

Impact of continued medical therapy in patients with refractory chronic rhinosinusitis

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Background: Patients with refractory chronic rhinosinusitis (RCRS) have persistent symptoms despite best medical therapy. Some evidence suggests continued medical therapy (CMT) is appropriate for patients with RCRS. The primary objective of this study was to evaluate the clinical impact of CMT in patients with RCRS who have significant reductions in baseline disease-specific quality of life (QoL) and would be considered candidates for endoscopic sinus surgery (ESS).

Methods: A prospective longitudinal observational study was undertaken between August 2011 and June 2013. Inclusion criteria: age >18 years, CRS defined by American Academy of Otolaryngology (AAO) adult sinusitis guidelines, failed medical therapy (defined by a 3-month minimum of topical intranasal steroid, minimum 7-day course of systemic corticosteroid, $\pm$ 2-week course of broad spectrum systemic antibiotic), and elected ESS. Primary outcomes were change in disease-specific QoL and endoscopic scores between enrolment and immediately prior to ESS. Secondary outcomes included medication consumption and work days missed.

Results: A total of 31 patients were enrolled. Following CMT for a mean of 7.1 months, there was an absolute wors-

ening in mean 22-item Sino-Nasal Outcomes Test (SNOT-22) score between baseline and preoperative follow-up, 57.6 to 66.1, respectively ($p = 0.006$). There was a significant worsening of mean endoscopic score between baseline and preoperative follow-up, 6.9 to 7.7, respectively ($p = 0.002$). There was an increase in budesonide irrigations along with a reduction in use of topical nasal steroid sprays prior to ESS. Patients experienced a mean increase of 3.6 work days lost while receiving CMT ($p = 0.023$).

Conclusion: Results from this study suggest that patients with RCRS who have significant reductions in baseline disease-specific QoL do not experience clinical improvement while receiving CMT. © 2013 ARS-AAOA, LLC.

Key Words:

chronic rhinosinusitis; sinusitis; medical therapy; refractory; quality of life; endoscopy; sinus surgery

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Chronic rhinosinusitis (CRS) is a ubiquitous inflammatory disease with an estimated prevalence of between 6% and 16% in the general population.^{1,2} Although the diagnosis of CRS is improving,^{3,4} the optimal management strategy for CRS remains debated. Medical therapy is gener-

ally accepted as the most appropriate first-line management strategy, with the goal of reducing mucosal inflammation and optimizing sinonasal function. However, a subset of patients will remain symptomatic despite the best medical therapy, which often includes topical high-volume saline irrigation, topical corticosteroids, short courses of systemic antibiotics, and systemic corticosteroids.^{5–7}

Refractory chronic rhinosinusitis (RCRS) patients represent a subset of patients with CRS who remain symptomatic despite management with best medical therapy. Although the degree of persistent symptoms can be highly variable, in general it is believed that these patients are least likely to improve with continued medical therapy. Based on the results from several large prospective cohort studies performed in multiple different countries, most clinicians would offer endoscopic sinus surgery (ESS) to patients with RCRS due to the demonstrated significant improvement in several clinical outcomes, including disease-specific quality of life

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(QoL).^{8–11} Despite strong evidence for ESS, some studies have suggested that continued medical therapy is as effective as ESS in patients with RCRS.^{12–14} However, based on the minimal previous medical therapy before enrolment, most clinicians would not consider the patient population in these studies to have RCRS. Thus, the true effect of ongoing medical therapy in patients with RCRS who have persistent significant reductions in disease-specific QoL is unknown.

The purpose of this study was to evaluate clinical outcomes in patients with RCRS who received ongoing medical therapy while ESS was pending. Primary outcomes were change in disease-specific QoL and endoscopic outcomes. Secondary outcomes included changes in medication usage and work days missed. Our hypothesis is that patients with RCRS who have significant reductions in baseline QoL will receive no further clinical benefit from ongoing medical therapy.

Patients and methods

Study design

This study was a prospective longitudinal observational study that enrolled patients between August 2011 to June 2013 (Clinical trial NCT01332136). Eligible patients were recruited at a tertiary level rhinology clinic by the principle investigator at the University of Calgary. Institutional ethics review board approval was obtained and informed consent was obtained from all patients.

Patient sample

Inclusion criteria included age >18 years, diagnosis of CRS based on the 2007 Adult Sinusitis Guidelines,⁴ failure of medical management, and elected ESS. Failure of medical therapy was defined as persistent symptoms and reduced disease-specific QoL despite a 3-month minimum of high-volume saline irrigations and topical intranasal steroid with a minimum 7-day course of systemic corticosteroid (Prednisone 30 mg/day) $\pm$ 2 week course of broad spectrum systemic antibiotic.

