

Comparison of Sinonasal Histopathological Changes in Biological Treatment of Eosinophilic Chronic Rhinosinusitis

Jacqueline Ho, MD^{1,2} , Raquel Alvarado, PhD¹,
Janet Rimmer, MD^{1,3,4}, William A. Sewell, PhD^{2,5} ,
Sophie Walter¹, Peter Earls, MBBS⁶,
Raewyn G. Campbell, MD^{1,7,8}, Raymond Sacks, MBBCh^{1,8,9},
Larry H. Kalish, MMed^{1,9}, and Richard J Harvey, PhD^{1,8}

Abstract

Background: Biologic therapies such as mepolizumab and benralizumab are currently utilised in the treatment of eosinophilic asthma, and are emerging in the management of eosinophilic chronic rhinosinusitis (eCRS). These biologics inhibit the interaction of IL-5 with its receptor, thus impairing cytokine signalling and eosinophil inflammation. Mepolizumab does so by targeting IL-5, whereas benralizumab targets the α chain of the IL-5 receptor. This study compares the sinonasal tissue response to anti-IL-5 biologic therapies in patients with eCRS.

Methods: A cross-sectional study of adult eCRS patients who had completed at least 2 cycles of biologic therapy and underwent endoscopic sinus surgery as part of their management were included. Sinonasal mucosal tissue biopsies were obtained intraoperatively and assessed with structured histopathological examination. Comparisons of tissue histopathology outcomes following treatment with mepolizumab or benralizumab were performed.

Results: 18 patients (age 49.6 ± 14.2 years, 47% female, 100% co-morbid asthma) were included in this study, comprising 10 patients managed with mepolizumab and 8 patients managed with benralizumab. Even after mepolizumab, the tissue had predominantly eosinophilic inflammation compared to benralizumab (90% v 0%, $p < 0.01$), which demonstrated a greater lymphoplasmacytic inflammation (10% v 75%, $\chi^2(2) = 14.53$, $p < 0.01$). Compared with benralizumab, mepolizumab had increased tissue eosinophil count (100% v 37.5% > 10 eosinophils/HPF, $\tau^b = -8.47$, $p < 0.001$) and more severe subepithelial oedema (80% v 37.5% severe, $\tau^b = -2.37$, $p = 0.02$).

Conclusion: Tissue histopathologic outcomes reflect the differing mechanism of action of mepolizumab and benralizumab in eCRS. Further analysis at the tissue level will provide further information to guide application of mAbs in type 2 inflammatory diseases.

Keywords

biologic, chronic rhinosinusitis, eosinophilic chronic rhinosinusitis, eosinophils, monoclonal antibody

¹Rhinology and Skull Base Research Group, St Vincent's Centre for Applied Medical Research, University of New South Wales, Sydney, Australia

²St Vincent's Clinical School, Faculty of Medicine, University of New South Wales, Sydney, Australia

³Woolcock Institute, University of Sydney, Sydney, Australia

⁴Faculty of Medicine, Notre Dame University, Sydney, Australia

⁵Immunology Division, Garvan Institute of Medical Research, Sydney, Australia

⁶Department of Anatomical Pathology, St Vincent's Hospital, Sydney, Australia

⁷Department of Otolaryngology Head and Neck Surgery, Royal Prince Alfred Hospital, Sydney, Australia

⁸Faculty of Medicine, Health and Human Sciences, Macquarie University, Sydney, Australia

⁹Department of Otolaryngology, Head and Neck Surgery, Concord General Hospital, University of Sydney, Sydney, Australia

Corresponding Author:

Jacqueline Ho, 67 Burton Street Darlinghurst, New South Wales 2010, Sydney, Australia.

