



A Critical Look at the Efficacy and Costs of Biologic Therapy for Chronic Rhinosinusitis with Nasal Polyposis

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Abstract

Purpose of Review Chronic rhinosinusitis with nasal polyps (CRSwNP) is a highly prevalent disease that results in significant healthcare-related costs as well as costs to society with lost productivity and time. Unfortunately, a significant percentage of patients who suffer with this disease will not find relief from current standard of care medications and surgery. With ongoing efforts to understand the pathophysiology of CRSwNP has come the introduction of monoclonal antibodies, or “biologics,” targeting specific elements of the inflammatory pathway in CRSwNP. Despite efficacy, these come at significant cost and, to date, no studies on the cost-efficacy of these biologics in CRSwNP have been published.

Recent Findings Multiple studies have now demonstrated efficacy for biologics in the treatment of CRSwNP as a primary indication. However, the gains in quality of life and objective measures, while consistent, are small and, arguably, the clinical significance is still unclear. In addition, the high cost of these medications may be hard to justify when evaluated in cost-efficacy studies against standard of care therapy in CRSwNP. Furthermore, while the current literature is most robust in showing the benefit of the biologics in asthma, it does not fully support cost-efficacy for biologics.

Summary This review evaluates the current literature regarding efficacy of monoclonal antibodies for the treatment of CRSwNP and considers this efficacy in light of the cost implications to individuals and society.

Keywords Chronic rhinosinusitis · Nasal polyps · Monoclonal antibodies · Biologics · Cost-efficacy · Dupilumab

Introduction

Chronic rhinosinusitis (CRS) is a disease marked by inflammation of the paranasal sinuses lasting for at least 3 months. With nasal congestion, nasal discharge, facial pressure, and reduction/loss of smell, CRS is a frustrating diagnosis for patients and is estimated to impact 5–16% of the US population at some point in their lives. Furthermore, the disease is a significant drain on healthcare resources as well as society as a whole with an estimated \$22–60 billion spent yearly on medical treatments, physician visits, surgery, and lost time off work [1, 2, 3, 4, 5].

Traditionally, physicians divide CRS phenotypically into disease with polyps (CRSwNP) or without (CRSsNP).

However, the presence or absence of polyps may not truly define the underlying pathophysiology of either disease. While it is clear that chronic inflammation is at the root of these conditions, it is also clear that no one theory explains the etiology of this chronic inflammatory process. There are three states of inflammation currently under exploration. CRSsNP is more commonly associated with a type 1 inflammation characterized by an increase in inflammatory factors IL-2, interferon, and TNF-alpha. CRSwNP is more commonly associated with a type 2 inflammatory pathway with an increase in inflammatory factors IL-4, IL-5, IL-13, and IgE. A variant of CRSwNP has recently been associated with the Th17 inflammatory pathway that is characterized by an increase in inflammatory factors IL-6, IL-7, and TNF-alpha [6].

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Current Management Strategies

Management goals for all CRS patients include improving quality of life symptoms while being cost-conscious and minimizing untoward side effects, allowing for rapid return to

normal activities. Current therapies for CRS are designed to decrease inflammation or dilute the factors that may be causing inflammation. For example, in CRSwNP, saline irrigation and steroids (both intranasal and oral) are commonly utilized, while antileukotriene inhibitors and oral antibiotics are optional or as needed therapies [1]. These are generally inexpensive therapies that have good data to support their use. When medical therapy does not resolve a patient's symptoms, functional endoscopic sinus surgery (FESS) has been found a cost-effective strategy in the treatment of CRS, both with and without nasal polyps [7, 8]. Surgery is a means to debride polypoid tissue and to open the drainage pathway of the paranasal sinuses, effectively removing inflammatory tissue from the sinuses, while also improving mucociliary activity and allowing patients a more effective way to apply topical therapies. While it is rarely a curative option for patients with CRS, it is an effective tool to help manage their chronic disease.

Unfortunately, these two options have not been a panacea. Not infrequently, CRS patients have recurrent symptoms or symptoms that are incompletely treated. This subset of patients may be trialed on a variety of therapies that have less proven efficacy and/or require revision surgeries. In addition, current therapies are not without risk. Surgery has rare but serious potential risks, and frequent use of oral steroid courses leads to significant metabolic derangement, fat redistribution, psychiatric changes, and, rarely, avascular necrosis of the hip. There is therefore great interest in finding novel therapeutics for CRS.