Exclusion criteria included the inability to complete questionnaires or clinical evaluations in English, contraindication to medical therapy, or the presence of any of the following: systemic inflammatory disease, ciliary dysmotility or cystic fibrosis.

Intervention: continued medical therapy

All enrolled patients continued medical treatment until the date of their ESS. A pragmatic approach to ongoing medical therapy was adopted to reflect common clinical practice. Continued medical therapy included appropriately prescribed saline irrigations, standard topical steroid sprays, high-volume budesonide-saline irrigations, rescue systemic antibiotics and systemic corticosteroids for acute exacerbations, prolonged macrolide antibiotic therapy, systemic antihistamines, and leukotriene (LT) recep-

tor antagonists. Although use of high-volume corticosteroid therapy in the preoperative setting has limited sinus penetration compared to post-ESS, we commonly implemented a preoperative high-volume irrigation strategy to improve sinonasal delivery rather than a low-volume spray technique.¹⁵

Outcomes

The primary outcome was change in disease-specific QoL using the 22-item Sino-Nasal Outcome Test (SNOT-22)¹⁶ and endoscopic scores using the Lund-Kennedy standardized scoring system.¹⁷ Secondary outcomes included disease-specific medication usage within the previous 90 days and work days missed.

All data was collected using survey evaluations delivered at the time of baseline enrolment and at a follow-up visit prior to receiving ESS. To avoid obtaining baseline data that reflects the treatment effect of systemic corticosteroid $\pm$ antibiotic therapy, the baseline enrolment measurements were taken 3 to 4 months after this initial therapy.

Statistical analysis

Data was collected, transcribed, and manually scored after each clinic visit of standardized clinical research forms. All data was deidentified and securely stored during the collection period.

Statistical analysis was performed using Stata statistical software (StataCorp LP, College Station, TX). Descriptive statistics (means, standard deviation, ranges, and frequencies) and distributions were assessed for all patient cofactors, surgical procedures, endoscopic scores, and QoL outcome variables. Paired *t* tests were used to test for significant changes between baseline and preoperative mean SNOT-22 scores, endoscopy scores, medication consumption, and work days lost. A *p* value of <0.05 was considered significant.

Results

Baseline cohort characteristics

A total of 31 patients with RCRS who elected ESS were enrolled between August 2011 and June 2013. The mean duration of ongoing medical therapy prior to receiving ESS was 7.1 months (range, 3 to 11.5 months) and there were no dropouts during the study period. Table 1 outlines the baseline characteristics for this study cohort.

Disease-specific QoL and endoscopic outcomes

There was an absolute mean worsening of 8.5 points between baseline and preoperative follow-up for the SNOT-22 score, which was statistically significant (*p* = 0.006) (Table 2).

There was a significant absolute mean worsening in endoscopic score between baseline and preoperative follow-up, 6.9 to 7.7, respectively (*p* = 0.002) (Table 2). There were 2 patients (9%) who received an endoscopic improvement of

TABLE 1. Baseline characteristics for cohort with RCRS

Characteristic	
Gender, n (%)	Female: 19 (59)
	Male: 12 (41)
Age (years), mean (range)	45.3 (20–65)
Asthma, n (%)	12 (39)
Allergy, n (%)	10 (33)
ASA intolerance, n (%)	3 (10)
Smoker, n (%)	3 (10)
Nasal polyposis, n (%)	4 (12.5)
Primary ESS, n (%)	25 (81)
Sinus CT score (Lund-Mackay), mean (range)	13.4 (8–24)

ASA = acetylsalicylic acid; CT = computed tomography; ESS = endoscopic sinus surgery; RCRS = refractory chronic rhinosinusitis.

TABLE 2. Comparison between baseline and preoperative disease specific outcomes

Primary measure	Baseline ^a	Preoperative ^a	<i>p</i>
SNOT-22	57.6 ± 17.1	66.1 ± 18.4	0.006
Endoscopic score	6.9 ± 2.7	7.7 ± 2.9	0.002

^aValues are mean ± SD.

SD = standard deviation; SNOT-22 = 22-item Sino-Nasal Outcome Test.

1 point, whereas all other patients had the same or worse endoscopic scores at preoperative follow-up.

CRS-specific medication consumption outcomes

There was a significant increase in the use of off-label topical steroid therapy (budesonide irrigations) ($p < 0.001$) and saline irrigations ($p = 0.020$) between baseline and preoperative follow-up. This was most likely related to changes in medical therapy to optimize the delivery of topical steroid into the paranasal sinuses. There was a significant reduction in the use of standard topical nasal steroid sprays ($p = 0.005$), which reflects the switch from a low-volume nasal delivery technique to a high-volume sinonasal delivery technique (ie, budesonide irrigations). There were no other significant changes in medication consumption between baseline and preoperative follow-up (all p values >0.234) (Table 3).

