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Clinical Research Needs for the Management of Chronic Rhinosinusitis with Nasal Polyps in the New Era of Biologics. A National Institute of Allergy and Infectious Diseases Workshop

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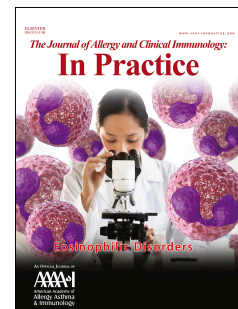
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**Clinical Research Needs for the Management of Chronic Rhinosinusitis with Nasal Polyps
in the New Era of Biologics. A National Institute of Allergy and Infectious Diseases
Workshop**

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53 Robert Naclerio reports serving as an advisory board member and/or speaker for AstraZeneca,
54 GSK, Sanofi and Regeneron, consulting for the American Chemistry Council and Lyra, serving
55 on the speaker bureau of Optinose, and providing expert witness testimony in the last year; Fuad
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Larry Borish reports consulting for Sanofi-Aventis and receiving research support from Regeneron, GSK, and the NIH; Erica Brittain has no conflicts to disclose; Geoffrey Chupp reports serving as a board member, speakers bureau member (advisory), and being a clinical trial principal investigator for AstraZeneca, Genentech, GSK, Circassia, Sanofi-Genzyme, Regeneron, Boehringer Ingelheim, and Boston Scientific; Anat Fisher has no conflicts to disclose; Wytske Fokkens reports consulting/speaking arrangements with Sanofi and Lyra Therapeutics and receiving research support from GSK, Sanofi, Novartis Chordate, Mylan, ALK, and Allergy diagnostics; Philippe Gevaert reports consulting for Sanofi, Regeneron, Novartis, Roche, Genentech, AstraZeneca and 3NT and receiving research support from Argenx and 3NT; David Kennedy reports consulting for GSK, Intersect ENT, Medtronic, and Neurent, serving on the advisory board of Sinuwave, and patent licensing arrangements with Medtronic Xomed; Jean Kim reports consulting for Genentech; Tanya M. Laidlaw reports consulting for GSK and Regeneron; Jake J. Lee has no conflicts to disclose; Jay F. Piccirillo reports patent licensing arrangements with the Washington University School of Medicine for a Sino-Nasal Outcome test; Jayant M. Pinto reports consulting/speaker arrangements with Sanofi, Regeneron, ALK, Genentech, and Stallergenes-Greer, owning stock/equity in Om Probiotics, and research support from the NIH; Lauren T. Roland reports serving as a consultant for Tissium; Robert P. Schleimer reports serving as a consultant for Intersect ENT, GSK, Allakos, Aurasense, Merck, BioMarck, Sanofi, AstraZeneca/MedImmune, Genentech, Exicure, Otsuka, Aqualung Therapeutics Corp, Actobio Therapeutics, Lyra Therapeutics, Astellas Pharm Inc, Genzyme/Sanofi Corp, and Celgene Corp, owning stock/equity in Allakos, Aurasense, BioMarck, Exicure, and Aqualung Therapeutics Corp, patent licensing arrangements with Allakos, and receiving research support from the NIH; Rodney J. Schlosser reports consulting and/or speaker arrangements with Stryker, Olympus, Optinose, GSK, Regeneron and Roche, owning stock/equity in Healthy Humming, and receiving research support from Gossamer, Stryker, Optinose, GSK, AstraZeneca, Regeneron, Roche, and Healthy Humming; Julie M. Schwaninger has no conflicts to disclose; Timothy L. Smith reports receiving research support from the NIH; Bruce K. Tan reports serving on the advisory board of Sanofi-Genzyme and Optinose and owning stock in Allakos; Ming Tan has no conflicts to disclose; Elina Toskala reports consulting for Fiagan, serving on the advisory board of Optinose, and receiving research support from Sanofi; Sally Wenzel reports consulting for Sanofi-Aventis, GSK, AstraZeneca and

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Abstract

The development of biologics targeting various aspects of Type-2 inflammation for the treatment of chronic rhinosinusitis with nasal polyps (CRSwNP) will provide clinicians with powerful tools to help treat these patients. However, other therapies are also available and positioning of biologics in a management algorithm will require comparative trials. In November 2019, the NIAID convened a workshop to consider potential future trial designs. Workshop participants represented a wide spectrum of clinical specialties, including otolaryngology, allergy and pulmonary medicine, as well as expertise in CRSwNP pathophysiology and in trial methodology and statistics. The workshop discussed the current state of knowledge in CRSwNP and considered the advantages and disadvantages of various clinical trial or observational study designs and various clinical outcomes. The output from this workshop, which is presented in this report, will hopefully provide investigators with adequate information and ideas to design future studies and answer critical clinical questions. It will also help clinicians understand the current state of the management of CRSwNP and its gaps and be better able to interpret the new information to come.