The Evolution of Biologics in Treating Rhinosinusitis

In 2003, the first monoclonal antibody, omalizumab (Xolair), was approved for the treatment of allergic asthma. This antibody against IgE has resulted in significant improvement in quality of life for a subset of asthmatic patients [9]. An ancillary benefit for patients with concurrent CRSwNP was subjective improvement in CRS symptoms as well as improvement in objective polyp burden as measured by CT. Several studies found similar findings, and an interest in biologic therapies for CRS was sparked [10, 11, 12]. Such results support the unified airway theory which posits that the health of the upper and lower airway is interconnected, and that the health of one impacts the health of the other.

Intuitively, this makes sense given the type 2 inflammatory factors associated with both CRSwNP and asthma. In a small retrospective study, Numata et al. found that asthmatics with comorbid eosinophilic CRS had greater improvement with mepolizumab injections than those without CRS [13]. Later studies demonstrated that biologics had benefit in CRSwNP as a sole indication. Gevaert et al. found that mepolizumab resulted in a significant improvement in nasal polyp score after

1 month of injections; subjects averaged a drop of 1.7 points on an 8-point scale [14]. Bachert et al. confirmed that mepolizumab resulted in significant improvement in nasal score and decreased need for surgery [15]. After 25 weeks of dosing every 4 weeks, only 5% of the study group needed surgery compared with 30% of controls dosed with placebo.

On the heels of these initial successes, several monoclonal antibodies are currently in trials for the primary indication of CRSwNP. All are designed against targets in the type 2 inflammatory pathway. There are several excellent manuscripts reviewing these, but briefly, these medications include omalizumab, medications targeting IL-5 (reslizumab, mepolizumab), a medication targeting the IL-5 receptor (benralizumab), and a medication targeting the IL-4 alpha receptor (dupilumab) [6, 10, 11, 16].

In June 2019, dupilumab (Dupixent) was approved by the US FDA as the first biologic with the primary indication to treat CRSwNP [17]. Again, the target of this drug is the IL-4 alpha receptor, which blocks the ligands IL-4 and IL-13 from advancing the type 2 inflammatory pathway. The largest phase 3 study published to date was a combination of two concurrently run, multi-institutional, randomized control trials titled LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52 [18, 19]. In both studies, enrollees had bilateral, symptomatic CRSwNP despite intranasal corticosteroids, oral steroids, and/or prior FESS. SINUS-24 randomized patients to 24 weeks of either dupilumab or placebo injections; the primary endpoints were change in nasal polyp score (on an 8-point scale) and subjective nasal congestion score (recorded daily using a scale from 0 to 3). The enrollees were then followed for another 24 weeks after injections were stopped. The SINUS-52 trial had the same primary endpoints but divided its enrollees into three groups. The first group received dupilumab injections every 2 weeks for the 52 weeks of the trial. The second group received dupilumab injections every 2 weeks for 24 weeks and then switched to an every-4-week injection schedule for another 28 weeks. The last group received placebo injections every 2 weeks for the full 52 weeks of the trial.

By week 24, in the SINUS-24 trial, there had been a significant drop in average nasal polyp score by 1.89 points and decrease in average nasal congestion score by 1.34 points. At that same timepoint in SINUS-52, the drop in nasal polyp score averaged 1.71 points, and the average nasal congestion score had improved by 1.25 points. In addition, in both studies, all secondary clinical outcomes significantly improved; these included Lund-Mackay CT score, total symptom score, smell test score (UPSIT), daily loss of smell, and SNOT-22 score. When injections were continued after 24 weeks in the SINUS-52 trial, patients continued to see benefit, and this benefit was slightly greater in the every-2-week dosing compared with that of every-4-week dosing. Moreover, adverse events were mild; the most common were nasopharyngitis,

worsening polyps, headache, worsening asthma, epistaxis, and injection site irritation.

