Systemic medication requirement in post-surgical patients with eosinophilic chronic rhinosinusitis*

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Abstract

Background: Eosinophilic chronic rhinosinusitis (eCRS) is contemporarily managed by surgical creation of a 'neo-sinus' cavity and corticosteroid irrigations. While most patients gain control of their disease with this approach, similar to preventive inhaler therapy in asthma, some patients need systemic therapies. This study aimed to define those patients needing ongoing systemic therapy for eCRS.

Methods: Consecutive adult patients (>18 years) who were seen at a tertiary referral clinic, diagnosed as eCRS and underwent endoscopic sinus surgery were included. Patients were followed up for a minimum of 12 months. All patients had a simple neo-sinus cavity surgically created and used initially a once daily topical corticosteroid irrigation maintenance therapy. Patients who required long term systemic oral corticosteroids and/or biologic therapy were compared to those who remained on topical control.

Results: 222 patients with eCRS were assessed (follow-up 2.76 years). Long term systemic therapy was required in 5.4% of patients. Receiver operating curve analysis predicted local treatment failure at an eosinophil count cut-off level 0.455x10^9/L. Asthma, atopy and aspirin sensitivity also predicted long term systemic therapy. There were no associations with nasal polyposis or revision surgery. Multivariate logistic regression showed elevated blood eosinophil count >0.455 x10^9/L was 9.27 times more likely to require for systemic medication.

Conclusion: Pre-operative blood eosinophil count >0.45 x10^9/L was associated with failure of local therapy following contemporary management of eCRS. The quantitative value of serum eosinophilia may be a useful predictor of disease progression and those patients in need of systemic therapies, such as biologic agents.

Key words: chronic rhinosinusitis, disease recurrence, endoscopic sinus surgery, eosinophils, patient reported outcome measures

Introduction

Eosinophilic chronic rhinosinusitis (eCRS) is an increasingly recognised subtype of chronic rhinosinusitis (CRS), characterized by an eosinophilic inflammation driven by Th2-type cytokines and a dysregulated sinus mucosa[(1)]. Compared with non-eCRS, eCRS patients often clinically present with loss of smell in early stages, bilateral polyps and diffuse inflammation in all sinuses on CT imaging[(2)]. It is often more difficult to treat, as it can be resistant to single modality approaches, associated with high disease recurrence, resulting in repeated corticosteroid courses and multiple revision surgeries to achieve disease control[(3,4)].

Contemporary management of eCRS is dependent on both surgical and medical interventions. Following endoscopic sinus

surgery (ESS), post-operative care of the neo-sinus cavity with regular nasal irrigation with topical corticosteroids to decrease sinonasal inflammation has been shown to decrease nasal polyp recurrence[5,6]. However, patients with recalcitrant disease may require treatment with systemic corticosteroids or further surgical intervention[7]. Failure of local therapy is often defined as need for long-term oral corticosteroids or progression onto new biologic therapies for eCRS. Biologic therapies, such as mepolizumab, have been shown to reduce the requirement for surgical management in severe nasal polyposis in CRS[8]. Mepolizumab is an anti-interleukin(IL)-5 humanised monoclonal antibody, administered as a 4 weekly subcutaneous injection of 100mg dose.

Predicting disease recurrence following ESS in eCRS is useful to rhinologists to determine and direct long-term management of patients with severe eCRS from the initial consultation. Matsuwaki et al previously demonstrated that a peripheral eosinophil count of 0.52 x10^9/L, asthma comorbidity and eCRS were independently more likely associated with recurrence at the 5 year follow up following functional endoscopic sinus surgery (FESS) [4]. However, in recent years, there has been a move towards a wide surgical exposure to ensure that local corticosteroid irrigations can be used for topical or local maintenance medical therapy.

The aim of this study was to determine the disease and patient factors that predicted the need for long-term systemic (corticosteroid and/or biologic) therapies, despite creation of a 'neo-sinus' cavity and post-operative topical corticosteroid irrigations.

Materials and methods

A retrospective cohort study was conducted of eCRS patients who underwent endoscopic sinus surgery and post-surgical corticosteroid irrigation regimen. This study received ethics approval from the St. Vincent's Hospital Research Ethics Committee (SVH 09/083) and patients provided informed consent for research data collection.

