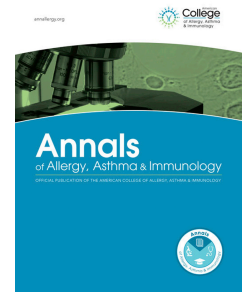


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**A call for cost-effectiveness analysis for biologic therapies in chronic rhinosinusitis
with nasal polyps**

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1 Introduction

2 Chronic rhinosinusitis (CRS) is a chronic disease of the upper airways that is both
3 common, as it affects more than 10 million Americans¹, and economically onerous, as it
4 is associated an annual loss of 60 paid work days missed per patient from both
5 absenteeism and presenteeism². CRS is associated with a significant decline in quality of
6 life (QOL)³. The majority of CRS patients do not improve with current medical options
7 and need to undergo repetitive surgeries. Not surprisingly, CRS is associated with a high
8 financial burden on society with an estimated 60 billion dollars per year⁴. The current
9 standard medical treatment for CRS has been limited to the use of topical steroids,
10 antihistamines, leukotriene antagonists, anticholinergic medications and antibiotics which
11 have been proven to be not effective enough in majority of cases who will need repeated
12 surgical intervention⁵. Unfortunately, we continue to witness recurrence of disease even
13 after pharmacotherapy and surgery in a large group of patients. More than 20% of CRS
14 patients need to undergo repeated surgery within 5 years⁶. The recurrence rate is even
15 higher in patients with nasal polyps, and those with coexisting asthma or aspirin
16 sensitivity. The overall recurrence rates for redevelopment of polyps in 5 years after a
17 surgical intervention has been estimated as 16%, 45%, and 90% in CRS with nasal polyps
18 (CRSwNP) patients, CRSwNP patients with asthma, and in those with aspirin
19 exacerbated respiratory disease (AERD) respectively⁷.

20 Research on pathogenesis of CRS has shown evidence for a significant Type 2
21 inflammatory pattern in a large group of cases, especially in those with nasal polyps⁸⁻¹⁰.
22 For example, in cluster analysis of 173 CRS patients, 98 (clusters 5 through 10) had
23 elevated proportion of eosinophilic cationic protein, interleukin-5 (IL-5),

immunoglobulin E, nasal polyps and asthma compared to other clusters¹⁰. This knowledge needs to be implemented and can help to guide future disease management approaches. In the past few years biological agents, which are monoclonal antibodies (mAbs), have become available for the treatment of respiratory inflammatory diseases with focus on asthma¹¹⁻¹⁶. Although none of these biologics are approved for CRS yet, controlled trials have tested their efficacy in this disease¹⁷⁻²². This review intends to analyze and discuss the need for cost effectiveness analysis of these biologic therapies for CRS.

The economic burden of CRS

With regard to its complexity, recurrence and high cost of medications, CRS stand among the ten most costly health conditions^{1, 23}. The total cost for medical treatment of one patient with CRS in the United States is estimated around \$2600 per year. The overall cost of outpatient endoscopic sinus surgery ranged from \$8,200 to \$10,500 USD per case in 2014²³. Beside the cost for medical treatments and surgical interventions, uncontrolled CRS is associated with a large indirect cost. The CRS-related direct healthcare costs have been estimated to be \$6.9 to \$9.9 billion USD per year, while the indirect costs were estimated as another \$13 billion USD per year in one study²³. The overall annual economic burden of CRS in the United States has been estimated to be \$ 22-60 billion USD per year in different studies^{4, 23}.

Effectiveness measures of CRS

Given the high burden and cost of CRS, effective treatments are needed. Effectiveness is often measured by quality of life, which takes into account the patient's preference. Pre-scored multi-attribute systems bypass the need to measure preferences by standard gamble or time trade-off technique²⁴. There are generic quality of life systems and disease-specific systems. Generic quality of life measures include 36-item Short Form survey (SF-36), or a shortened version such as the SF6D, can be used to compare the impact of on quality of life by different diseases²⁵. These generic quality of life measures have been used in CRS research. Studies have shown that CRS patients who selected endoscopic sinus surgery (ESS) had worse baseline quality of life as measured by the SF-6D²⁶. When generic instruments are not sensitive enough to change or when making comparisons between therapies of particular disease, a disease-specific quality of life measure, such as the validated 22-item Sino-Nasal Outcome Test (SNOT-22), which can be used in CRS²⁷. With the SNOT-22, higher numbers indicate worse severity. For CRS patients undergoing ESS, those with SNOT-22 scores 10-19, only 35.7% met the minimally clinically important difference of improvement after surgery compared to patients with SNOT-22 score of 20-29 who 75% met MCID after surgery²⁸. Thus, both generic and CRS-specific quality of life measures are useful to compare the clinical effectiveness of CRS treatments.

