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A NEW ERA: EXPLORING THE ROLE OF MONOCLONAL ANTIBODY THERAPY IN THE TREATMENT OF CHRONIC RHINOSINUSITIS WITH NASAL POLYPOSIS

INTRODUCTION

Chronic rhinosinusitis (CRS), in its simplest form, is inflammation of the paranasal sinuses that has been present for more than three months. The clinical diagnosis is characterized by nasal obstruction/congestion/discharge, facial pain and decreased/absent smell with signs of inflammation in the sinonasal mucosa on endoscopy or computed tomography. An impaired sense of smell and olfactory loss is a cardinal feature of patients with nasal polyps.[1]

CRS affects about 5-12% of the population according to recent epidemiological studies, with a peak prevalence of 16% between the ages of 50-59.[2,3] While the symptoms are often downplayed by patients themselves, the impact on quality of life has been shown to be on par with congestive heart failure, moderate chronic obstructive pulmonary disorder and Parkinson's disease.[4] The most common extra-nasal sequelae are fatigue and depression, with approximately half of patients surveyed reporting fatigue and one-quarter reporting depression.[6] The societal impact is significant with annual rates of absenteeism estimated at 24.6 days a year, and at an overall productivity cost estimated at $10,077 per patient.[6]

A CRS patient's phenotype has generally been classified by the presence or absence of nasal polyps as CRSwNP and CRSsNP, respectively. This phenotyping is also reflected in therapeutic choice for disease management; CRSwNP is generally treated with topical and or oral corticosteroids, and CRSsNP with intranasal corticosteroids and antibiotics. However, as our understanding of the underlying pathophysiology evolves, the treatment strategy is shifting to a more tailored approach. Many different factors have been implicated in the development of CRS including superantigens, microbiome disturbance, biofilm formation, epithelial barrier disturbance, allergy, vitamin D deficiency and genetic predisposition.

Today, most studies concentrate on endotype-driven inflammation in the sinus mucosa. In recent years, Type 2 inflammation has been the most studied, characterized by the presence of interleukins [4,5,9,13] and eosinophils in peripheral blood or nasal mucosal biopsies.[7] Other inflammatory pathways such as Th-17/Th-22, Th1, and neutrophilic inflammation have also been implicated and appear to be more common in the CRSsNP patient population. Other type 2 inflammatory conditions, such as allergic rhinitis, atopic dermatitis and asthma, are highly prevalent among CRS patients, with up to 66% of CRS patients suffering from comorbid allergic asthma.[8] The severity of clinical symptoms and radiographical findings of CRS has been shown to corelate well with the severity of asthma.[9,10] Perhaps the most recalcitrant and severe form of CRS is NSAID-exacerbated respiratory disease (NERD), a clinical syndrome combining CRSwNP, asthma and non-IgE mediated allergy to aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) that is also associated with type 2 inflammation.[11]

Management of CRS

It is important for both the physician and the patient to understand that CRSwNP is a chronic disease. The main goal of management is to achieve and maintain clinical symptomatic control of the disease, using appropriate medical therapy, with minimal side effects and the requirement for surgical intervention only when needed. The mainstay of medical therapy is the

use of saline irrigation and intranasal corticosteroid therapy typically dosed b.i.d. but may vary depending on the spray used, both of which are supported by high levels of evidence.[5] High volume nasal corticosteroid delivery by adding corticosteroid to the saline irrigation appears to provide incremental benefit without additional risk. Systemic corticosteroid therapy can provide immediate transient relief of many CRS symptoms, but regular use is associated with significant side-effects and risk, and escalation of therapy should be considered if it is required more than one to two times per year.[12]

In general, endoscopic sinus surgery (ESS) is indicated in CRSwNP patients that fail to achieve symptomatic control with pharmacologic therapy (**Figure 1**). It is important to emphasize that surgery is not curative but rather performed to remove inflammatory polypoid tissue, improve sinus drainage and, most importantly, to allow for effective delivery of topical corticosteroid to the inflamed sino-nasal mucosa.