Introduction

Chronic rhinosinusitis (CRS) is a common inflammatory condition affecting more than 10% of the population in western countries(1, 2), 8-11% of the population in Asia(3, 4), and roughly 38 million Americans(2). Chronic rhinosinusitis with nasal polyps (CRSwNP), which represents less than 25% of CRS, is diagnosed by a combination of subjective sinonasal symptoms and objective evidence of nasal polyps(5). The implications of this disease extend well beyond the nose and paranasal sinuses as CRSwNP has wide-reaching impact on patient-reported quality of life, with well-described associations with depression(6), cognitive impairment(7), and overall health state utility values equal or worse to other chronic diseases such as congestive heart failure, end-stage renal disease, and chronic obstructive pulmonary disease(8).

Over the last several decades the inflammatory processes underlying CRSwNP continue to be better understood. Although the exact pathways leading to the generation of nasal polyps have yet to be delineated, it is now widely accepted that, in the large majority of Western hemisphere patients, the sinonasal mucosa is characterized by Type-2 inflammation and its chronic remodeling consequences. Biologics that target this type of inflammation are being used in asthma and atopic dermatitis(9, 10). Several studies involving these biologics have been conducted with success on patients with CRSwNP and the first Type-2 inflammation-targeting biologic has been approved for use in this condition(11, 12). As these therapies receive regulatory approval, the question of how to incorporate them into the treatment paradigm for CRSwNP and thus provide better care for patients was the topic of a workshop organized in November 2019 by the Division of Allergy, Immunology and Transplantation of NIAID. Workshop participants included clinical experts and trialists from the fields of otolaryngology, allergy, and pulmonary medicine, as well as mechanistic researchers, trial methodologists and statisticians. Scientists representing the industry were invited and participated in the discussions. The workshop agenda and speakers are listed in **Table S1**. This report summarizes all presentations, as well as the discussion on trial or other study designs with which the workshop concluded. It is hoped that this report will be used by researchers to design clinical trials and observational studies that will address the positioning of biologics in CRSwNP and will help in

the development of clinical guidelines for appropriate, evidence-based, incorporation of these new therapeutic modalities into the CRSwNP treatment algorithm.

Current Management of CRSwNP

The basic paradigm for the treatment of CRSwNP has revolved around the use of intranasal corticosteroids(13). For patients not responding to those agents, oral corticosteroids are used to induce better disease control followed by intranasal corticosteroids as maintenance anti-inflammatory treatment. For patients not responding to this scheme, endoscopic sinus surgery (ESS) is offered followed, again, by medical treatment with topical corticosteroids in an effort to prevent relapse (**Figure 1**). In addition, we use antibiotics for acute exacerbations presumed to be of bacterial origin. Some practitioners may use off-label leukotriene receptor antagonists or a 5-lipoxygenase inhibitor, but the data in support of efficacy for these agents are weak. It is generally believed that this paradigm works for the majority of patients, but a number of patients are not adequately controlled and may have residual symptoms (e.g. olfactory impairment) or recurrence of polyposis. In addition, there are patients who, for various reasons, do not want to or cannot undergo surgery.

In recent years, the FDA has approved a novel delivery system for the distribution of intranasal corticosteroid in the form of an exhalation device(14) and sinus implants containing corticosteroids(15). Other post-operative treatments include aspirin desensitization in patients with aspirin-exacerbated respiratory disease and budesonide/mometasone large volume irrigations. The latter approach appears to be more effective than intranasal corticosteroids(16-18), but definitive data as to what proportion of patients further benefit from those treatments are not available.

One biologic, dupilumab, an antibody against the alpha subunit of the IL-4 receptor, which blocks signaling of both IL-4 and IL-13, has been approved by the FDA having shown to be effective and safe in the treatment of CRSwNP(19). Additional biologics are in Phase III clinical trials seeking regulatory approval and may become available in the future.

Economic Impact

CRS (with and without nasal polyps) has long-term ramifications with regard to treatment, associated total cost, as well as the impact of disease on patient productivity(20-22). *Total costs* are often divided between *direct* and *indirect* costs where direct costs primarily refer to traditional healthcare costs like physician visits, prescription medical therapy and surgery, while indirect costs refer primarily to lost productivity in those suffering the index disease(23). Conservative estimates suggest that for CRS, total costs are in excess of \$30 billion USD per year in the US with more than \$20 billion accounted for by indirect costs(24).