Cost-effectiveness analysis and how it can be applied to CRS

As defined in the most recent guidelines, cost effectiveness analysis (CEA) is a form of economic evaluation that assesses the health outcomes and costs designed to improve people's health^{29,30}. CEA involves estimating the net, or the 'incremental' costs and

effects of an intervention compared with some alternative^{29, 30}. All costs associated with the delivery of the comparing interventions are included consistent with the perspective of the study. All health effects, both beneficial and detrimental, are included in the analysis. The costs and health effects included in the study are determined by the perspective of the study, whether that would be healthcare payer perspective or societal perspective, the latter being important as it would include all costs so as to not miss any cost-shifting. Thus, cost-effective analysis is a technique to assess an interventions cost and health impact in comparison to a competing alternative.

Cost-effectiveness analysis and other economic analyses have been performed in CRS comparing ESS to medical therapy. In a Markov model, ESS was cost-effective in comparison to medical therapy, with an incremental cost-effectiveness ratio (ICER) of \$ 5,901.90/quality adjusted life year (QALY)³¹. Other studies found that ESS was cost-effective in comparison to medical therapy with an ICER of \$ 13,852.26/QALY³². In the sensitivity analysis, the authors noted that medical therapy was more cost-effective only when the revision rate exceeded 24%. As the recurrence rate of nasal polyposis after ESS can be as high as 38% at 12 months,³³ more recent data has shown that in fact the revision rates can be high for CRSwNP. In a long-term 10-year observational study, 10 of 59 CRS patients required revision³⁴. The revision rate was higher in CRS patients that would have Th2 phenotype, with 8 of these 10 patients having CRSwNP and 4 of these 8 CRSwNP patients having AERD. Clearly there is a need for more targeted therapies and to determine the cost-effectiveness of therapies in these subgroups.

The evolving understanding of inflammation in CRS

Current medical treatment of CRS is based on defined clinical characteristics and phenotypes described in the US and European guidelines^{5, 35}. However, like asthma, in future the treatment approaches need to be stratified on biomarkers and endotypes to address the central pathophysiologic mechanism linked to the disease subtype^{36, 37}. Endotypes of CRS could be differentiated based on different biomarkers such as the cells involved (e.g. eosinophils) or levels of cytokines and allergic antibody (IgE) in serum or tissue. In the context of availability of new biological agents that specifically target mediators such as cytokines or their receptors, individualizing the treatment based on these biomarkers will become an important tool in management of CRS.

CRS is a chronic inflammatory disease affecting the sinonasal cavity with a heterogeneous pathophysiology resulting in wide phenotypic variation. The differential expression of type 1, 2, or 3 immune responses results in heterogeneity in CRS^{38, 39}. Furthermore, the dominance of immune responses can vary across different populations with varied racial backgrounds^{9, 40}. In a large study attempting to cluster CRS patients based on clinical and pathophysiologic characteristics, 10 different clusters were shaped; out of which 6 were heavily type 2 driven¹⁰. The cumulative results of previous studies have demonstrated that majority of white and black patients with CRSwNP in Western countries have a type 2 inflammatory profile with high rate of asthma comorbidity, featured by upregulated levels of IL-4, IL-5, IL-13, local IgE and tissue eosinophilia⁸⁻¹⁰. In CRS patients without nasal polyps (CRSsNP), a variable percentage of patients have type 1, 2 or 3^{10, 38}. In US, similar to other western countries the vast majority of

CRSwNP^{38, 41} and at least one third of CRSsNP patients³⁸ have evidence for a type 2 (Th-2) inflammatory pattern and increased eosinophils. Of note, the inflammation in CRS involves type 2 innate lymphoid cells (ILC2s), which release similar pattern of type 2 cytokines including IL-4, IL-5 and IL-13⁴².