Consecutive adult patients (≥18 years) seen at a tertiary referral clinic, who were diagnosed with eCRS, failed medical therapy (according to the European Position Paper on Rhinosinusitis and Nasal Polyps [EPOS][9]) and underwent ESS as part of the management of their disease were included. eCRS was defined by histopathological assessment of sinus mucosal biopsies showing more than 10 eosinophils/high power field (HPF) (magnification x400) on at least 2 separate HPFs[10].

Surgery was performed by a tertiary rhinologist in a period ranging from June 2010 to August 2017. The surgery utilised here was not simple or limited sinus surgery but the complete dissection of the paranasal sinus cavity to create a simple single 'neo-sinus' cavity for the purposes of: removal of inflammatory polyps, prevent mucostasis and plugging, correct ventilation and establish a cavity that is accessible to topical medications[6].

Maintenance therapy

All patients utilised a once-a-day 1mg betamethasone or 1mg budesonide irrigation delivered by 240ml nasal irrigation device (Sinus Rinse, Neilmed, Santa Rosa, CA, USA). The irrigations started in the first 3 weeks post-surgery. They were continued daily until 3-6 months after surgery. Once mucosa had normalized, or a stable state was achieved at this 3-6 month period, patients were allowed to adjust their corticosteroid irrigation usage.

Need for long-term systemic medication use

Failure of local therapy was defined as need for 1) continuous oral corticosteroids for ≥3 months, or 2) biologic therapy (mepolizumab (anti-IL-5)); despite corticosteroid sinus irrigation regimen in the post-surgery sinus cavity. The decision for commencement of long term systemic therapy (long term oral corticosteroids or biologics) was made based on symptom relapse, repeated use of systemic medications to manage exacerbations and clinical assessment with endoscopy.

Exclusion criteria

Patients with less than 12 months follow-up or with CRS secondary to other conditions, such as odontogenic, fungal ball and concomitant secondary systemic conditions, were excluded. All patients had ceased systemic corticosteroid medications at least 4 weeks prior to surgery.

Baseline characteristics

Age, gender, smoking status, aspirin sensitivity, prior sinus surgery, asthma status, and atopic status, were collected. Smoking status was defined as those patients who smoked weekly or more and were actively smoking or had ceased in the last 12 months. Aspirin sensitivity was defined as a well-described history of bronchospasm after aspirin or non-steroid anti-inflammatory (NSAID) use, or a positive oral or nasal lysine aspirin challenge test with a >15% reduction in FEV1 or a >40% increase in total nasal airway resistance on rhinomanometry. Prior sinus surgery was self-reported by the patient. Asthma status was indicated either through current use of bronchodilator or inhaled corticosteroid therapy and/or a >15% change in FEV1 post bronchodilator on spirometry. Atopic status was determined by automated immunoassay (ImmunoCap®) to detect serum-specific Immunoglobulin (Ig) E antibodies to the following 4 aeroallergen mixes: 1) grass mix; 2) dust mite; 3) mould and 4) animal epithelium. A serum-specific IgE level of greater than 0.35 KU/L for any of these aeroallergen mixes was considered a positive result. Patients were identified as atopic if this test was positive, and non-atopic if this test was negative.

Table 1. Comparison of baseline characteristics between patients requiring long term systemic therapy and patients managed on local treatment only in eCRS.

	Long-term systemic therapy (n=12)	Local treatment only (n=210)	p-value
Age (years mean ± SD)	49.8±18.9	55.1±13.3	0.19
Gender (%F)	66.7	41.9	0.09
Smoking (%)	8.3	12.6	0.67
Asthma (%)	83.3	49.5	**0.02****
Atopic (%)	83.3	51.4	**0.03****
Aspirin sensitivity (%)	25.0	6.7	**0.02****
Prior CRS surgery (%)	66.7	48.6	0.22

** denotes significant result

Table 2. Comparison of local disease characteristics between patients requiring long term systemic therapy and patients managed on local treatment only in eCRS.