Work days missed

There was a statistically significant mean absolute increase of 3.6 work days lost between baseline and preoperative follow-up ($p = 0.023$) (Table 4).

TABLE 3. Medication usage comparison between baseline and preoperative follow-up

Medication	Baseline ^a	Preoperative ^a	<i>p</i>
Saline irrigation	46.0	60.1	0.020
Topical steroid spray	46.5	22.3	0.005
Budesonide irrigations	17.4	53.3	<0.001
Systemic antibiotic	16.0	16.4	0.947
Systemic steroid	8.7	8.2	0.773
Systemic antihistamine	10.4	10.0	0.903
LT receptor antagonist	11.6	14.9	0.234
Topical decongestant	4.8	8.5	0.293

^aValues are mean number of days used in prior 90 days.

LT = leukotriene.

TABLE 4. Comparison of work days lost between baseline and preoperative follow-up

Primary measure	Baseline ^a	Preoperative ^a	<i>p</i>
Work days lost	2.5 ± 5.3	6.1 ± 9.0	0.023

^aValues are mean ± SD.

SD = standard deviation.

Discussion

This study was a prospective longitudinal study examining the clinical impact of continued medical therapy on patients with RCRS who elected ESS and were waiting to undergo surgery. With an average duration of continued medical therapy duration for 7.1 months, patients with RCRS demonstrated a significant worsening in disease-specific QoL and endoscopic grading while waiting for ESS. Furthermore, there was a significant average increase of 3.6 work days lost between enrolment and preoperative follow-up. There was an increase in off-label topical steroid therapy and saline irrigations along with a reduction in standard topical nasal steroid sprays. Although there is limited evidence to suggest that a high-volume irrigation technique improves the delivery of topical steroid into the sinuses prior to ESS, the change in medical therapy in this study likely reflects a strategy to try to optimize topical steroid delivery in the preoperative period. Results from this study suggest that a management strategy which involves treating RCRS patients, who have significant reductions in their baseline QoL, with ongoing medical therapy alone often results in worse clinical outcomes and highlights the importance of ESS in this patient population.

Due to overwhelming positive evidence from several large prospective observational studies,^{8–11} ESS has become an important component in the management of patients with RCRS. Primary goals of ESS include improving the delivery of topical medical therapy,¹⁸ removing diseased tissue, and improving sinus patency. However, despite

strong evidence for ESS, a few studies have questioned the beneficial role of ESS as compared to medical therapy alone in patients with CRS. In 2006, a Cochrane review by Kahlil and Nunez¹² evaluated 3 randomized control trials (RCTs) and concluded that there was insufficient evidence to support the role of ESS in patients with CRS. However, the 3 RCTs included in this analysis failed to use appropriate comparison groups reflective of current standard practice. Specifically, patients were randomized prior to failing initial medical therapy, which does not reflect current surgical patient selection. In 2010, a RCT by Ragab et al.¹⁴ compared ongoing medical therapy to ESS in a group of patients who had persistent symptoms despite only a trial of topical nasal steroid spray and saline irrigations. They demonstrated improved disease-specific QoL in both groups with no differences between the medical therapy or ESS groups. However, their definition of failed medical management before enrolment was very limited and most clinicians would agree their study population would benefit from further medical interventions such as broad spectrum antibiotics and potentially systemic corticosteroids before considering ESS. Therefore, conclusions from both the Cochrane review¹² and RCT by Ragab et al.^{13,14} have limited applicability in elucidating the impact on ongoing medical therapy in patients with RCRS.

To better evaluate the role of ESS compared to medical therapy in patients with RCRS, Smith et al.¹⁹ performed a prospective, nonrandomized, multiinstitutional study comparing ongoing medical therapy to ESS coupled with ongoing medical therapy. Intervention allocation consisted of patients self-selecting into either medical vs ESS groups. Results demonstrated that patients with RCRS who underwent ESS received significant improvements in disease-specific QoL along with reductions in systemic antibiotic consumption and reduced missed work days compared to the medical therapy group. However, patients with RCRS in the ongoing medical therapy group had better baseline QoL and thus represented a different cohort than the RCRS patients who elected ESS. Therefore, results from this study suggest that patients with RCRS who elect ESS have a higher degree of disease-specific impact and benefit from ESS. Meanwhile, there may be a subset of patients with RCRS who have a lower degree of disease-specific impact and would benefit from a trial of ongoing medical therapy. Thus the effects of ongoing medical therapy in patients with RCRS who have significantly reduced baseline QoL is still unknown.