Additional interesting points from this study included the quick onset of efficacy with patients appreciating statistically significant clinical improvements only 2–4 weeks after starting therapy. Furthermore, the primary endpoints in both studies demonstrated significant improvement at patients' first evaluations between weeks 4 and 8. However, in SINUS-24, when patients were followed after cessation of injections, all primary metrics trended back towards baseline, indicating that dupilumab effectively masked but did not correct the underlying type 2 inflammatory environment. The implication is that this drug would need to be a chronic medication, either continuously or intermittently administered. The study also noted changes in patients' bloodwork over the course of the study, including nasal and serum IgE, indicating that the proposed mechanism of action does likely modulate the type 2 inflammatory pathway.

The Risks Associated with Biologics

At this time, the side effects appreciated with biologics have been relatively minor, and the medications are overall well-tolerated. Early studies found issues with nasopharyngitis, headache, rare allergic reaction, and site-injection reaction. A recent meta-analysis of dupilumab for moderate to severe eczema reported that conjunctivitis was the most common adverse event noted in 8% of patients [20]. However, a post-marketing analysis noted an incidence of conjunctivitis of 38% [21]. Clearly, as these medications are observed in the real-world, our understanding of their risks will change. There is a risk of transient hypereosinophilia, and several studies of dupilumab found that a few participants developed eosinophilic granulomatosis with polyangiitis (i.e., Churg-Strauss syndrome) or eosinophilia with associated arthralgias [18, 21, 22]. However, the numbers for these studies were too small to draw a causative relationship.

There is also theoretical increased risk of malignancy with biologics. In early efficacy studies of omalizumab, a slight increase in the baseline incidence of malignancy in the study groups compared with that of controls was noted. In the previously mentioned post-marketing study of dupilumab, there was one case of cutaneous T cell lymphoma [21]. Initial studies evaluating the TNF-alpha inhibitor etanercept in treatment of psoriasis found a potential increased risk of malignancy [23]. However, a large post-marketing study of omalizumab found no increased malignancy risk but instead an elevated risk of thromboembolic events. The authors concluded that this was difficult to separate from the increased severity of asthma in the study population [24, 25]. The bottom line is that these medications are new, and there are many unknowns concerning pharmaceutical manipulation of the immune

system that may only be identified in prolonged post-marketing analyses. These will be chronic medications, and the medical community will need to continue long-term follow-up to evaluate for unforeseen adverse events.

Evaluating the Cost-Efficacy of Biologics

The goals of treating patients with CRSwNP are to improve quality of life, control disease progression, and to treat with therapies that have few side effects [1]. Both the SINUS-24 and SINUS-52 trials have provided us with evidence that dupilumab meets all these criteria. However, in the setting of skyrocketing healthcare expenditure around the world, one cannot ignore the consideration of cost. This has led to interest in improving the value of therapy, where value is defined as the quality of a therapy divided by its cost. Therefore, the value of therapy is increased by either improvements in quality or a lowering of therapeutic costs. To help quantify value, health economists have developed the concept of the quality-adjusted life year (QALY).

Briefly, a QALY is a year of life that has utility quantified between 0 (death) and 1 (perfect health). The benefit of a therapy can be measured in the number of QALYs that are added to a patient's life. The cost per QALY gained can be used as a means of estimating a particular treatment's value. While varying from country to country, in the USA, health economists generally accept a value of \$50,000–100,000 as the range of acceptable costs for a single QALY [26]. However, these numbers are somewhat arbitrary, and therefore, most cost-efficacy studies evaluate therapies at multiple willingness-to-pay (WTP) thresholds [26, 27].

These concepts have been applied to current medical and surgical standard of care for CRS. In 2015, Rudmik et al. designed a Markov decision tree model estimating the value that FESS added to medical treatment of CRS [7]. Their model took into account the rates of both intraoperative complications of surgery including CSF leak, orbital injury, or bleed and post-operative complications including CSF leak, infection, or bleed. Running this model through a 30-year time frame found that treating with medical therapy alone resulted in 17.13 QALYs and cost \$28,948.98. The addition of FESS costs a total of \$48,838.38 but yielded a greater total of 20.50 QALYs. The addition of FESS therefore resulted in an incremental cost-effectiveness ratio (ICER) of \$5901.90 per QALY which led the authors to conclude that addition of FESS to medical management of CRS was a cost-effective strategy.

In 2017, Scangas et al. designed a similar Markov model over a 36-year time period separating patients with CRSwNP and CRSsNP [8]. This study compared the costs of FESS between these patient populations and found similar results. In CRSwNP and CRSsNP, the addition of FESS resulted in ICER of \$5687.41 and \$5405.44 per QALY, respectively.