The majority of CRSwNP patients benefit from surgery, the success of which is largely dictated by the underlying severity of disease and the extent of surgery. Most patients undergoing surgical treatment are able to obtain good control of (most) symptoms with post-operative medical therapy. One retrospective review of 29,934 patients with CRSwNP found that 15.9% required 1 repeat surgery over a mean follow-up of 9.7 years.[13] Performing a "complete/full house FESS" surgery versus "targeted surgery" has been shown to confer a greater improvement in quality of life scores (SNOT-22), smell and endoscopic scores.[14] Targeted surgery vs. complete/full house endoscopic sinus surgery does not confer different risk. The risk to skull base or orbital injury is largely the same in experienced hands, especially with the use of navigation.

CRSwNP patients suffering from co-morbidities such as asthma and N-ERD have a more severe phenotype of CRSwNP, and often need multiple treatments and recurrent surgeries for symptom control.[15,16] It is within this patient population that targeted therapy with monoclonal antibodies appear to offer the most utility.

Biologic agents

OMALIZUMAB
(Anti-IgE antibodies):
The interest in monoclonal antibodies for

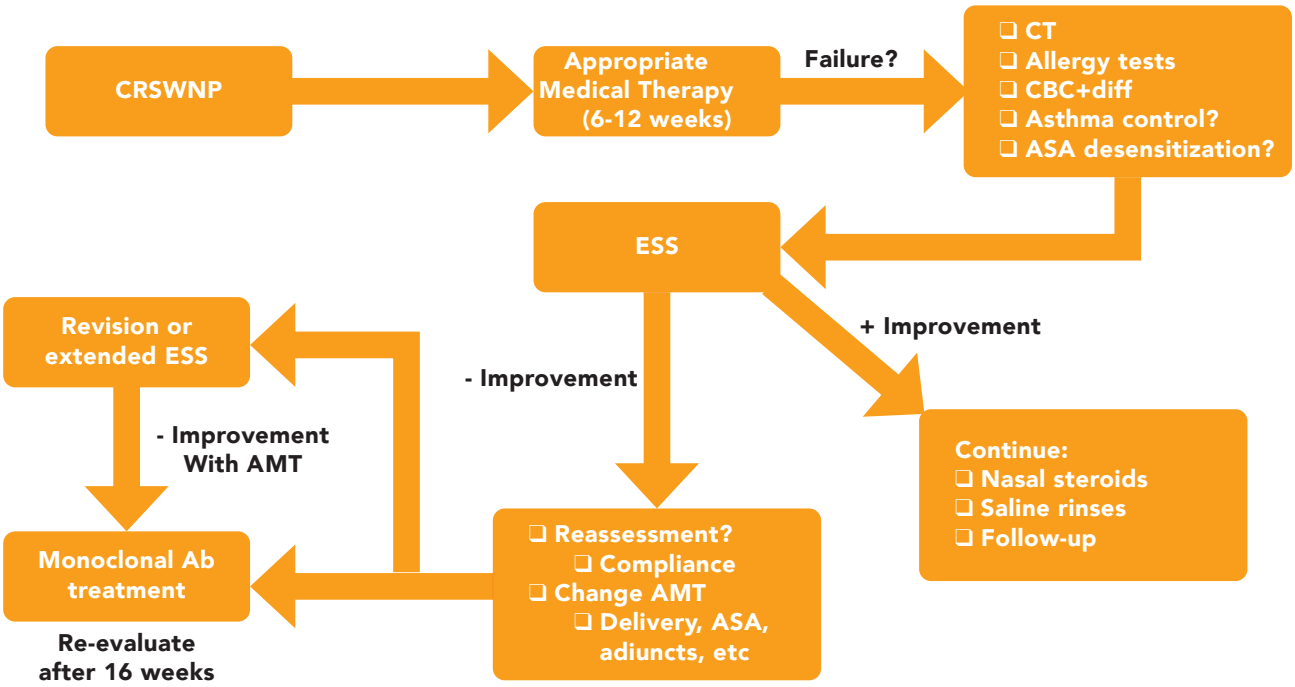

Figure 1. CRSwNP treatment recommendations; adapted from EPOS guidelines,

CRSwNP started when improvements in CRS symptoms were seen with the use of omalizumab for the treatment of asthma. In December 2020, the U.S. Food and Drug Administration (FDA) approved omalizumab for use in CRSwNP patients. This was followed by Health Canada approval in the summer of 2021.