Email: drjacquelineho@gmail.com

Introduction

Targeted biologic therapy is emerging in the treatment of eosinophilic chronic rhinosinusitis (eCRS), an often refractory disease unable to be controlled with single-modal approaches.¹ Monoclonal antibody (mAb) therapies previously approved for severe eosinophilic asthma have shown to have associated benefits for co-morbid chronic rhinosinusitis (CRS).² Both eCRS and severe eosinophilic asthma are driven by eosinophil mediated Th2 inflammation, with local tissue hypereosinophilia. A key cytokine mediating the Th2 inflammatory process is interleukin (IL)-5, which is the major cytokine responsible for the growth and differentiation, activation and survival of eosinophils.³

Mepolizumab (NucalaTM; GlaxoSmithKline, UK) is a humanised IgG1 κ IL-5 antagonist monoclonal antibody (mAb). It acts by binding to IL-5 and blocking its interaction with the α -chain of the IL-5 receptor complex expressed on the eosinophil cell surface.⁴ This inhibits IL-5 signalling, resulting in the limitation of eosinophil production and survival.⁵ It was approved by the United States Food and Drug Administration (FDA) in November 2015 for the treatment of severe eosinophilic asthma for patients >12 years of age.⁶ It has also been trialled as a treatment for wide spectrum of eosinophilic driven disorders including eCRS, eosinophilic oesophagitis, hypereosinophilic syndrome and eosinophilic granulomatosis with polyangiitis.⁷

On the other hand, benralizumab (FasenraTM, AstraZeneca, UK) is an anti-IL-5 receptor- α mAb. It is a humanised IgG1 κ mAb which acts by binding directly to the α -subunit of the IL-5 receptor, thus blocking IL-5 mediated survival of eosinophils. Its Fc portion binds to the Fc γ RIIIa receptor (CD16a) expressed by natural killer cells, resulting in eosinophil apoptosis by antibody-dependent cell-mediated cytotoxicity.⁸ It was approved by the FDA in November 2017 for the treatment of severe eosinophilic asthma for patients >12 years of age.⁹

Tissue changes in bronchial mucosal and submucosal samples from patients treated with biologics in asthma have been studied, however, research has been limited due to the invasive nature of obtaining bronchial airway tissue for analysis.⁹ Instead, peripheral blood eosinophil count and fractional nitric oxide concentration in exhaled breath, have been the mainstay of assessing treatment response to biologic therapy in eosinophilic asthma.^{10,11} On the other hand, in eCRS, sinonasal tissue biopsies can be safely obtained without significant complications, hence histopathological assessment can be routinely performed for clinical purposes according to a structured histopathology reporting protocol, which allows for objective assessment of inflammation.

The benefits of biologic therapy in eCRS have been demonstrated,¹² however to date, no studies have compared the histopathological findings following treatment with biologics for chronic rhinosinusitis. This study compared the tissue histopathology outcomes following treatment with mepolizumab and benralizumab for eCRS.

Methods

Study Population

Adult patients (>18 years) with eCRS, as defined following the European Position Paper on Rhinosinusitis and Nasal Polyps criteria, and currently receiving biologic therapy (mepolizumab or benralizumab), were included. These patients underwent endoscopic sinus surgery as part of the management for their disease. This study received ethics approval from the St Vincent's Hospital Human Research Ethics Committee (2019/PID13822). Written informed consent was obtained from all patients.

Patients had been diagnosed as eCRS based on sinonasal tissue eosinophilia (>10 eosinophils per high powered field [eos/HPF]) prior to initiation of biologic therapy. Patients qualified for government subsidised biologic therapy due to severe eosinophilic asthma, however these patients also presented with severe eCRS, requiring continuous courses of oral corticosteroids for ≥ 3 months. All patients ceased oral corticosteroids prior to starting on biologic therapy. All patients except one had ceased oral corticosteroids at least 4 weeks prior to operative intervention. Patients had to have completed a minimum of two months of treatment prior to sinus surgery to be included in this study.

Asthma status was determined by either FEV1 reversibility $\geq 12\%$ and ≥ 200 mL at baseline within 30 minutes after administration of salbutamol (200 to 400 μ g), airway hyperresponsiveness >20% decline in FEV1 during a direct bronchial provocation test or >15% decline during an indirect bronchial provocation test or peak expiratory flow (PEF) variability >15% between the 2 highest and 2 lowest peak expiratory flow rates during 14 days. Atopy was defined as at least one positive result in either skin prick allergy testing (SPT) or 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 and classified as atopic. Blood eosinophilia was defined as >300 per microlitre in the last 12 months. Patients with established immunodeficiency, coagulation

disorder, pregnancy, classic allergic fungal sinusitis or cystic fibrosis were excluded from the study.