	Long-term systemic therapy (n=12)	Local treatment only (n=210)	p-value
CRSwNP (%)	91.7	71.9	0.13
Tissue eosinophilia (%)			
10-100 eos/HPF	58.3	65.2	0.63
>100 eos/HPF	41.7	34.8	

CRSwNP, Chronic rhinosinusitis with nasal polyps; (e)CRS, (eosinophilic) chronic rhinosinusitis, eos/HPF, eosinophils per high power field.

Local disease characteristics

Patients were classified as either CRS with nasal polyps (CRSwNP) or CRS without nasal polyps (CRSsNP) phenotypes based on intraoperative endoscopic findings. Degree of tissue eosinophilia was assessed using histopathological assessment of sinus mucosal biopsies and classed into 10-100 eosinophils/HPF or >100 eosinophils/HPF[10].

Systemic disease characteristics

A pre-operative blood sample was taken and assessed for total blood eosinophil count (x10^9 cells/L), white cell count (WCC) (x10^9 cells/L), immunoglobulin E (IgE) (kU/L), C-reactive protein (CRP) (mg/L) and erythrocyte sedimentation rate (ESR) (mm/h) by automated analysis. Eosinophil ratio was calculated by dividing the eosinophil count by the WCC and expressed as a percentage. All parameters were assessed in a blinded fashion.

Statistical analysis

Comparisons between patients requiring long term systemic therapy and patients controlled with topical therapy were performed. Statistical analysis was performed using SPSS Statistics v25 (IBM, Chicago, IL, USA). Parametric results were expressed as mean ± standard deviation. Non-parametric results were expressed as median[interquartile range].

Continuous data was assessed with independent samples t-test and proportional data was assessed with Chi-square test. Receiver operating characteristic (ROC) analysis was utilized to determine the optimal cut-off for the prediction of need for systemic therapy, and the area under the curve (AUC) was calculated. Binary logistic regression analysis was performed for multivariate analysis of predictive factors of requirement for systemic therapy post surgery. Odds ratios were reported with a 95% confidence interval. All p values were 2-tailed and a value of $p < 0.05$ was considered statistically significant.

Results

A total of 222 patients (age 54.8 ± 13.6 years, 43.2% female) with eCRS were included and followed for 2.76[2.24] years. 51.4% had asthma, 52.7% were atopic and 7.7% had aspirin sensitivity. 12 patients (5.4%) required long term systemic therapy. Of these, 7 patients (3.2%) utilised long term oral corticosteroids and 5 patients (2.2%) mepolizumab therapy.

Baseline demographics and long-term systemic therapy

A comparison of patient characteristics between patients requiring long term systemic therapy and patients managed on local therapy is presented in Table 1. Asthma (83.3% v 49.5%, $\chi^2(1)=5.19$, p=0.02), atopy (83.3% v 51.4%, $\chi^2(1)=4.63$, p=0.03) and aspirin sensitivity (25.0% v 6.7%, $\chi^2(1)=5.40$, p=0.02) were associated with need for long term systemic therapy. There was no significant association with age, gender, smoking status or previous CRS surgery.

Disease characteristics

Local disease characteristics

The polyp phenotype (CRSwNP) ($\chi^2(1)=2.25$, p=0.13) and degree of tissue eosinophilia ($\chi^2(1)=2.24$, p=0.63) were not significantly associated with need for long term systemic therapy (Table 2).

Systemic disease characteristics

Blood eosinophilia was significantly associated with need for long systemic therapy in eCRS post-surgery (0.7±0.3 v. 0.4±0.3, p=0.001). ROC analysis predicted long term systemic therapy at an eosinophil count cut-off level 0.455x10^9/L (sensitivity 83.3%, specificity 70.8%, AUC: 0.793, p<0.001) (Figure 1). This cut-off level produced a positive predictive value (PPV) 14.1%, negative predictive value (NPV) 98.7%, positive likelihood ratio (LR+) of 2.85 and negative likelihood ratio (LR-) of 0.24. The diagnostic