Biologic therapies for Th2 inflammation

Most approaches that have been used to differentiate endotypes of CRS are based on presence and abundance of eosinophils and IgE, which are linked to Th-2 inflammation. Differentiation and classification of CRS based on Th-2 inflammatory mediators is most relevant for use of biologic agents, which are designed to block IL-5, IL-4 and IL-13, or IgE. These medications have been approved for treatment of severe asthma which in most cases is a Th-2 driven disease⁴³. The 5 biologics that are approved for asthma all target Th-2 inflammatory mediators and include mepolizumab, reslizumab, benralizumab, omalizumab and dupilumab (Figure 1)⁴³. Mepolizumab, reslizumab reduce the activation and survival of eosinophils by targeting IL-5⁴⁴. Benralizumab targets the alpha subunit of the interleukin-5 receptor (IL-5R α) and results in direct and almost complete depletion of eosinophils through natural killer cell-mediated antibody-dependent cellular cytotoxic effect^{16, 45}. Omalizumab recognizes and attaches to free IgE at the same site as the high-affinity IgE receptor (Fc ϵ RI), which results in inactivation of the molecule⁴⁶ and stopping the allergic signal sent to the mast cells and basophils. Dupilumab is designed to recognize the alpha subunit of the IL-4-receptor (IL-4R α) that is common for signal transduction through both IL-4 and IL-13⁴⁷. In summary, Type 2 inflammation is the predominant inflammatory pattern in CRS and an opportune quarry to precisely target.

Out of these mAbs, omalizumab, mepolizumab and dupilumab have been investigated in CRS^{20-22, 48}. The clinical trials of these mAbs are summarized in Table 1. From the currently available data of controlled trials in patients with CRSwNP, all three of these biologics have been helpful in decreasing the nasal polyp scores and reduction of sinonasal symptoms in CRSwNP patients^{20-22, 48}.

Biologic therapies in CRSwNP

Omalizumab has been used for asthma for over 15 years, having been FDA approved in 2003⁴⁹. This is the first biologic agent used for Th-2 type inflammatory diseases and is frequently used for both allergic asthma and idiopathic urticaria. Few studies have so far evaluated the effect of Omalizumab in CRS. In a randomized, double-blind, placebo-controlled study of CRSwNP patients with comorbid asthma subjects received 4 to 8 subcutaneous doses of either omalizumab (n = 16) or placebo (n = 8) for 16 weeks²⁰. There were significant decreases in nasal endoscopic polyp scores and quantitative measurement of sinus inflammation in imaging (Lund MacKay CT scores) in the omalizumab group compared with placebo. Furthermore, omalizumab had a significantly higher beneficial effect on upper airway symptoms including nasal congestion, anterior rhinorrhea and loss of sense of smell, as well as lower airways symptoms including wheezing and dyspnea. Importantly, Omalizumab was also associated with improved quality-of-life scores (SF-36 and Rhinosinusitis Outcome Measure-31) in CRSwNP and asthma patients²⁰. In another randomized, double blind, placebo controlled clinical trial of refractory CRS; subjects were randomized to receive omalizumab or placebo for 6

months¹⁸. Treatment with omalizumab was associated with significant improvement in the Sino-Nasal Outcome Test (SNOT-20) at multiple time spans including 3, 5, and 6 months follow ups compared to baseline, while there were no significant changes in the control group.

Mepolizumab was approved by the FDA in 2015⁵⁰. In a randomized, double-blind, placebo-controlled trial of one hundred CRSwNP patients aged 18 to 70 years, patients received either 750 mg of Mepolizumab (n = 54) or placebo (n = 51) every 4 weeks for a total of 6 doses in addition to daily nasal corticosteroid treatment²². Mepolizumab was associated with a decrease in need for surgery; a significantly lower number of patients in the mepolizumab group compared with the placebo group needed surgery at Week 25 (30% vs. 10%, respectively; P = 0.006). Furthermore, patients on Mepolizumab had a significant improvement in endoscopic nasal polyp score and Sino-Nasal Outcome Test (SNOT), a patient-reported outcome score compared with patients who were on placebo. The side effect profiles were similar in the placebo and Mepolizumab groups²².

The third mAb studied in CRS, dupilumab was approved by the FDA in 2017⁵¹. In a multi-center randomized, double-blind, placebo-controlled study, 60 adults with CRSwNP underwent either 600 mg loading dose followed by 300 mg weekly of subcutaneous dupilumab (n=30) or placebo (n=30) in addition to mometasone furoate nasal spray for 16 weeks. Among the 60 patients who were enrolled, 51 completed the study. Dupilumab group had a significant reduction in the nasal polyp score and Lund-Mackay CT scores. These reductions were significantly higher in Dupilumab compared

with control group. Dupilumab was also associated with higher improvement of symptoms measured by SNOT-22 and sense of smell assessed by Pennsylvania Smell Identification Test.