Two randomized, multi-center, phase 3 trials – POLYP 1 and POLYP 2 – evaluated the efficacy and safety of omalizumab in CRSwNP across 82 centers in the U.S and Europe.[17] Patients with CRSwNP and an inadequate response to intranasal corticosteroids were randomized to receive weight and IgE-based dosing of s.c. omalizumab (75-600 mg every 2-4 weeks) or placebo with mometasone nasal spray for 24 weeks. At week 24, the mean changes from baseline for omalizumab versus placebo for POLYP 1 and POLYP 2 were as follows: Nasal polyp score (maximum score 8), -1.08 versus 0.06 and -0.90 versus -0.31; Nasal Congestion Score (maximum score 3), -0.89 versus -0.35 and -0.70 versus -0.20; and SNOT-22 score (patient reported symptoms, maximum score 110), -24.7 versus -8.6 and –21.6 versus -6.6. Clinical improvements were observed as early as 4 weeks for most endpoints, and at 8 weeks for olfaction. An improvement in the objective measurement of olfaction was seen at the end of the trial in comparison to both placebo and baseline (3.8 and 3.4 points, maximum score 40). In smaller studies, omalizumab also exhibited improvement in patient-reported outcome scores.[18,19]

DUPILUMAB
(Anti-IL-4/IL-13 Antibodies) :
Dupilumab is a monoclonal antibody that targets the ∝ subunit of the IL-4 receptor resulting in interruption of IL-4 and IL-13 binding. IL-4 promotes Th2 differentiation, activation of B cell lymphocytes, induces IgE B-cell class switching, trafficking of eosinophils, and M2 macrophage polarization. The function and differentiation of macrophages are controlled by multiple factors. M1 macrophages (classically activated macrophages) are induced by INF-gamma, and M2 macrophages (alternatively activated macrophages) are induced by either IL-4, IL-13, IL-10, or glucocorticoid. Both IL-4 and IL-13 generate their effects on the inflammatory cascade via this receptor pathway, thus, blocking the IL-4 receptor has an effect on both cytokines. In August 2020, Health Canada approved dupilumab as add on therapy for the treatment of CRSwNP in adults. A small study with 60 patients demonstrated an improvement in polyp score, SNOT-22 scores and radiological findings in patients treated with dupilumab versus placebo over 16 weeks.[18] This led to two larger multicenter, randomized controlled phase 3 trials (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52).[19]

In SINUS-24, 276 CRSwNP patients were randomized to receive dupilumab 300 mg s.c. or placebo with mometasone spray every 2 weeks for 24 weeks and then followed for an additional 24 weeks. At the end of the treatment period, a significant decrease in polyp score (-1.89 versus 0.17, maximum score 8) and in nasal congestion score (-1.34 versus -0.45, maximum score 3) were seen. However, after discontinuing dupilumab injections at 24 weeks, a worsening in nasal polyp score and nasal congestion score trending back to baseline was seen.

In SINUS-52, 448 patients were randomized into 3 arms, all of whom received mometasone spray concurrently; the first arm received dupilumab every 2 weeks for 52 weeks, the second arm received dupilumab every 2 weeks for 24 weeks and then every 4 weeks until 52 weeks, and the third arm received placebo. A pooled analysis of the treatment groups demonstrated improvement in nasal polyp score (-1.71 versus 0.10, maximum score 8) and nasal congestion score (-1.25 versus –0.38, maximum score 3). An incremental improvement was seen in nasal polyp score and CT grading in the q2 weekly versus the q4 weekly groups; nasal congestion and other secondary endpoints were similar between groups. The q2 weekly group was also found to have fewer treatment-emergent events of sinusitis and asthma exacerbations.

Both studies demonstrated a significant improvement in measured olfaction with an improvement of 11.3 points on the University of Pennsylvania Smell Identification Test (UPSIT) in SINUS-24 and 9.8 points (maximum score 40) in SINUS-52. Improvement in the primary endpoints were seen as early as 4 weeks in both studies.