The purpose of this study was to evaluate the impact of ongoing medical therapy in the group of patients with RCRS who have serious enough reductions in baseline QoL to make the choice to elect ESS. Because there is overwhelming evidence to support ESS in this patient population, it is challenging to withhold ESS and study the impact of ongoing medical therapy. Prolonged surgical wait times in Canada offer a unique opportunity to study the impact of ongoing medical therapy in patients with RCRS who have elected ESS.

This prospective longitudinal study followed 31 patients with RCRS who elected ESS for a mean of 7.1 months of ongoing medical therapy. The mean baseline SNOT-22 score for our cohort was 57.6 ± 17.1 , consistent with a recent study by Soler et al.²⁰ which demonstrated that the mean SNOT-22 score of patients electing ESS was 54.6 ± 18.4 . Our results demonstrated a statistically significant mean worsening SNOT-22 score of 8.5 points ($p = 0.006$) and a mean worsening endoscopic score of 0.8 points ($p = 0.002$). This clinical deterioration occurred despite continuing appropriate medical therapy that included intermittent rescue systemic antibiotics, corticosteroids, and other agents in the waiting period. It must be noted that the majority of patients in this trial had RCRS without nasal polyposis (CRSsNP) (27/31, 87%) and thus the results most likely reflect ongoing medical therapy in this CRS cohort. There is evidence to support that topical corticosteroids have limited value in patients with CRSsNP prior to ESS, and our study supports this evidence.^{3,21}

It must be noted that it is challenging to apply the conclusions from this study to CRS patients with nasal polyposis (CRSwNP). Due to a limited sample size we were unable to perform a meaningful statistical subgroup analysis; however, the mean baseline SNOT-22 score for the 4 CRSwNP patients in this trial was 44.6 and after a mean of 6.8 months the mean preoperative SNOT-22 was 63.0. This demonstrates a worsening of disease-specific QoL with an absolute mean difference of 18.4. Although we cannot draw any meaningful conclusions from this small subgroup analysis, the data suggests that despite continued medical therapy, patients with nasal polyposis and significantly reduced baseline QoL levels likely continue to clinically deteriorate.

Overall, there was minimal difference in medication consumption between baseline and preoperative follow-up periods. The only significant medication changes were the increase in off-label budesonide irrigations and saline irrigations and a reduction in standard topical nasal steroids sprays. The increase in budesonide irrigations likely reflects both the practice of trying to optimize sinus delivery of topical steroid compared to low-volume nasal sprays, and trying to maintain some form of topical corticosteroid therapy in patients who are frustrated with using low-volume nasal sprays and want a change in management strategy. Despite the increase in budesonide irrigations in this study, it must be noted that there is no evidence to suggest that this therapy improves sinus delivery in the unoperated sinus patient. This lack of change in medication consumption with ongoing medical therapy is in contrast to the results after ESS, which have shown significant reductions.^{19,22,23} Assessment of work days lost demonstrated that the absolute value more than doubled (2.5–6.1 days) with a mean increase of 3.6 days lost, which was statistically significant ($p = 0.0229$).

Although this study provides a unique evaluation of ongoing medical therapy in patients with RCRS who have significant baseline reductions in disease-specific QoL, there

are several limitations that must be considered. First, there was no standardized protocol for ongoing medical therapy. We purposely adopted a pragmatic approach to ongoing medical therapy to most accurately reflect clinical practice. Thus we cannot comment on the effect of a specific “medical therapy protocol”; rather, we can only make conclusions pertaining to a general ongoing medical therapy approach. Second, due to inherent challenges in studying this patient population, our sample size is relatively small, which limits the ability to detect small differences between baseline and preoperative follow-up time points. However, most clinical outcomes worsened in this study and reached statistical significance despite a small sample size. Last, our mean follow-up was relatively short (7.1 months); thus, we cannot make conclusions about the impact of long-term ongoing medical therapy in patients with RCRS who have significant reductions in baseline disease-specific QoL. Due to the chronicity of this disease, there is a potential for patients to adapt to their RCRS and slowly experience improvement

in disease-specific QoL over time. Despite these limitations we feel the findings are strengthened by the prospective longitudinal methodology, stringent data collection, and adoption of a pragmatic approach to medical therapy.

Conclusion

This prospective longitudinal observational study evaluated the impact of continued medical therapy in patients with RCRS. All patients elected ESS, thus representing a RCRS patient cohort with significant reductions in baseline disease-specific QoL. Results from this study showed that patients with RCRS do not experience clinical improvement in both disease-specific QoL and endoscopic outcomes while receiving continued medical therapy. Furthermore, there was an increase in work-days lost and minimal effect on medication consumption. We conclude that continued medical therapy lacks beneficial effects in patients with RCRS who have significant reductions in baseline QoL. 

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