The need for cost-effectiveness analysis of biologics in CRSwNP

Given the recent introduction to the market of new biologic therapies for asthma, cost-effectiveness analyses of these medications are only recently being reviewed. These findings have been recently summarized⁵². A PubMed search of “chronic rhinosinusitis”, “nasal polyp” “cost-effectiveness analysis” and “biological therapy” or “mepolizumab” or “omalizumab” or “benralizumab” or “dupilumab” yielded 0 articles. This early stage of development of trials of biologic therapies in the treatment of CRSwNP provides an opportunity to raise important issues in future cost-effective analyses and to perform these analyses alongside the trials.

As with most cost-effective analyses, future cost-effectiveness analysis of biologic therapies in CRS should adhere to recent recommendations^{53, 54}. The perspective should utilize both the societal and healthcare perspective⁵⁴. Cost-effectiveness analyses should be performed alongside ongoing and future studies, and can also be done as a secondary analysis of completed studies. Another general recommendation is the use of an inventory checklist³⁰. The published manuscript of the cost-effectiveness analysis should adhere to reporting guidelines^{30, 53}. These guidelines help maintain transparency and interpretability of the results by the audience.

These guidelines indicate situations that could specifically pertain to use of biologic therapies in CRSwNP. This call for cost-effectiveness analysis of biologic therapies is timely, as the FDA recently approved dupilumab in the treatment for CRSwNP⁵⁵. As the results are to be generalized to the allergy/immunology clinic and also the adult primary care clinic where referrals will come from, as well as the otolaryngology clinic, the source data should include recruitment from these clinics. This would minimize any sample bias, which would exclude those patients whose preference is to delay surgery, and may not show-up to an otolaryngology clinic. The analysis should compare the mAb to endoscopic surgery, as the evidence of effectiveness over sinus surgery in CRSwNP is not always satisfactory⁵⁶. As endoscopic sinus surgery is associated with a significant revision rate, the analysis should not be a one-time decision tree, but a Markov model, which are useful for analyses with recurring events and over long-term time horizons²⁴. This would also account for increasing risk of complication with each surgery⁵⁷. Structuring the analysis this way would account for patient-preference to avoid any first surgery. This recurrent structure would importantly allow for initial medical treatment the underlying inflammatory process. Other analyses should examine combination strategies, such as if the biologic therapy is used before surgery, in a neo-adjuvant strategy, would the biological therapy improve surgical outcomes. There can be also analyses that consider different medical strategies, such as using biologic therapies on a short-term basis to allow aspirin desensitization⁵⁸.

It is noteworthy that the use of biologics is especially helpful in patients with comorbid asthma. All of these biologics result in significant improvement of quality-of-life and

asthma control tests⁴³. Based on the united airway concept the inflammation in upper and lower airways is interconnected. Inflammation in the sinuses is directly linked to lower airways pathology and point to the importance of keeping the upper airways disease in control⁵⁹. Biologic agents can treat both conditions simultaneously which makes them an idea therapy in patients with severe asthma and CRS. Use of biologics such as mepolizumab²² can result in decreased need for surgery which will be beneficial by saving the direct and indirect costs of a surgical intervention. Furthermore these agents could to be first line treatment options for patients who are not candidate for surgery due to coexisting contradictory medical problems or those who are hesitant to undergo a surgical procedure. However biologics are expensive treatments and involve multiple visits to the provider. Therefore it is important to assess their efficacy after an appropriate course of treatment trial and should be continued if they result in reduction of symptoms. It is noteworthy that the studies on use of biologics in CRS have been limited to 16 weeks durations of treatment and no information is currently available on their efficacy for longer duration. Cost effective analysis of data, especially in prospective cohorts with long term follow up, can help elucidate this area with an unmet research need and to develop updated therapeutic guidelines for treatment of this complex chronic disease of airways.