MEPOLIZUMAB
(anti IL-5 antibody):
Mepolizumab , an anti-IL-5 antibody was approved for the treatment of CRSwNP in Canada in November 2021. IL-5 is considered to be a primary cytokine in eosinophil activation, and as such, monoclonal therapy targeting IL-5 was felt to hold great promise.[20]

In 2017, researchers reported the results of a randomized double blind placebo-controlled trial assessing the efficacy of 750 mg of mepolizumab in the treatment of CRSwNP.[21] In this study from 2017, 105 patients received 750 mg of

IV mepolizumab or placebo every 4 weeks for a total of 24 weeks (6 doses) in addition to daily topical corticosteroid treatment. In the mepolizumab group, a significantly greater proportion of patients no longer required surgery at Week 25 (16 [30%] vs 5 [10%], respectively; P = .006) A significant improvement in nasal polyposis severity VAS score was also observed in the mepolizumab group (-4.2 versus -2.4, maximum score 10).[21]

That initial study led to SYNAPSE, a randomized, double-blind, placebo-controlled study with 414 patients of whom 407 patients were included in the final analysis.[21] Patients received either 100 mg mepolizumab subcutaneously or placebo, every 4 weeks for 52 weeks, in addition to mometasone nasal spray. During the 52-week treatment period, the risk of nasal surgery was significantly lower with mepolizumab versus placebo (9% versus 23% of patients underwent surgery respectively). The change in nasal obstruction VAS score was -4.4 versus -2.5 in the placebo group (maximum score 10). The improvement in total endoscopic nasal polyp score was significantly higher with mepolizumab (-0.9 versus -0.1, maximum score 8). In the mepolizumab group, 73% of patients had a clinically significant improvement from baseline in SNOT-22 score versus 54% in the placebo group – a numerical improvement of -29 versus -16 respectively (maximum score 110). Objective measures of olfaction were not statistically significant but subjective measures of olfaction improved from baseline by 2.8 in the mepolizumab group versus 1.4 in the placebo group (out of 10).

BENRALIZUMAB
(anti IL-5 receptor antibody):
Benralizumab is a monoclonal antibody that targets the IL-5R ∝ chain. It reduces the blood eosinophil count in peripheral blood and airway mucosa, and may have greater eosinophilic effects than mepolizumab.[23] In the OSTRO study, patients were randomized to benralizumab 30 mg sq or placebo every 4 weeks for the first 3 doses and every 8 weeks for 48 weeks with concurrent mometasone spray.[24] A significant improvement in the total mean nasal polyp score was seen in the benralizumab group compared to placebo at week 40 (-0.42 versus 0.15, maximum score 8). Nasal blockage scores were also improved with benralizumab (-0.71 versus –0.44, maximum score 3) by week 40. Improvement in SNOT-22 scores was seen in both groups (-16 versus –11, maximum score 110), however, the difference between groups did not achieve statistical significance. The time to first surgery was similar between groups and there was no difference between groups in objective measures of olfaction.

Emerging therapeutic agents:

IL-33 and thymic stromal lymphopoietin (TSLP) are mediators of type 2 inflammation. TSLP triggers dendritic cell-mediated Th2 inflammatory responses, and IL-33 targets Th2 cells (i.e., eosinophils, mast and dendritic cells) via the IL-1 receptor. These two innate cytokines can drive Th2 cytokine production and induce and maintain the type 2 inflammation cascade. In recently published data, tezepelumab (anti-TSLP) reduced the number of asthma exacerbations, blood eosinophil count, and IL-5 and IL-13 levels.[25] Etokimab (anti-IL-33) has also demonstrated good results in the treatment of eosinophilic asthma.[25] A clinical trial for etokimab has been completed for CRSwNP but results are not yet published[26], and there is an active phase 3 trial underway for tezepelumab. Thus, these new medications may serve as future therapies for CRSwNP.

No head-to-head studies have yet been completed comparing monoclonal antibodies with each other. A recent meta-analysis[27] examined 29 RCTs evaluating 8 treatments (n=3,461) and compared the outcomes of monoclonal antibodies and aspirin desensitization for treatment of CRSwNP. All biologic agents had a better outcome than placebo, however, dupilumab had superior results in patient-reported outcomes, polyp score, olfactory testing, endoscopic and radiographic scores when compared to other biologics and aspirin desensitization (**Figure 2**). It is also important to note that the placebo group in the majority of trials demonstrated clinical improvement in outcome measures. This may be reflective of the importance and efficacy of stringent adherence to medical therapy with nasal corticosteroid as it is seen in both subjective and objective measures.