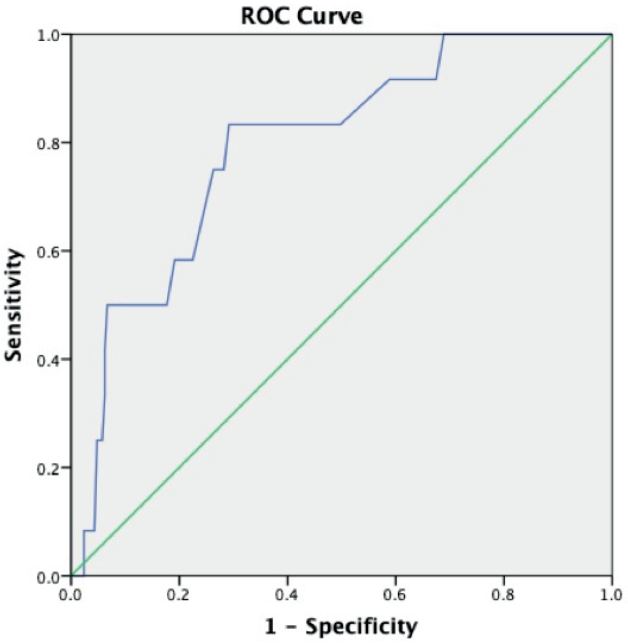

Figure 1. Receiver operating characteristic (ROC) curve of blood eosinophils to predict need for long term systemic therapy in post-surgical eosinophilic chronic rhinosinusitis (eCRS) patients.

odds ratio (DOR) calculated was 12.09, reflecting the significant strength of an eosinophil count >0.455x10^9/L as a predictor of patients with requiring systemic therapy post-surgery.

Furthermore, eosinophil to white cell count (WCC) percentage was significantly elevated in patients requiring long term systemic therapy (9.0±4.2 v. 5.7±4.2 %, p=0.008). ROC analysis predicted long term systemic therapy at an eosinophil to WCC percentage of 6.02% (sensitivity 83.3%, specificity 63.6%, PPV 11.6%, NPV 98.5%, AUC 0.741, p<0.01).

Acute phase reactants represent non-specific markers of systemic inflammation. There were no significant associations with WCC, IgE, CRP or ESR levels and need for systemic therapy (Table 3).

Regression analysis

A logistic regression model with blood eosinophilia, asthma, aspirin sensitivity and atopy was significantly predictive of the requirement for systemic medication post-surgery ($\chi^2(4) = 22.357$, p<0.001); however, asthma, aspirin sensitivity and atopy were not significant contributors to the model (p>0.05). Multivariate logistic regression revealed that high blood eosinophilia was an independent risk factor, as patients with a blood eosinophil count of >0.455 x10^9/L were 9.28 times [95%CI: 1.9-45.6] more likely to require for systemic medication post-surgery (p=0.006) (Figure 2).

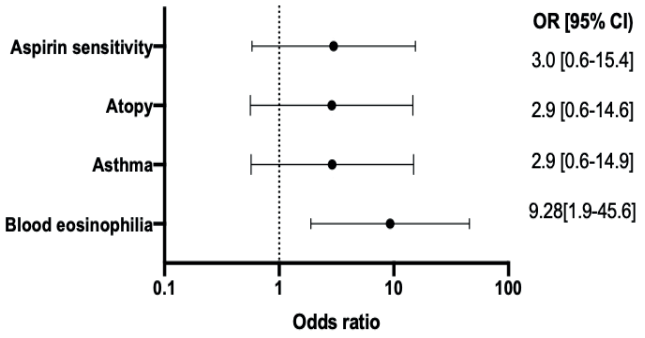

Figure 2. Logistic regression analysis of predictive factors of need for long term systemic therapy in post-surgical in post-surgical eosinophilic chronic rhinosinusitis (eCRS) patients.

Discussion

eCRS is a condition that requires more than surgery to manage it successfully and is associated with high rate of recurrence from single modality interventions, and significant impairment to quality of life[11]. There are an increasing number of studies recognising the role of tissue eosinophilia as a marker for abnormal inflammatory state and risk for long term recurrence[12]. Although, tissue sampling and simple hematoxylin and eosin prepared analysis can provide this information, it is unfortunately not widely assessed from sinus surgery and still remains limited to tertiary practice. Research assessing non-histopathological predictors of treatment failure in eCRS remains limited. The current study aimed to determine the predictors of those patients needing systemic therapy.