Biologic Therapy

Choice of biologic was initiated independently by a respiratory physician or otolaryngologist based on clinical assessment. Mepolizumab was administered as a 100mg subcutaneous injection once every 4 weeks. Benralizumab was administered as a 30mg subcutaneous injection once every 4 weeks for the first 3 doses, then every 8 weeks thereafter. Dosing intervals of biologics were in line with current guidelines of usage, based off clinical trials data. The 8-weekly dosing of benralizumab was shown to be of no detriment, compared to a more frequent weekly dosing regimen.^{13–15}

Tissue Collection

All patients had a neo-sinus cavity created as part of management of their severe eCRS as described in Li et al.¹⁶ Representative sinonasal mucosal tissue biopsy from the ethmoid sinus was obtained intraoperatively and placed in formalin. These were then processed with standard hematoxylin and eosin (H&E) staining and assessed by pathologists blinded to the clinical data. Structured histopathological assessment included degree of inflammation (absent, mild, moderate, severe), inflammatory predominance (eosinophilic, lymphoplasmacytic, neutrophilic, lymphohistiocytic, other), eosinophil count (<10 , $10\text{--}100$, >100 eos/HPF), neutrophil infiltration (absent, focal, diffuse), subepithelial oedema (absent, mild, moderate, severe), basement membrane thickening (<7.5 , $7.5\text{--}15$, $>15\mu\text{m}$), hyperplastic change (absent, present), mucosal ulceration (absent, present), squamous metaplasia (absent, present) and degree of fibrosis (absent, present).

Overall degree of inflammation was defined as absent (virtually no inflammatory cells in subepithelial stroma), mild (single and small groups of inflammatory cells identified focally; inflammatory infiltrate does not distort mucosal structures), moderate (inflammatory cells form larger, more confluent aggregates, yet the distribution is still patchy; may be some distortion of mucosal structures; may be any degree of stroma oedema) and severe (confluent, often dense aggregates and sheets of inflammatory cells which distort, expand or obscure normal mucosal structures; oedema is usually mild to severe; some areas of absent inflammation may still be observed). Inflammatory predominance was based on assessment of the most numerically predominant inflammatory cell type. The lymphoplasmacytic category is for inflammatory infiltrates composed predominantly of a mixture of lymphocytes and plasma cells, each being at least 10% of the total inflammatory cell population.

Eosinophils were counted from the 3 most dense collections of eosinophils in the stroma and defined by having at least 2 areas in the same category on two separate high powered fields. High tissue eosinophil count was defined as >10 eos/HPF. Neutrophil infiltration was assessed by presence of focal or diffuse neutrophils seen in epithelium or stroma, including adjacent to areas of ulceration. Normal sinonasal basement membrane thickness was defined as $<7.5\mu\text{m}$. Subepithelial oedema was defined as absent, mild (focal or perivascular only), moderate (distortion of mucosal structure) or severe (diffuse/polypoid change).

Patient Reported Outcome Measures

Validated asthma quality of life questionnaire (5-question asthma control questionnaire [ACQ-5]) was completed prior to commencement of biologic therapy. ACQ-5, 22-item sinonasal outcome test [SNOT-22] as well as nasal symptom score [NSS] was collected 3 months post-operatively where available.

Statistical Analysis

Comparisons between patients on mepolizumab and benralizumab therapy were performed. Statistical analysis was conducted using SPSS Statistics version 26 (IBM Corp., Armonk, NY). Independent samples *t*-test and Mann-Whitney U test were used for parametric and non-parametric continuous variables respectively. Chi square and Fisher's Exact tests were performed for relationships of nominal variables. Kendall's tau-B was used for ordinal values. All *p*-values were two-tailed, and a value of $p < 0.05$ was considered statistically significant.