Cost of biologic therapy:

The cost of monoclonal antibody therapy is significant in comparison to traditional therapy. The treatment cost per year is between $20,000-$33,000, in contrast to the estimated annual cost of functional endoscopic sinus surgery (FESS) of $3,510 in Canada.[28] A recent Markov analysis compared the cost effectiveness of ESS treatment versus dupilumab in CRSwNP patients; FESS was more cost-effective than dupilumab regardless of the frequency of revision surgery and at any yearly cost of dupilumab above $855. More studies are needed to isolate potential phenotypes or endotypes that will benefit most from dupilumab in a cost-effective manner.[29]

Figure 2. Summary of meta-analysis findings.

	Patient-Important Outcomes						Surrogate Outcomes	
	HRQoL SNOT-22 (0-110)†	Symptoms VAS (0-10 cm)	Smell UPSIT (0-40)†	Rescue OCS	Rescue Polyp Surgery	Adverse events	Nasal Polyp Size (0-8)	CT Score LMK (0-24)
Standard Care*	50.11	6.84	14.04	31.96%	21.05%	73.78%	5.94	18.35
Dupilumab	-19.91 (-22.50, -17.32)	-3.25 (-4.31, -2.18)	10.96 (9.75, 12.17)	-21.73 (-24.61, -18.22) RR 0.32 (0.23, 0.43)	-16.35 (-18.13, -13.48) RR 0.22 (0.14, 0.36)	0.13 (-8.12, 9.88) RR 1.00 (0.88, 1.13)	-2.04 (-2.73, -1.35)	-7.51 (-10.13, -4.89)
Omalizumab	-16.09 (-19.88, -12.30)	-2.09 (-3.15, -1.03)	3.75 (2.14, 5.35)	-12.46 (-23.65, 12.78) RR 0.61 (0.26, 1.40)	-7.40 (-11.04, -2.43) RR 0.65 (0.48, 0.88)	-2.60 (-15.58, 13.28) RR 0.96 (0.79, 1.18)	-1.09 (-1.70, -0.49)	-2.66 (-5.70, 0.37)
Mepolizumab	-12.89 (-16.58, -9.19)	-1.82 (-3.13, -0.50)	6.13 (4.07, 8.19)	-10.23 (-15.98, -2.88) RR 0.68 (0.50, 0.91)	-12.33 (-15.56, -7.22) RR 0.41 (0.26, 0.66)	-3.07 (-13.44, 9.07) RR 0.96 (0.82, 1.12)	-1.06 (-1.79, -0.34)	
Benralizumab	-7.68 (-12.09, -3.27)	-1.15 (-2.47, 0.17)	2.95 (1.02, 4.88)	-9.91 (-16.30, -0.96) RR 0.69 (0.49, 0.97)	-2.53 (-9.05, 7.16) RR 0.88 (0.57, 1.34)	-1.48 (-13.28, 12.54) RR 0.98 (0.82, 1.17)	-0.64 (-1.39, 0.12)	-1.00 (-3.83, 1.83)
Reslizumab					-18.82 (-20.93, 20.56) RR 0.11 (0.01, 1.98)	-2.55 (-19.49, 19.18) RR 0.97 (0.74, 1.26)		
AK001						2.54 (-27.11, 51.03) RR 1.03 (0.63, 1.69)	-0.20 (-1.61, 1.21)	
Etokimab	-1.30 (-8.99, 6.40)					188.14 (-59.76, 4879.1) RR 3.55 (0.19, 67.13)	-0.33 (-1.58, 0.92)	
ASA desensitization	-10.61 (-14.51, -6.71)	-2.74 (-3.92, -1.57)	2.72 (-1.17, 6.61)		-16.00 (-19.79, 0.21) RR 0.24 (0.06, 1.01)	209.21 (8.30, 901.87) RR 3.84 (1.11, 13.22)	-0.95 (-2.44, 0.55)	-0.31 (-3.50, 2.88)