In clinical practice, patients who are unable to have their disease inflammation controlled on local therapy (topical intranasal corticosteroid irrigations) are managed with a short-term course of systemic oral corticosteroids[13,14]. However, some patients with severe CRS require repeated courses of systemic corticosteroids for disease control or in some cases, become dependent on long term systemic corticosteroids[15]. Long term systemic corticosteroid therapy is associated with significant side effects including osteoporosis, adrenal suppression, avascular necrosis, glaucoma and mood changes[16].

The vast majority of patients can be controlled with ESS and maintenance corticosteroid sinus irrigations. This study confirmed that 94.6% patients were adequately managed by these means but that 5.4% were not. In this latter group, 3.2% required long term oral corticosteroids and 2.2% required biologic therapy in the form of mepolizumab. Over the 7 year retrospective period, patients who failed were all initially placed on maintenance oral corticosteroids, and transitioned to biologic therapy when these medications became available on the Australian government subsidy based on asthma severity criteria, however

Table 3. Comparison of systemic disease characteristics between patients requiring long term systemic therapy and patients managed on local treatment only in eCRS.

	Reference range	Long-term systemic therapy (n=12)	Local treatment only (n=210)	p-value
Eosinophils (x10^9 cells/L)	0.0-0.4	0.7±0.3	0.4±0.3	**0.001****
WCC (x10^9 cells/L)	4.0-11.0	7.9±2.2	7.0±2.2	0.18
Eosinophil:WCC (%)	-	9.0±4.2	5.7±4.2	**0.008****
Serum total IgE (kU/L)	0-180	139±76	185±270	0.56
CRP (mg/L)	<5.0	4.0±4.1	2.6±4.9	0.32
ESR (mm/hr)	2-25	7.7±4.8	8.8±8.8	0.67

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IgE, immunoglobulin E; WCC, white cell count. ** denotes significant result.

transition was limited due to access. Patients who did not meet lower airway criteria for access to biologics remained on oral corticosteroids.

Biologic therapy is an emerging modality in the treatment of severe chronic rhinosinusitis, in particular in eCRS[17]. These target specific inflammatory pathways associated with the pathophysiology of the disease and are less likely to have systemic side effects. Biologic therapies currently investigated and used in CRS include mepolizumab (targeting IL-5)[18], reslizumab (targeting IL-5)[19], omalizumab (targeting IgE)[20] and dupilumab (targeting IL-4Rα)[16].

This study showed an ideal blood eosinophil count cut-off of >0.45 x10^9/L to predict local treatment failure in the management of eCRS post FESS. This result had moderate sensitivity (83.3%) and high diagnostic odds ratio of 12.09 showing that it is an effective predictor of disease outcomes, which would reflect the overall systemic eosinophilic inflammation driving the disease in severe eCRS. Significantly, this cut-off had a strong NPV of 98.7%, revealing that patients without significant blood hypereosinophilia were unlikely to require systemic therapy in the long term. Furthermore, multivariate logistic regression showed that patients with eosinophil count >0.45 x10^9/L were 9.28 times more likely to require long term corticosteroids or mepolizumab following surgery.

The standard cut-off applied for Australian government subsidised provision of mepolizumab for eosinophilic asthma is a blood eosinophil count of 0.3 x10^9/L. It has been previously shown that a blood eosinophil level of 0.24 x10^9/L predicts tissue eosinophilia (>10 eosinophils/HPF) and thus eCRS[21]. As shown in this current study, given the significant NPV of blood eosinophils in predicting failure post FESS in eCRS, a blood eosinophil count of 0.45 x10^9/L may be a useful threshold for predicting the likelihood of requiring or indicating biologic therapy in severe eCRS. Further investigation with a prospective study would be useful to assess the role of blood eosinophil count as a biomarker to direct duration of corticosteroid therapy and for the initiation of biological therapies.

While the eosinophil/WCC percentage was significantly elevated in the systemic therapy group, the ROC analysis of eosinophil/WCC percentage was inferior to ROC analysis of absolute blood eosinophils (AUC 0.741 v. 0.793). Thus, blood eosinophils appear a superior marker as a cut-off for predicting need for systemic therapy in eCRS.