A 2009 study provided an assessment of the additional disease burden of CRSwNP(25). Differences in medication costs were noted for patients with recurrent polyps after surgery (\$866) compared to CRS without nasal polyps (\$570) and primary CRSwNP (\$565). The same investigators found that annual incremental costs were \$11,507 higher for patients with CRSwNP versus those without CRS(26, 27). Costs were higher in subgroups undergoing ESS, with comorbid diagnosis of asthma or those receiving oral corticosteroids.

Most of our understanding of indirect costs has been gleaned from the study of CRS in general rather than of CRSwNP. Consistent with other chronic diseases, the indirect costs of CRS are much greater than the direct costs. Since 85% of patients with CRS are of working age (range: 18-65 years old), indirect costs such as missed workdays (absenteeism) and decreased productivity at work (presenteeism) significantly add to the economic burden of the disease(28).

Goetzel et al. attempted to quantify the indirect costs of rhinosinusitis(29). Their 2003 study resulted in rhinosinusitis being listed as one of the top ten most costly health conditions to U.S. employers. Episodes of illness were linked to missed workdays and disability claims, accurately correlating absenteeism to the disease. In a large sample size (~375,000 employees), total healthcare payments per employee per year for sinusitis (both acute and chronic) were found to be \$60.17, 46% of which came from the cost of absenteeism and disability.

In 2003, patient-completed surveys from 322 patients were used to estimate the direct and indirect costs of CRS(30). The report concluded that the cost of treating CRS per patient totaled \$1,539 per year with forty percent of this related to indirect costs of missed work; the mean number of missed workdays in this sample was 4.8 days/year (95% CI: 3.4 - 6.1). The study was followed up in 2009 and 2012 using data from the National Health Interview Survey between 1997 and 2006 encompassing nearly 315,000 individuals and reported that patients with sinusitis missed on average 5.7 days of work per year(25). In 2014, Rudmik and colleagues specifically evaluated recalcitrant CRS and found that patients with this more severe form of CRS had mean annual presenteeism and absenteeism rates of 25 - 39 days per patient per year, equating to an average indirect cost of over \$10,000 USD per patient per year(31).

More recent data have emerged which demonstrate changes in productivity after treatment of CRS(32-36). These data suggest that successful management of CRSwNP can result in significant improvements in productivity and reduction of indirect costs.

Additional factors need to be considered. For example, the cost of disease needs to consider disease time horizon. If the age of persons undergoing ESS for CRSwNP is in their 40s, then they will probably be burdened with disease for 30 years. Therefore, as with any chronic condition, we cannot just focus cost estimation on one-year time intervals. Equally important is the observation that ESS followed by post-operative medical management can restore and maintain health utility to normal and this may also need to be taken into account in long-term cost calculations and modeling(37).

Current and Upcoming Biologics for the Treatment of CRS with Nasal Polyps

Knowledge of the inflammatory mechanisms of CRSwNP continues to grow. Monoclonal antibodies developed for the management of asthma and atopic dermatitis have been tested in studies of CRSwNP since these diseases share some inflammatory processes. For example, in the majority of CRSwNP patients tissue eosinophils are increased and, in many patients, blood eosinophils as well as total serum IgE concentrations are increased compared to healthy

controls(38). Tissue Type-2 cytokines such as interleukin (IL)-4, IL-5 and IL-13 are increased in patients with more severe radiographic disease and asthma.

Several biologics that target components of the Type-2 inflammatory response such as IgE, IL-5, the IL-5 receptor, and the IL4 receptor alpha that initiates signals for both IL-4 and IL-13 have been evaluated for efficacy in CRSwNP. Proof-of-concept studies involving omalizumab (anti-IgE)(39), mepolizumab (anti-IL-5)(40, 41), reslizumab (anti-IL-5)(42) and dupilumab (anti-IL-4 receptor alpha chain)(43) have been performed; all generated promising results in reducing polyp size and disease burden (**Table 1**)(11). Building upon a successful phase 2 study(43), two successful phase 3 studies with dupilumab have also been published(19). As a result, this biologic has received approval for use in CRSwNP by the FDA as add-on maintenance treatment in adult patients with inadequately controlled disease. These studies not only provide safety and efficacy data, but also a lot of information for designing future clinical trials. Two 24-week long, phase 3 trials with omalizumab have been successfully performed, but detailed results have not yet been published.

Overall, these studies have taught us about the importance of Type-2 inflammation in CRSwNP, but also underline the heterogeneity of the disease since only a percentage of each study population showed substantial clinical response. Importantly, these studies did not compare any of these biologics to each other or to other treatment options and have not clearly identified the patients who would benefit most from biologics. These questions need to be addressed.