Classification of intervention (colour)			Certainty (shading)	
Among most beneficial	Among intermediate beneficial	Among least beneficial/ not clearly different from placebo	No data (blank)	High/moderate (solid)
Among most harmful	Among intermediate harmful			Low/very low (dotted line)

HRQoL, health-related quality of life; SNOT-22, sino-nasal outcome test 22; VAS, visual analog score; UPSIT, University of Pennsylvania Smell Identification Test; OCS, oral corticosteroids; CT, computed tomography; LMK, Lund-Mackay

**The expected risk of each outcome with standard care is reported in the grey row*

Numbers in the colored cells are the estimated mean differences (95%CI) for HRQoL, symptoms, smell, nasal polyp size and CT score and absolute risk differences (95%CI) per 100 patients (with accompanying relative risks [95% CI]) for rescue OCS, rescue nasal polyp surgery and adverse events versus standard care.

tThe only scale presented where higher is better. Higher scores indicate worse outcome for all other scales shown. GRADE certainty24• 29

High certainty - Further research is very unlikely to change our confidence in the estimate of effect

Moderate certainty - Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

Low certainty - Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate

Very low certainty - Any estimate of effect is very uncertain

Conclusion:

Monoclonal therapy in treatment of CRSwNP is truly life-changing for patients with severe disease., Most CRSwNP cases can be effectively managed with intranasal corticosteroids and complete surgery. Biologic therapy should be discussed with the patient as part of a potential treatment algorithm and offered when surgical therapy is either contraindicated or already complete in extent. The extent of surgery performed for CRSwNP is subject to wide variability. Patients can undergo multiple polypectomies without complete or adequate response, thus necessitating the important role of CT and review with an experienced surgeon in determining appropriate next steps. The presence of co-morbidities may also help with appropriate patient selection, such as patients with AERD.

Authors from different countries continue to attempt to define a clear protocol for treatment of CRSwNP with biologic agents.[30-32] These consensus statements and published guidelines universally conclude that biologic agents should be considered in patients with recalcitrant disease after appropriate medical and surgical therapy, as well as those with significant co-morbidities.

A Canadian rhinology consensus was published with 11 statements intended to provide guidance on biologic therapy for CRSwNP.[33] In these statements, a key consideration prior to initiation of therapy is whether adequate sinus surgery was performed. This same Canadian rhinology consensus group note that biologics in Canada indicated for asthma can range between $600 to $4000 per vial/ syringe. A recent econometric evaluation demonstrated that upfront surgery for CRSwNP is a more cost-effective option than dupilumab, However, it is clearly evident from the published guidelines that patients who may require revision surgery more than once will likely require it repeatedly and that the time interval between surgeries will diminish with each surgery. Therefore, a cost utility analysis in this clinical scenario is required to address the question of whether biologics or surgery are the most cost-effective approach and in which specific patient populations the benefit may be greatest,[33] Additionally, patients' response to biologic therapy should be evaluated objectively by endonasal endoscopy or CT scan 16 weeks after the onset of the treatment. This clinical assessment can be done with fiber-optic nasal endoscopy or CT scan. In asymptomatic patients with improved subjective scores using questionnaires and improved objective endonasal scores, a CT scan is not needed. In general, endoscopic assessment is recommended as it is easier, less costly and has no radiation associated with it (although the radiation associated with a CT sinus is minimal, and equivalent to approximately 6 chest x-rays). If there is a loss of response, comparing pre vs. post-CT scans would allow for those without access to endoscopy to evaluate if continuing on biologics is warranted.

In summary, CRSwNP is a complex chronic disease that afflicts about 10% of the population. The understanding of the pathophysiology of this disease continues to evolve while the current treatment landscape encompasses the use of therapeutic agents and surgical interventions. Advanced surgical techniques and good adherence to topical therapy can achieve excellent control of symptoms in the vast majority of CRSwNP patients. As newer monoclonal antibodies emerge, it will be important to ensure that appropriate risk-benefit calculations are taken into account for biologic therapy in a targeted CRSwNP patient in addition to an appreciation of the direct and indirect costs to the health system as clinicians strive to achieve optimal outcomes for their CRSwNP patients.

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