Results

18 patients were included in this study (age 49.6 ± 14.2 years, 47% female). 10 mepolizumab and 8 benralizumab biopsies were assessed. 100% patients had comorbid asthma and 88.2% were classed as atopic. There were no significant differences in baseline demographics including age, sex, duration of therapy, asthma, atopy or pre-treatment blood eosinophil count between the two groups (Table 1). Both groups showed significant decrease of peripheral blood eosinophils following initiation of biologic treatment with mepolizumab ($p = 0.001$) and benralizumab ($p = 0.02$). Blood eosinophil count after biologic therapy was significantly higher in the mepolizumab group compared to the benralizumab group (0.15 ± 0.15 v 0.00 ± 0.01 , $p = 0.02$).

Comparison of Histologic Features

Comparisons in mucosal outcomes between mepolizumab and benralizumab summarised in Table 2.

Table 1. Comparison of Demographic Data Across Biologic Therapy.

	Mepolizumab	Benralizumab	p-Value
n	10	8	
Age (mean $\pm$ SD years)	50.2 $\pm$ 16.2	49.1 $\pm$ 9.5	0.88
Sex (%female)	40	50	0.99
Duration of biologic therapy (median [IQR]) (months)	9.0 (15.0)	6.3 (19.2)	0.83
Asthma (%)	100	100	N/A
Atopy (%)	90	87.5	0.56
Pre-treatment blood eosinophil count ($\times 10^9/L$)	0.73 $\pm$ 0.73	0.58 $\pm$ 0.43	0.67
Post-treatment blood eosinophil count ($\times 10^9/L$)	0.15 $\pm$ 0.15	0.00 $\pm$ 0.01	0.02*

SD = standard deviation; IQR = interquartile range.

Table 2. Comparison of Histologic Outcomes Across Biologic Therapy.

	Mepolizumab	Benralizumab	p-Value
n	10	8	
Degree of inflammation (%)			0.08
Mild	0	12.5	
Moderate	60	75	
Severe	40	12.5	
Inflammatory predominance (%)			0.001*
Eosinophilic	90	0	
Lymphoplasmacytic	10	75	
Neutrophilic	0	25	
Lymphohistiocytic	0	0	
Other	0	0	
Eosinophil count / high power field (%)			<0.001*
<10	0	62.5	
10–100	40	37.5	
>100	60	0	
Neutrophil infiltration (%)			0.13
Absent	40	25	
Focal	50	25	
Diffuse	10	50	
Basement membrane thickening (um) (%)			0.63
<7.5	40	37.5	
7.5–15	40	25	
>15	20	27.5	
Subepithelial oedema (%)			0.02*
Absent	0	12.5	
Mild	0	25	
Moderate	20	25	
Severe	80	37.5	
Presence of hyperplastic change (%)	40	12.5	0.31
Presence of mucosal ulceration (%)	20	25	0.99
Presence of squamous metaplasia (%)	60	62.5	0.99
Degree of fibrosis			0.96
Absent	50	50	
Partial	40	37.5	
Extensive	10	12.5	

*p-value <0.05.

Representative H&E stained photomicrographs of mepolizumab and benralizumab treated biopsies are shown in Figures 1 and 2 respectively. Mepolizumab treated tissue (Figure 1) demonstrates abundant

eosinophils with scattered lymphocytes and plasma cells, whereas benralizumab treated tissue (Figure 2) showed scattered lymphocytes and plasma cells, few neutrophils and absence of eosinophils.

Even after mepolizumab, the tissue had predominantly eosinophilic inflammation compared to benralizumab (90% mepolizumab patients v 0% benralizumab patients, $p < 0.01$), whereas benralizumab patients demonstrated a greater lymphoplasmacytic inflammation (10% mepolizumab patients v 75% benralizumab patients, $\chi^2(2) = 14.53$, $p < 0.01$). There was no significant association between severity of inflammation between the two groups ($\tau^b = -1.76$, $p = 0.08$).