They concluded that the addition of FESS was therefore cost-effective when compared with treatment with medical therapy alone. The authors compared their results with other procedures for nonterminal disease processes, cataracts (\$2020/QALY), and knee replacements (\$18,300/QALY), and determined that the cost of FESS was appropriate.

There has not yet been a cost analysis of dupilumab for treatment of CRSwNP compared with the current standard of care. In the USA, Sanofi pharmaceuticals lists the whole-sale acquisition cost of dupilumab (Dupixent) as \$3019.50 per 4-week supply which translates to \$36,234 per year [28]. This pricing assumes a biweekly injection and might therefore be less expensive if patients could perform a once monthly injection as suggested by the SINUS-52 trial. However, there have been multiple studies evaluating the value of biologics in treatment of asthma with mixed results.

Anderson et al. reviewed the current literature and found multiple studies examining the cost-efficacy of omalizumab, mepolizumab, and reslizumab for allergic asthma, all drugs with similar costs to dupilumab [29–32]. For omalizumab, studies were mixed in their conclusions, but the authors determined that the drug trended to be cost-efficient only in a subset of patients who are poorly controlled with standard of care [29, 31]. A cost-efficacy study of mepolizumab determined that the high cost of the medication resulted in ICER of \$385,546 per QALY gained, twice that of their WTP threshold of \$150,000 [30]. Reslizumab was similarly expensive, with an ICER of \$697,403 per QALY [32]. All of these studies recommended that pharmaceutical companies decrease their prices by 60–80% to make their drugs more cost-effective.

Finally, the nonprofit, nonpartisan Institute for Clinical and Economic Review published a 2018 review of all approved biologics for the treatment of asthma [26]. The study examined the literature and compared ICER at multiple cost break points: \$50,000, \$100,000, and \$150,000. The authors concluded that none of the approved biologics was cost-efficient under those WTP thresholds but that there was no doubt of the drugs' efficacy. The study noted that biologics resulted in significant improvements in overall quality of life, decrease in asthma exacerbations, and decrease in oral steroid prescriptions. They concluded that the costs might be better justified if drug-makers lowered prices and if clinicians focused on subgroups such as clear responders and those requiring more frequent oral steroid prescriptions.

At this time, there are only these few studies on which to base clinical practice in asthma and to extrapolate to treatment of CRSwNP. There has been a call to the academic community for studies similar to those described above evaluating the effectiveness of biologics in treatment of nasal polyps [3•]. Such studies would ideally use Markov models similar to those previously described to estimate the ICER between current medical standard therapy, addition of FESS, and/or addition of biologics. However, there is little long-term data to

extrapolate future costs given that the novelty of these drugs precludes knowledge of their long-term side effects. Additionally, there should be a community discussion on what is an acceptable WTP threshold for treatments in CRSwNP; otherwise, the results may not help guide management.

Cystic Fibrosis as a Model

The introduction of biologics into the field of rhinology and allergy is a potential game changer, adding a completely new therapeutic category, with potentially significant efficacy. However, the increased costs that these novel medications bring must be considered. How much are we willing to pay for these medications? What is an acceptable ICER for treatments for CRSwNP? Who should bear the costs of these medications? One example of the introduction of novel mechanism medications can be seen in the case of cystic fibrosis (CF). In 2012, the US FDA approved ivacaftor, a CFTR potentiator, and in 2015, the FDA approved a dual therapy agent, ivacaftor plus lumacaftor, a molecule that facilitates the shuttling of CFTR molecules to the cellular membrane. The combination of these drugs has been extremely effective for a subset of CF patients, but the high cost raises some of the same questions that biologics now face.

One study examined efficacy using an ICER that balanced cost per FEV1 percentage point gained [33]. This study pitted ivacaftor/lumacaftor against data from randomized control trials using placebo. The authors found that the ICER for an improvement of one FEV1% was \$95,016; they opted not to calculate ICER per QALY because long-term outcomes of the medication were not yet known. However, they noted that the Ireland National Health Service estimated the ICER to be \$415,350 per QALY. Another group examined the change in the yearly cost of CF therapy in the USA during the early part of the last decade [34]. The authors noted that between 2010 and 2016, the median spending on CF patients nearly doubled from \$67,000 per patient to approximately \$131,000, adjusted for inflation. This was explained largely by the introduction of CFTR potentiators; following the introduction of ivacaftor/lumacaftor, expenditures jumped by 33% per year.