The Use of Biologics Targeting Type-2 Inflammation in Asthma

The CRSwNP field draws from the experience with biologics in the treatment of asthma. Biologics for the treatment of severe asthma have been in development and use for over 20 years, beginning with omalizumab/anti-IgE in the late 1990s. These therapies have been instrumental in both the treatment of asthma and in helping to develop new mechanistic insights regarding severe asthma and Type-2 inflammation. They have also promoted the development of both predictive and responsive biomarkers, helpful in identifying appropriate patients for therapy and measuring their responses to that therapy. Currently, there are 5 monoclonal

antibodies approved by the FDA for the treatment of asthma, targeting 3 aspects of the Type-2 inflammatory pathway, IgE, the IL-5 pathway and the IL-4 receptor.

Omalizumab was the first biologic therapy approved for patients with moderate to severe persistent allergic asthma whose symptoms are inadequately controlled with inhaled corticosteroids. It has shown efficacy in many clinical trials, primarily in reducing asthma exacerbations. Its efficacy in “all-comer” adults with severe allergic asthma, as currently defined, is modest with about a 25% reduction in exacerbations over 48 weeks(44). However, a post hoc analysis of that trial identified biomarkers of Type-2 inflammation (blood eosinophils, fraction exhaled NO (FeNO)) as better predictors of response than total or specific IgE levels(45)

Three antibodies targeting the IL-5 pathway, two against IL-5 (mepolizumab, reslizumab) and one against its receptor (benralizumab), are approved for the treatment of severe asthma with an eosinophilic phenotype. The pathway is critical for eosinophil maturation, migration and survival. When patients with modest elevations in either lung or blood eosinophils and European Respiratory Society/American Thoracic Society defined severe asthma are targeted, highly consistent efficacy with a ~50% reduction in asthma exacerbations is observed across all three antibodies(46-50). In addition, two of these antibodies (mepolizumab and benralizumab) have shown efficacy in corticosteroid dependent asthma, each leading to a significant reduction in oral corticosteroid dose. Overall, these agents have been well-tolerated, but are not efficacious in patients without at least modest elevations in blood eosinophils.

Dupilumab, an antibody against the alpha chain of the IL-4 receptor, has been efficacious in patients with severe asthma and blood eosinophilia, even if only modest(51-53). FeNO is a good predictive biomarker for response and there is some evidence to suggest that elevations in both FeNO and blood eosinophils identify the best responders to dupilumab. Dupilumab has been approved for the treatment of patients with moderate to severe asthma with an eosinophilic phenotype or with oral corticosteroid-dependent asthma, with or without blood eosinophils, similarly allowing for reductions in oral corticosteroid dose as compared with anti-IL-5/5R approaches. The drug has generally been well-tolerated, but blood eosinophils regularly increase in a subset of patients and there have been cases of eosinophils reaching up to 50% of

all peripheral white blood cells. Rare cases of eosinophilic granulomatosis with polyangiitis (EGPA) have been reported(51).

Although the use of biologics in asthma has had significant impact in the management of severe disease and substantial clinical experience has been accumulated that may help in the application of these agents in CRSwNP, many questions remain regarding optimal use of biologics in asthma, including:

1. Who are the best patients for each type of biologic and could better biomarkers or clinical phenotyping help identify them?
2. What is the long-term safety and efficacy?
3. Is there a possibility for long-term modification of the natural history of the disease?
4. Can background medications (e.g., inhaled corticosteroids, long-acting beta agonists) be stopped?
5. Can management plans get developed that will optimize cost-effectiveness in the use of each of these biologics?

The same questions will probably apply to the use of biologics in CRSwNP and future biologics in development.

CRSwNP Patients who Could Qualify for Therapy with Biologics

The majority of patients with CRSwNP in the USA have a Type-2 inflammatory pattern in the sinonasal mucosa and therefore would potentially be eligible for anti-Type-2 monoclonal antibody therapy. Given the high cost associated with biologics, patient selection is crucial in order to implement such therapies into chronic respiratory disease care pathways. A multidisciplinary expert board meeting organized by the European Forum for Allergy and Airway Diseases (EUFOREA) suggested a set of criteria (**Table 2**) that may be used to select appropriate patients(54). Some concerns have been raised because, based on these criteria, non-Type-2 CRSwNP could also be eligible for treatment, no stopping rules are defined, and the criteria for responsiveness to treatment are not clear. Yet, these are the first criteria developed in the field. This group suggested that less criteria are necessary if patients had prior ESS.

Arguments in support of this recommendation were the mid-term high efficacy of ESS (in 60-90% of cases, disease does not recur within 5 years)(37, 55, 56) and the fact that the sinuses are better accessible to local (corticosteroid) treatment after surgery.

