treatment course (preoperatively to >6 months postoperatively) the macrolide therapy was initiated.

Haruna et al. specifically examined patients who demonstrated a poor response to macrolide therapy [21]. These patients were more likely to have polyposis, increased eosinophil infiltration in their polyps, and bronchial asthma. Haruna et al found that neither allergic rhinitis nor allergy were associated with a poor responder [21]. These findings, along with data presented in this study, support the use of macrolide therapy in patients with low serum or tissue eosinophilia. If these diagnostic tests are unavailable, then clinical judgment based on patient inflammatory phenotype may help identify those more likely to benefit from macrolides, such as patients without nasal polyposis, asthma, or allergy histories, or those who have previously been poor steroid responders. However, considering the higher proportion of non-polypoid patients with eosinophilic tissue and polyp patients without tissue eosinophilia, simple phenotyping is unlikely to accurately guide therapy and simple histopathological assessment is warranted [17].

Tissue neutrophilia was not found to be correlated with outcomes in either the Suzuki et al. study or the present study. This helps illustrate that it is not specifically the neutrophilia of the CRS that causes it to respond better to macrolide therapy, but has more to do with its distinction from the highly eosinophilic/Th2-mediated inflammatory condition, as discussed previously. Concurrent bacterial exacerbations or super-imposed infections within the eosinophilic patients might result in mixed neutrophilic and eosinophilic patterns. Our full understanding of the disease pathway and mode of treatment intervention to explain this remains limited.

Duration of macrolide therapy is critical to its effectiveness. Hashiba et al. showed that improved subjective and endoscopic assessment correlated with duration of macrolide therapy, from 4.7% at 2 weeks to 71% at 12 weeks [22]. Patients who respond to macrolide therapy at 3 months have also been shown to have continued improvement in symptom scores and saccharine transit time at 12 months when maintained on the medical therapy [8]. There does not appear to be a significant difference between 14 or 15-member ring macrolide options [22,23], nor does there appear to be sustained improvement beyond when the therapy is discontinued [10]. Patients who had a positive response to macrolides were continued at 3 doses per week for 12 months. Many of these elected to stay on therapy indefinitely due to the magnitude of their disease control. Duration of long term therapy requires further study.

Strengths of the study include the prospective routine collection of uniform objective preoperative and intraoperative data from all patients. The use of a standard histopathologic assessment by our pathologists designed specifically for the evaluation of CRS patients provided useful and consistent information for comparison. This data was reviewed retrospectively to identify phenotypic differences between responders and non-responders after treatment, which was determined based on clinician evaluation and preference. Possible selection bias for macrolide therapy therefore cannot be eliminated in this model. All patients were treated by a single surgeon, which eliminated variability amongst medical and surgical management and clinical evaluations. Use of strictly endoscopy to determine a responder versus a non-responder allowed the analysis of correlations between patient characteristics, in the form of serum and tissue data, to CRS findings, in the form of endoscopy, to all be kept on an objective playing field. However, it did limit our ability to assess how patients were doing subjectively, and given that subjective patient-reported outcomes and objective findings, such as endoscopy and imaging, do not always correlate, it may

have prevented a whole picture evaluation. Future research would benefit from including this subjective data, as well as a larger sample size.

Conclusion

Macrolide therapy, as an immunomodulatory and anti-inflammatory intervention, is associated with a dramatic disease response in only a small group of CRS patients. The CRS phenotype that appeared to respond to macrolide therapy had low serum and tissue eosinophilia. Consideration can be made for tissue sampling and post-surgical macrolides in those patients with <10 eosinophils/HPF who are not responding to routine care.

Authorship contribution

Study design and data collection: GO, JC, RS, PE, RH.
Drafting manuscript: GO, RS, RH.

Conflict of interest

Richard J. Harvey is a consultant with Medtronic, Olympus and NeilMed, Advisory Board for Sequiris and has received grant support from ENTTech, Stallergenes and NeilMed. Raymond Sacks is a previous consultant with Medtronic. Gretchen M. Oakley is a consultant for Stryker. Jenna M. Christensen and Peter Earls have no financial disclosures and no conflicts of interest.

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