The American Thoracic Society released a position paper examining the increasing cost of prescription medications and their importance for their patients [35]. The authors note that in the USA, out-of-pocket expenses have been persistently rising, causing a financial hardship on roughly a quarter of families. These increased costs are due to a complex system of drug development, distribution, insurance formularies, and prescriber habits. The complexity of this system results in frequent patient nonadherence in an attempt to lower individual costs. The paper recommended federal intervention through the creation of a nonpartisan, independent advisory committee to identify “evidence-based recommendations on

pharmaceutical policy.” The complexity of the US healthcare market system means that there is significant debate about how to fix the high cost of medications [36]. There is a broad understanding that healthcare in the USA is “rationed” as a net effect of these high costs [37]. The question moving forward is whether the USA is okay with its current system of rationing based on economic disparity or whether the system can be reworked to be more equitable. However, even in a more equitable system, questions of cost-efficacy and value will still need to be raised and answered.

The introduction of breakthrough specialty medications has been of immense value to patients but has also resulted in the introduction of sudden new costs to the healthcare system. One can look to the introduction of CFTR modulating medications as an example of how the introduction of medications can quickly change the pharmacoeconomics of a disease. However, we should be cautious to equate CF and CRS. New medications in CF are incredibly expensive and fall well above the typical ICER standard. But because CF is considered an orphan disease, the higher costs for medications are better tolerated. In fact, despite their price tag, several CFTR potentiators have been approved by socialized medical systems like the UK’s NHS which tend to hold low ICER thresholds [34].

Conclusions

Biologic therapies offer a novel therapeutic class in the treatment of CRSwNP which has the potential to be a “game changer” for patients. The discovery of these medications goes hand in hand with improved understanding of the underlying pathophysiology of this entity. Several biologics are currently in the pharmaceutical pipeline and still more targets are being discovered [38]. Next steps include better characterizing which patients benefit most from these medications and to identify biomarkers that can be used to direct therapy. For now, serum IgE and eosinophilia serve as general markers of type 2 inflammation. These biomarkers help broadly delineate patients who may benefit from biologics. In our practice, we follow an algorithm that considers biologics for CRSwNP only as an adjunct therapy in patients with clear evidence of type 2 inflammation or for those patients with persistent symptoms following failed medical management and FESS [11]. As we better understand the underlying inflammatory pathways and endotypes of CRS, we are optimistic that we will further improve individualizing treatment paradigms.

For now, the only biologic medication approved for treating CRSwNP is dupilumab, an IL-4 alpha receptor antagonist. Multiple studies have confirmed dupilumab’s efficacy, but it is not yet clear in which patients the drug will have greatest clinical significance. In addition, dupilumab is extremely expensive, especially when compared with the cost of current standard of care medications and FESS. While this medication is effective, in the changing healthcare climate,

Table 1 Biologic therapy in the treatment of CRSwNP

The benefits:

- Biologics are demonstrating efficacy in the treatment of CRSwNP.
- Dupilumab is an effective medication for patients with CRSwNP refractory to standard medical and/or surgical therapy.

The costs:

- Biologics are very expensive and may be chronic medications.
- Cost-efficacy studies are ambivalent when evaluating biologics for the indication of asthma.

Future needs:

- Cost-efficacy studies evaluating the long-term use of biologics compared with current standard of care for CRSwNP
- Novel biomarkers to better delineate which patients will benefit from biologics.
- Post-market analyses to identify adverse events associated with biologics

physicians, patients, insurers, and government payers will not have the luxury of separating cost from decision-making. At this time, there is minimal data examining the cost-efficacy of dupilumab for the indication of CRSwNP. To better understand that cost, studies should be designed to estimate the value of ICER per QALY in CRSwNP [3•]. However, in interpreting such data, the rhinology and allergy community needs to confront a difficult question: How much is a QALY worth? Healthcare funding is not unlimited, and patients are already rationing and/or prioritizing medications to avoid costs. It is not fair to ask patients to pursue a potentially life-long medication without understanding the financial hardship it may ask of them. While biologics hold incredible promise in our field, these tricky monetary questions may be just as important in directing future care (Table 1).

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