CRSwNP has a prevalence of 1-2.5% (57, 58). For the United States (adult population 255×10^6), this means there is an estimated minimum of 2,550,000 patients with CRSwNP. Most of these patients are generally treated with nasal corticosteroids and an occasional short course of systemic corticosteroids (**Figure 1**). Based on calculations derived from recent data in California, 0.013% of the general population undergoes ESS yearly(59), which translates to a minimum of 33,000 CRSwNP patients having ESS yearly in the United States. Also, data from the United States and the United Kingdom show a revision rate in a 5-6 year period of 10-20% resulting in an estimated yearly incidence of at least 3,300-6,600 patients that could potentially qualify for biologic therapy in the United States per year(37, 55, 59). It is unclear, however, how many of these patients would also fulfill the additional EUFOREA criteria that include significant impairment of quality of life, reduced smell, asthma and the need for (at least 2) courses of systemic corticosteroids in the past year (**Table 2**). It is possible that these criteria would further reduce the number of candidates for biologic therapy to a minimum of 2,000-4,000 new patients per year. Another possible way to estimate the number of eligible patients is to assume the rate of using biologics in CRSwNP would be the same as the use of biologics in asthma, which is 3/1000 of the total asthma population(60).

Based on these data the following hypothetical scenarios can be envisioned for the minimum number of new CRSwNP patients in the USA that would be eligible for biologics every year:

- 1,000 CRSwNP patients based on population needing ESS and data from asthma (3/1000)
- 2,000 CRSwNP patients based on EUFOREA criteria
- 9,000 CRSwNP patients based on the total CRSwNP population and data from asthma (3/1000)

- 33,000 CRSwNP patients if all CRSwNP patients receiving ESS every year were eligible for biologic therapy

These estimates do not take into account that a proportion of these patients will also have severe asthma and receive biologics because of their asthma. In addition, the total number of patients on biologics at any given time cannot be easily estimated due to the fact that the real-life duration of treatment is unknown.

In reviewing these estimates, one realizes that fundamental information that will allow us to optimize the use of biologics in CRSwNP is missing. For example, the major assumption that ESS may need to precede the use of biologics and that ESS needs to fail before biologics are used is not based on any clinical evidence deriving from randomized clinical trials (such trials have not been conducted) or from any available experience from clinical practice given that these agents are just being introduced in the CRSwNP patient population. It is also important to consider that the clinical phenotypes and biomarkers that predict unfavorable mid to long-term outcomes of surgery are comorbid asthma, aspirin exacerbated respiratory disease (AERD), allergic fungal rhinosinusitis and high tissue eosinophils, IL-5 and IgE concentrations(61). The same co-morbidities and markers are linked to Type-2 inflammatory disease, which is targeted by current and upcoming biologics.

In the years to come, in addition to new evidence derived from well-designed studies, the dynamics between forces that range from guidelines and payers' policies to patients' and physicians' preferences (which will be based on real-world efficacy, safety and ease of use), but also other factors, will determine the use and impact of biologics in CRSwNP.

Future Therapeutic Targets in CRSwNP

As the inflammatory process of CRSwNP becomes better understood, potential new targets to intervene will undoubtedly arise. Several targets have already been identified and are discussed below. Improvements in our approach towards existing targets are also possible.

At least 80% of patients with CRSwNP in western countries have Type-2 inflammation in nasal polyps, and the biologics referred to above are able to shrink polyps by blocking elements of the Type-2 immune response(38). Though not the topic of this report, Type-2 inflammation also occurs in about 50% of patients with CRS who do not have nasal polyps; thus, information gained from studying CRSwNP may be also applicable in those patients as long as clear diagnostic criteria are developed and the impact of the disease can be documented and justify the use of biologics. Our current approach for inhibition of Type-2 inflammation relies on monoclonal antibodies because the contact region for Type-2 cytokine (IL-4, IL-5 and IL-13) binding to respective receptors is large. Potential improvement in this domain may derive from molecules that are inhaled. For example, an inhaled protein that binds to and inhibits the IL-4/IL-13 receptor, a derivative of lipocalin-1, has been shown to inhibit signaling in individuals with asthma(62). Type-2 signaling can also be disrupted through inhibition of transcription factors using low molecular weight inhibitors, which could theoretically be used as oral drugs. The main transcription factors involved in Type-2 skewing, GATA3 and STAT6, have been difficult to disrupt with low molecular weight drugs. However, a GATA3-specific DNAzyme has been developed that inhibits Type-2 and experimental asthma in humans(63). In addition, a new class of STAT6 inhibitors has been developed which show promise in preclinical models of allergic disease(64). Also, inhibitors of JAK-STAT signaling have proven to be effective in atopic dermatitis and are worth testing in CRSwNP(65).