As with previous studies, comorbid asthma was demonstrated to be significantly associated with treatment failure in eCRS and CRS, reflecting the united airway hypothesis between the upper and lower airway and the shared TH2 inflammatory pathogenesis[22,23]. Along with asthma, this study also confirmed other recognised risk factors including atopy and aspirin sensitivity, reflecting the need to consider management of these conditions in CRS[22,24]. However, these factors within a logistic regression model were not statistically significant and were not major contributors to patients requiring long term systemic therapy.

The polyp phenotype (CRSwNP), previous CRS surgery or degree of tissue eosinophilia were not significantly associated with need for long term systemic medications in this study. However, analysis of tissue eosinophilia in this study was assessed based on division into groups of 10-100 and >100 eosinophils/HPF which may not identify the true effect of tissue eosinophilia in this population. It is important to recognise the role of surgery in decreasing the inflammatory load in the local disease environment and creating a neo-sinus cavity which may control for these local disease factors and allows for effective delivery of topical therapy[6,25,26].

Systemic markers of inflammation such as WCC, CRP, ESR and IgE were not significantly associated with local treatment failure. The mean results for all these parameters were either below the

upper limit of the reference range, or in the case of total serum IgE in the local treatment only group, just above the reference range. They have been previously demonstrated to be poor predictors in eCRS and CRS, reflecting their low sensitivity for inflammation in CRS compared with blood eosinophilia[21,27]. By contrast, the mean blood eosinophil concentration in the long-term systemic therapy group was well above the reference range.

There remains significant variance in the literature regarding the definition of degree of tissue eosinophilia defining eCRS, with variance between >5 eosinophils/HPF to >120 eosinophils/HPF. There is currently no consensus regarding a clear definition of eCRS within the field. A recent systematic review and meta-analysis showed that high tissue eosinophilia >55 eosinophils/HPF was associated with disease recurrence in patients followed up at least 12 months post functional endoscopic sinus surgery (FESS)[12]. However, this systematic review included many historical studies in which a variable surgery was applied as single modality intervention and maintenance therapy was either not applied or not declared. This present study uses a definition of >10 eosinophils/HPF which has been generally associated with poorer outcomes and overall prognosis[10,28].

Despite the large cohort of eCRS patients recruited and followed up, this study is limited by the small number of patients that failed local therapy (n=12). Within this study, all patients were recruited, operated on and managed by a single rhinologist ensuring consistency in surgical technique, tissue sampling and post-operative management. Whilst meta-analysis by McHugh et al. [12] reported higher rates of failure and disease recurrence following FESS (16.7% in Western populations, 28.9% in Asian populations), this study demonstrates that eCRS may be well managed with close follow up, regular intranasal corticosteroids and intermittent systemic corticosteroid courses with a failure rate of 5.4%.

Biologic therapy in CRS also remains under clinical trials and access is currently limited secondary to cost and other factors. Biologics are likely to become increasingly utilised in eCRS within the next few years, once approved for use. Within a tertiary rhinologic practice, most patients will get control of their disease with appropriate surgery and compliance with corticosteroid irrigations. However, there are 5.4% of patient needing further treatments such as biologic antibody therapies. Longer term studies following this cohort to assess the five-year treatment failure and disease recurrence rate may be useful in validating the data obtained within this study.

Conclusion

Pre-operative blood eosinophil count >0.45 x10^9/L is associated with the need for long term systemic therapy following surgery and corticosteroid irrigation management of eCRS. This may represent an important predictor of disease progression and prognosis in eCRS, allowing clinicians to identify the small 5.4% of patients that require close follow-up and need for systemic therapy, such as biologic medications.

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Authorship contribution

JH was responsible for data collection and statistical analysis. WL and JWG were responsible for data collection and data analysis. RJH, WS, JR and RA were responsible for study concept and design, as well as results review. All authors contributed to writing and editing the manuscript.

Conflict of interest

Richard J Harvey is a consultant with Medtronic, Olympus and NeilMed pharmaceuticals. He has also been on the speakers' bureau for Glaxo-Smith-Kline, Seqiris and Astra-Zeneca. Janet Rimmer has honoraria with Sanofi Aventis, Novartis, Mundipharma, BioCSL and Stallergenes. All other authors have no financial disclosures or conflicts of interest.

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