Patients treated with mepolizumab were more likely to have a high tissue eosinophil count compared with patients treated with benralizumab ($\tau^b = -8.47$, $p < 0.001$). There was no significant difference in

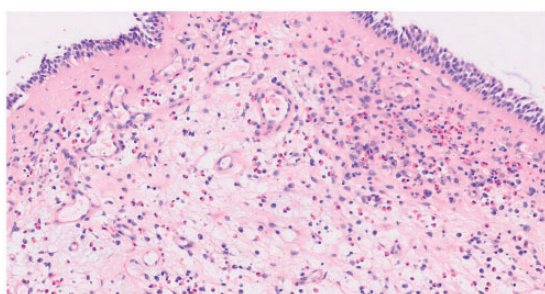


Figure 1. Sinonasal mucosal histology after mepolizumab treatment. H & E staining at 20x magnification shows abundant eosinophils and scattered lymphocytes and plasma cells.

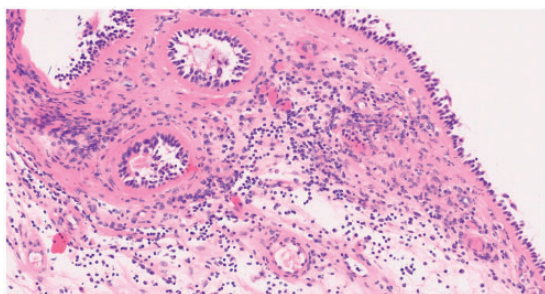


Figure 2. Sinonasal mucosal histology after benralizumab treatment. H & E staining at 20x magnification shows scattered lymphocytes and plasma cells and few neutrophils, but no eosinophils.

degree of neutrophil infiltration between the two groups ($\tau^b = -1.51$, $p = 0.13$).

Subepithelial oedema was more severe in patients treated with mepolizumab than with benralizumab ($\tau^b = -2.37$, $p = 0.02$). There was no significant difference between the two groups in basement membrane thickening ($\tau^b = 0.48$, $p = 0.63$), presence of hyperplastic change ($p = 0.31$), mucosal ulceration ($p = 0.99$), squamous metaplasia ($p = 0.99$) and degree of fibrosis ($\tau^b = 0.05$, $p = 0.96$).

Quality of life outcomes. Patient reported outcome data was available for 7 mepolizumab patients and 5 benralizumab patients. There was no significant difference between baseline ACQ-5 between mepolizumab and benralizumab patients prior to commencement of biologics (2.3 ± 1.7 v. 2.5 ± 1.4 , $p = 0.85$) or 3 months post-operatively (1.2 ± 0.7 v. 1.4 ± 1.4 , $p = 0.72$) (Table 3). Similarly, post-operatively there were no significant differences between the two groups in SNOT-22 (18.3 ± 15.9 v. 21.8 ± 21.6 , $p = 0.74$) and NSS (5.0 ± 4.1 v. 5.8 ± 5.7 , $p = 0.77$).

Discussion

This pilot study compared the mucosal outcomes following biologic therapy for eCRS. Few studies have detailed the exact local downstream effects for these biologics on IL-5-induced, eosinophilic diseases and further analysis at the tissue level would provide more information to guide application of mAbs in type 2 inflammatory diseases.^{17–19} To date, no studies have compared the direct tissue histopathology effects between biologics in eosinophilic asthma or eCRS.

Included patients were initiated on biologic therapy for severe eosinophilic asthma, which had the potential to aid in their ongoing management of their suboptimally-controlled severe eCRS. Biologic was independently selected based on their asthma status and factors included patient preference of monthly vs. second-monthly dosing and medication availability. No patients had previously failed biologic therapy. There is limited data in the literature comparing mepolizumab

Table 3. Comparison of Patient Reported Outcome Measures Across Biologic Therapy.

	Mepolizumab	Benralizumab	p-Value
n	7	5	
Pre-treatment ACQ-5 (0-5)	2.3 ± 1.7	2.5 ± 1.4	0.85
Post-treatment ACQ-5 (0-5)	1.2 ± 0.7	1.4 ± 1.4	0.72
Post-treatment SNOT-22 (0-110)	18.3 ± 15.9	21.8 ± 21.6	0.74
Post-treatment nasal symptom score (0-25)	5.0 ± 4.1	5.8 ± 5.7	0.77

ACQ-5 = Asthma Control Questionnaire 5-question; SNOT-22 = 22 item SinoNasal Outcome Test.