Epithelial barrier dysfunction is a common feature of Type-2 inflammatory diseases of the skin (atopic dermatitis), nose (allergic rhinitis and CRS), lung (asthma) and gut (food allergy and eosinophilic gastrointestinal diseases). A recent study in CRSwNP concluded that there is an aberrant basal epithelial cell progenitor differentiation that locks basal cells in an uncommitted state(66). In addition, Sergejs Berdnikovs has presented data suggesting that limited endocrine dysfunction, especially insulin resistance or reduced expression of insulin or members of the insulin growth factor family, may lead to epithelial barrier dysfunction both *in vitro* and *in vivo*(67, 68). In this respect, restoration of insulin signaling in patients with endocrine dysfunction is an approach worthy of consideration. Another potential therapeutic target is oncostatin M, a cytokine implicated in CRSwNP epithelial dysfunction. An antibody against oncostatin M is available, but has not been tested in CRSwNP(69-71).

New studies demonstrate that nasal polyp tissue is largely composed of crosslinked fibrin and there is reduced fibrinolysis (due to reduced tPA) and increased fibrin crosslinking (due to increased levels of factor XIIIa) in polyp tissue(72). Tetsuji Takabayashi and coworkers showed that incubation with nattokinase, a tPA-like enzyme that activates fibrinolysis, can reduce polyp tissue by 90% while having no effect on healthy tissue (which lacks cross-linked fibrin)(73). In addition, the viscosity of mucus in CRS patients is dramatically diminished by fibrinolytic treatment, suggesting that fibrin crosslinking mediates the viscosity and stickiness of mucus in CRS patients. Notwithstanding potential bleeding side-effects, use of anticoagulant compounds, either locally or systemically, may be an interesting approach to nasal polyp size reduction.

Several years ago, it was discovered that nasal polyp tissue contains large numbers of B cells, plasmablasts and plasma cells and that considerable quantities of autoantibodies are produced(74, 75). Subsequent studies showed that some of these antibodies activate complement in polyp tissue(76). This raises the possibility of B-cell targeting drugs (e.g. those employed in autoimmune diseases) getting tested in patients in whom an autoimmune component appears dominant.

It has been known for some years that the arachidonic acid metabolizing enzyme 15-lipoxygenase is elevated and activated in patients with nasal polyps, asthma or other severe Type-2 illnesses in the airways(77, 78). Recent studies by Whitney Stevens and colleagues have shown that patients with AERD have highly elevated levels of 15-LO as well as a major 15-LO product and that these elevations correlate with severity of disease (unpublished observations). A genetic study has shown that a loss of function variant of 15-LO protects against the development of CRS(79) and Sally Wenzel's group has presented evidence that 15-LO is an important inducer of inflammatory mediators(80). Finally, Bing Yan et al have shown that 15-LO products are likely to play a role in epithelial dysfunction(81). Taken together, these studies raise the hypothesis that inhibition of the 15-LO pathway may benefit patients with CRSwNP.

Clinical Research Questions in CRSwNP

Many unanswered questions about the management of CRSwNP exist and more questions have been generated with the introduction of biologics. Workshop participants were given the task to identify important questions on how to position biologics in the management of CRSwNP. Two major areas of interest arose from this discussion.

- Among CRSwNP patients who have undergone sinus surgery, does treatment with biologics prevent recurrence of disease and improve outcomes better than standard medical therapy? This question has two aspects: A) Does post-operative treatment with biologics offer an advantage compared to currently available medical treatment? B) In cases where surgery fails despite appropriate post-operative medical management, would biologics help avoid revision surgery?
- Among CRSwNP patients who have not undergone sinus surgery and have persistent, bothersome symptoms despite medical therapy, is treatment with biologics more effective than surgery and how would cost-efficiency evaluations influence this comparison? This question, as will be discussed later, may require longitudinal studies.

In designing studies to address these questions, significant consideration should be given to the fact that, with various technical and methodologic alterations, surgical outcomes and revision rates have improved and the number needed to treat with a biologic to prevent revision surgery may be very large and the duration of such a trial very long. Some workshop participants suggested that 5-year observations may be required. Also, we need to consider the fact that we do not know whether available and upcoming biologics have differential effectiveness depending on the patient's phenotype or endotype, something suggested by the experience accumulated in asthma. On this basis, workshop participants discussed whether it would be more appropriate to resolve this matter first with large trials that compare several biologics and include a wide range of patients before engaging in studies comparing biologics to surgery. Additional, relevant and more detailed questions are listed in **Table 3**.