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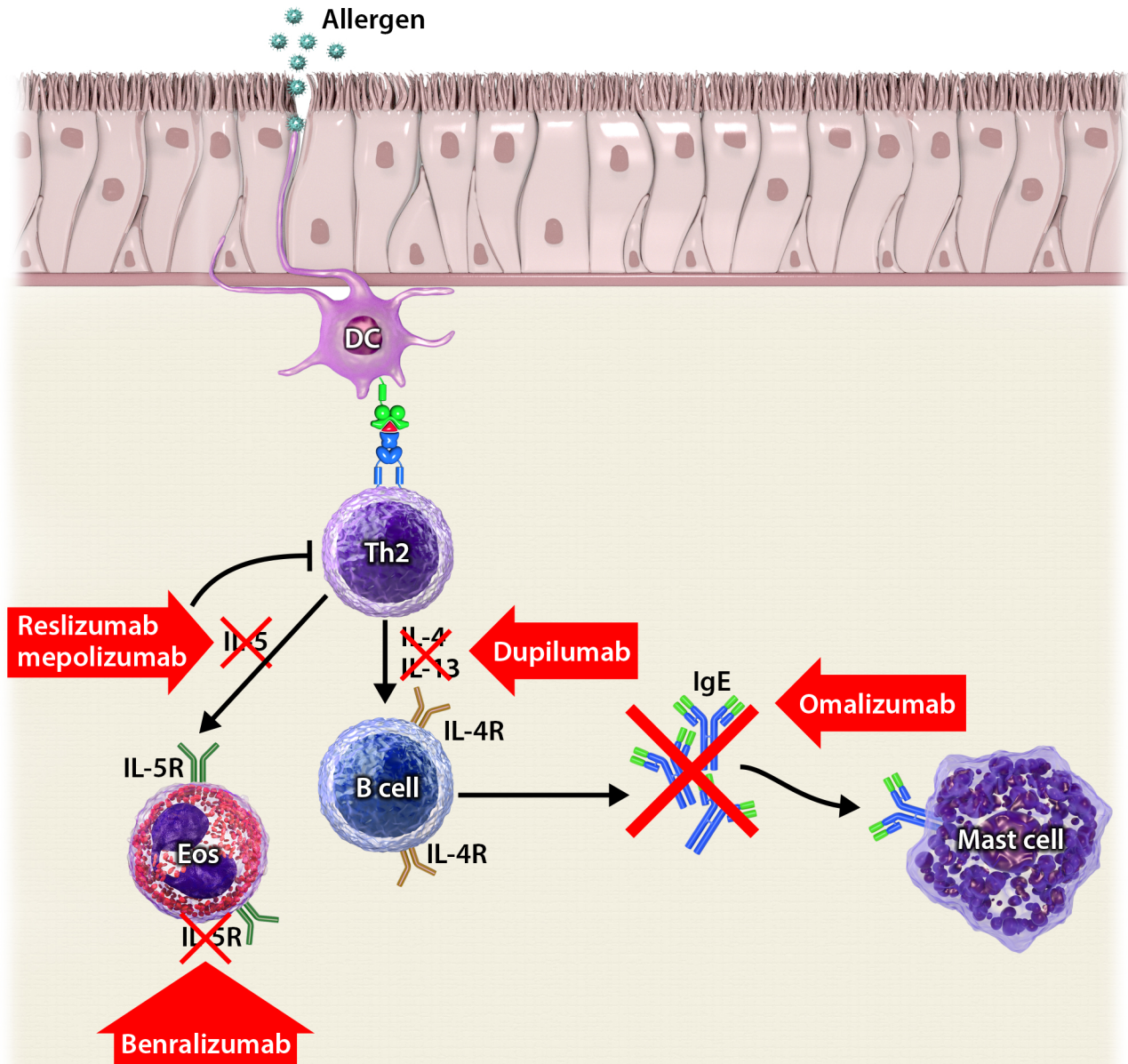
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Figure 1: Molecular targets of biologic therapies in CRS

Dendritic cells sample the external environment by extending processes between the respiratory epithelial cells. The activated dendritic cells interact with Th cells, which can differentiate into Th2 cells, secreting interleukin-4 (IL-4), interleukin-5 (IL-5) and interleukin-13 (IL-13). The IL-4 and IL-13 can stimulate B-cells to class switch to immunoglobulin E (IgE). Dupilumab (anti-IL-4R α) targets the α -chain of the IL-4 receptor (IL-4R α), preventing IL-4 from binding. Omalizumab (anti-IgE) targets free IgE, preventing binding to IgE-receptors on mast cells and basophils. IL-5 can activate eosinophils. Reslizumab and mepolizumab, both anti-IL5, target free IL-5 preventing binding to IL-5 receptor (IL-5R). Benralizumab (anti-IL-5R α) targets the α -chain of the IL-5 receptor (IL-5 α), preventing IL-5 from binding to IL-5R. An additional attribute of benralizumab is that it can activate antibody-dependent cellular cytotoxicity.

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