Data presented as mean $\pm$ standard deviation.

and benralizumab for both respiratory physicians and otolaryngologists to guide biologic choice.

Patients underwent endoscopic sinus surgery as part of management of their eCRS.¹⁶ This study was limited to patients with disease sub-optimally controlled clinically and symptomatically to warrant operative management. In patients with eCRS, multimodal therapy with surgery, topical medication irrigations and systemic medications (corticosteroids, biologics) has been shown to be successful in most patients to control disease and reduce symptoms.¹⁶ The objective for surgery was to provide a wide-open suitable cavity to maximise the postoperative delivery of corticosteroids to the sinonasal mucosa. Operations included revision polypectomy in patients who had recurrent disease/polypoid despite a previously adequately widened sinonasal cavity, to more extensive sinus surgery including Lothrop procedure.

eCRS is defined by local tissue hypereosinophilia and associated with poorer outcomes.²⁰ Histologically, it is characterised by eosinophilic-dominant inflammation with tissue eosinophil count >10 per HPF, as well as remodelling changes (basement membrane thickening, subepithelial oedema, mucosal ulceration and hyperplastic change) when compared with non-eCRS.^{21–24} No tissue eosinophil differences have been identified between patients later requiring mepolizumab therapy and patients controlled with local therapy only.²⁵

In this study, eCRS patients treated with mepolizumab still showed marked tissue eosinophilia, although there was a significant reduction in blood eosinophil levels. The results of this study are consistent with previous reports in asthma, showing that mepolizumab only partially depletes eosinophils in lower airway mucosa and bone marrow.^{26,27} Whether or not the remaining eosinophils in the sinonasal tissue are activated or inactivated after mepolizumab treatment requires further investigation.

In asthma, mepolizumab shows limited effect on lower airway eosinophil activation markers, suggesting that eosinophils maintain their functionality, albeit in reduced numbers.²⁸ Whilst in eosinophilic asthma, mepolizumab reduces frequency and severity of exacerbations compared with placebo,^{29–31} it is also associated with a suboptimal response in 52% of patients, with risk factors for failure including severe eosinophilic asthma, associated sinus disease and daily prednisolone requirement.³²

On the other hand, benralizumab precipitates an antibody-dependent cell-mediated cytotoxicity of eosinophils and basophils, resulting in their apoptosis.⁸ This therefore results in a significant reduction in tissue eosinophils as well as within the peripheral blood where the eosinophil count fell to near zero in benralizumab patients, whereas the fall in blood eosinophils was not as great with mepolizumab, as

demonstrated in this study. This effect has been similarly demonstrated in eosinophilic asthma, with reduction of peripheral blood and bone marrow eosinophils to undetectable levels, and significant reduction in lower airway mucosal and sputum eosinophils in response to benralizumab.³³

One of the main factors contributing to treatment failure to biologic therapy in eosinophilic disorders is thought to be suboptimal eosinophil suppression, thus benralizumab is thought to be more effective than mepolizumab in comparison.^{34–36} Whilst there have been no head to head trials of mepolizumab and benralizumab assessing tissue outcomes in eosinophilic asthma, the findings within this study demonstrate the complete eosinophil suppression in response to benralizumab as compared with mepolizumab in eCRS. Subdued eosinophilic inflammation may also limit associated eCRS remodelling changes, as shown in the significantly reduced severity of subepithelial oedema in this study, and the trend to decreased hyperplastic change (though not statistically significant in the current study).

It can be hypothesised that the predominance of the lymphoplasmacytic response in benralizumab may be due to ongoing Th2 driven inflammation consisting of Th2 lymphocytes and group 2 innate lymphoid cells without associated eosinophilic activation. Benralizumab patients in this study were characterised by the presence of diffuse tissue neutrophil infiltration (though not statistically significant). It has been shown that asthma exacerbations in patients treated with benralizumab are defined by non-eosinophilic neutrophilic inflammation, associated with increased sputum neutrophils.³⁷ This change is also associated with low circulating natural killer numbers in asthma, in contrast with mepolizumab.³⁸

One patient was included in both arms of the study, treated with mepolizumab for 2.9 years before transitioning to benralizumab. Whilst both biopsies showed lymphoplasmacytic inflammation, biopsy on mepolizumab therapy showed 10–100 eosinophils/HPF (eos/HPF) and absent neutrophils, compared with benralizumab treatment demonstrating greater depletion of eosinophils (<10 eos/HPF) and diffuse neutrophilic inflammation. This reflects the wider findings within this study.