The workshop also discussed potential study designs, clinical outcomes, and study participant inclusion/exclusion criteria. In deliberating on these matters, workshop participants identified some overall concerns about clinical trials. Although well-designed and executed clinical trials

should represent the gold standard in addressing questions related to the use of biologics in CRSwNP, it is important to realize that, given the extent and the complexity of these questions, clinical trials have limitations. For example, clinical phenotypes and biologic endotypes may play a major role in determining the optimal use of a new biologic; in such a case, mixing all phenotypes/endotypes in a trial (the “all-comers approach”) will most likely mask the effectiveness of a therapeutic agent. On the other hand, selecting a very specific phenotype or endotype narrows the generalizability of the results (if it is too hard to recruit patients, generalization of the results may be problematic), and conducting multiple trials or multi-arm trials to “cover” all phenotypes requires tremendous resources not available to the industry or to the public sector. Another important consideration is that, whereas achievement of statistical significance for a primary outcome of a clinical trial is typically a necessary prerequisite for the adoption of a new therapy, it is not sufficient. The totality of trial results will be scrutinized by numerous stakeholders, including regulators, payers, journal editors and reviewers, clinical experts, guidelines committees, physicians, patients and various critics.

Study designs

Real World Data - Registries/Administrative Databases

Real world data (RWD) are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources, such as reimbursement and billing activities (administrative data), electronic medical records, drug and disease registries(82). The data are already available for a large number of patients but a) the patients of interest must be found, b) treatments and outcomes are not pre-defined, and c) researchers can use only information that was collected. The reasons why RWD can be very helpful are because randomized clinical trials are a) expensive and take very long; b) usually follow participants for less than two years, whereas patients may be taking biologic treatments for the rest of their lives, c) participants in randomized clinical trials are not representative of the patients treated in real-world clinics(82,

83) and d) participants in clinical trials adhere better to trial treatment than patients in real-world setting(84).

Identifying patients with existing diagnosis of CRSwNP is possible in registries or electronic medical records, but is more challenging in administrative databases. To identify undiagnosed patients or to derive outcomes that are not readily available, this type of research becomes more challenging as valid and reliable algorithms that combine several requirements will need to be used. For example, an online search for validation studies for “Chronic Rhinosinusitis” in administrative data found two studies(85, 86), but an algorithm for CRSwNP probably does not exist and a study to create and validate such an algorithm will be needed.

Before planning a real-world study, researchers must confirm that the data capture the treatments of interest and that the outcome is measurable. They should ask at what time during the drug cycle the data capture new drugs, and if drugs obtained outside of a medication plan or over-the-counter drugs are recorded. Benefits, but also harmful effects, especially if rare or delayed, can be captured. Furthermore, predictors of response can be identified and drug effects in different populations can be assessed. The basic approach is to consider two dimensions: patient, drug. In a simple study design, one would keep one dimension constant and change the second. In a more complicated design, one can examine two dimensions at the same time using stratification.

A prospective registry may be a more feasible and cost-effective initial endeavor before embarking on clinical trials to address the questions identified by the workshop. Through a registry of CRSwNP patients from multiple institutions, one can prospectively collect information on symptoms, quality of life, endoscopic findings, adverse events, imaging and even serum, sinonasal mucosa or other biomarkers. These data would be collected from patients with CRSwNP who are ultimately treated with a biologic and those who are not. The registry participants would be evaluated by predetermined clinical outcome measures. These outcomes could be used to compare biologics, biologics against conventional treatment, and biologics against surgery. Furthermore, clinical outcomes could be correlated to biomarkers as serum and tissue can be collected at the time of enrollment. As new biologics emerge, the registry protocols can be adapted to allow for their investigation. This work can mirror prior successful database

registries that have been developed in cohorts of pulmonary disease patients such as the SubPopulations and InteRmediate Outcome Measures In COPD Study (SPIROMICS)(87) and the Cystic Fibrosis Foundation Patient Registry(88). The data from such a registry will help answer many of the questions that have been raised and will also improve planning of future randomized controlled clinical trials.

The most important limitation of registry data is that there is no randomization and the decision to manage a patient in a particular manner lies on factors related to the patient and the patient's clinician that are influenced by various forms of bias. It is possible to design the registry to include strict algorithms that will guide decision making, keeping in mind that this will, most likely, restrict the participant patient population. Although not the same as randomization, such a "hybrid" approach may be advantageous.

Randomized Clinical Trials - Head-to-Head Comparisons

Randomized clinical trials are the gold standard for comparisons between treatments. However, once a biologic has been shown to be effective against placebo, head to head comparisons between biologics may require substantially larger number of participants as differences in effect size may be relatively small. On the other hand, careful consideration and control for specific CRSwNP phenotypes and endotypes may reveal differences that are important in the context of personalized medicine.

Comparisons between biologics and surgery can be even more complicated. Double-blind designs are not possible unless sham nasal polypectomy was to be incorporated, something that could raise various ethical questions. Also, because surgery has a high rate of immediate beneficial effects and a relatively low rate of need for revision, comparative trials will probably need to be very large, long and, therefore, very costly.