Interestingly in one benralizumab patient, histology showed nodular fibrosis with focal clusters of histiocytes, associated with abundant plasma cells including IgG4 secreting plasma cells. There were no other systemic manifestations of IgG4 related disease and anti-neutrophil cytoplasmic antibody was negative. Whilst rare, IgG4 positive plasma cell infiltration has previously been documented in severe allergic type sinonasal disease and may not be associated to more systemic IgG4 related disease.^{39–42} This may represent a rare inflammatory

change associated with benralizumab treatment or reflect findings of severe eCRS. Histopathological endotyping is important in the management of patients with severe airway disease and in severe asthma has been shown to provide an alternate diagnosis in 10% of patients.^{43,44}

Given that this was a retrospective study and the recent availability of biologics for eCRS, patient care was not standardised. Patients were similar in terms of severity of symptoms based on quality of life measures (ACQ-5) at baseline. Despite mepolizumab being approved for use prior to benralizumab, there was no significant difference between the duration of treatment between the two groups (9.0 [15.0] v. 6.3 [19.2] years, $p=0.83$). The considerable data around blood eosinophil levels in response to both mepolizumab and benralizumab suggests that following 4 weeks of treatment, a steady state is achieved and maintained throughout the treatment period.^{13,14,45,46}

Timing and the extent of surgery in relation to initiation of biological therapy varied due to several factors, including, but not limited to, onset and severity of upper vs. lower airway symptoms, surgery being performed via the public vs the private system, duration of disease and history of prior interventions and changes in inclusion criteria for access to biologic therapy. In this study, at 3-months post-surgery, there was no significant differences between the two groups in ACQ-5, SNOT-22 or NSS. Standardising patient groups and interventions, as well as assessing sinonasal specific patient reported outcome measures, such as SNOT-22, would strengthen future studies assessing biologics in the eCRS population.

While both mepolizumab and benralizumab are clinically effective, the sinonasal tissue data shows that their use results in substantially different post treatment localised cellular profiles which is likely due to their different mechanisms of action. Whether this is relevant in the short or long term clinically is unknown, particularly as there are no randomised head to head studies in eCRS or in eosinophilic asthma.

There have been limited studies assessing the effect of biologic therapy on biomarkers in eCRS at the mucosal level.¹⁹ Further studies assessing tissue responses including other eosinophilic biomarkers will be of use to further quantify the reported data. In addition, tissue effects of dupilumab, an IL-4 α receptor mAb approved by the FDA for treatment of uncontrolled CRS with nasal polyposis should also be assessed. Finally, a comprehensive study looking at the effect of biologic therapies in eCRS and eosinophilic asthma on both upper and lower airway tissue as well as sputum and blood eosinophils would be vital in our understanding of the local and systemic effects of biologic therapies in the treatment of eosinophilic diseases.

Conclusion

In the treatment of eCRS, patients receiving mepolizumab demonstrated marked persistence of eosinophilic inflammation at the tissue level, whereas benralizumab treatment resulted in lymphoplasmacytic inflammation with associated reduction in tissue eosinophil count, reflecting their differing mechanisms of action. Additional studies are required to further assess the local tissue effect of biologics on sinonasal mucosa in eCRS.

Authors' Contribution

All authors contributed to the design and implementation of the research, to the analysis of the results and to the writing and editing of the manuscript. RJH and LK were responsible for tissue biopsy collection. PE was responsible for tissue histology analysis.

Declaration of Conflicting Interests

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ORCID iDs

Jacqueline Ho  <https://orcid.org/0000-0002-2765-8684>

William A. Sewell  <https://orcid.org/0000-0002-3586-8761>

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