The recent study by Bachert and colleagues(19) provides excellent data for designing future randomized, controlled trials. Based on this study, Table 4 illustrates sample size requirements to demonstrate efficacy of biologics in parallel arm trials; it is important to note, however, that

any definitive trial would likely require considerably more than 20 participants per arm to establish safety. Although the total number of participants will be larger, studies incorporating multiple biologics would be especially efficient to estimate all treatment comparisons.

A crossover design of multiple biologics that allows each patient to serve as her/his own control could be especially powerful in determining the phenotype and/or endotype of individuals best suited for each regimen. This might need to employ a relatively short-term outcome based on a biomarker to allow for multiple treatment periods per individual within a manageable time.

Sample size requirements would need to utilize more information from the Bachert et al dataset(19), and would depend on the specific study objectives. For a study like this to be meaningful, biomarkers that reliably predict the clinical response need to be available. Furthermore, a major issue for such a design is the duration of washout as it is currently unknown how long after discontinuation of a biologic CRSwNP returns to baseline disease activity. A platform adaptive trial approach (see below) that allows emerging biologics to enter the trial could be incorporated. A follow-on trial that finetunes biomarker thresholds adaptively could be conducted once knowledge about biomarkers is more mature.

A trial comparing biologic(s) to surgery is more complicated to design. First, since such study will probably not be blinded, it would be ideal to use an objective endpoint because a subjective *primary* endpoint could render the study results unconvincing. There is also some concern that the size of nasal polyps (nasal polyp score) would not be a fair or meaningful endpoint when comparing biologics to surgery. Another outcome, perhaps a smell test, might be a better alternative. The second, and perhaps most important complexity, is the need to devise an endpoint that accounts for the time-dependent performance of the two treatments that will change across a lengthy time frame. Perhaps an area under the curve approach could be utilized.

Bachert et al(19) used an approach where patients who were rescued (with surgery or systemic steroids) had their primary endpoint imputed by the worst observed value at the time of rescue. While this might be reasonable, one could make the rescue a more explicit part of the endpoint. One approach is to specify a binary or time-to-event endpoint defined by a) need for rescue, or b) need for rescue or poor performance on the primary endpoint.

604

605 *Adaptive Clinical Trial Designs*

606 In the recent released FDA guidance on adaptive designs, “an adaptive design is defined as a
607 clinical trial design that allows for prospectively planned modifications to one or more aspects of
608 the design based on accumulating data from subjects in the trial(89).” In other words, an adaptive
609 design allows proper changes to the trial design based on interim data analysis. An interim
610 analysis is any examination of data obtained from trial participants while that trial is ongoing.
611 Such data may fall under various categories including baseline, efficacy or safety,
612 pharmacokinetic, pharmacodynamic or other biomarkers.

613 Adaptive designs allow efficient use of resources, sample size re-estimation to increase
614 probability of trial success, adaptive randomization to have more participants receive the
615 winning treatment, dropping inferior treatments, adding new treatments and enriching a
616 particular population to show phenotype or endotype-specific benefit. Implementation of an
617 adaptive design is more complicated, and it is important to limit access to comparative interim
618 results to an independent team such as a Data Monitoring Committee.

619 One question that can be addressed by an adaptive design is whether the evidence for efficacy or
620 the lack of it (futility) is adequate with, let’s say, 60% of the originally planned participants. We
621 could perform an interim analysis calculating the conditional power (CP)(90), which is the
622 probability that the efficacy can eventually be claimed should the trial continue to the planned
623 end given the trend in the interim data. If the power is too low, say, below 20%, the trial would
624 not be likely to make it and we may claim futility, but if it is between 50% and 80%, we may
625 consider increasing the sample size. On the other hand, if CP is >80% or < 50%, the trial may
626 continue as planned(91). In a more extreme situation, if CP is 99%, the treatment effect is so
627 pronounced that efficacy can be proven with 60% of the originally planned participants. An
628 important statistical issue is that repeated analyses of interim data will inflate the probability of
629 making an erroneous claim of efficacy. A commonly used approach to address this problem is
630 that the criterion for significance test at each interim analysis is made more stringent so that the
631 overall type I error is controlled at the original desired level, say, 5%(92).

Similar approaches have been developed for non-inferiority trials and trials with multiple arms such as those that would include more than one biologic and a control. Power calculations for noninferiority trials cannot be estimated accurately before a trial, so interim data can be used to update the estimate and the number needed to treat. One strategy is to specify a time for interim analysis and then calculate the power.

Sequential, multiple assignment, randomized trial (SMART) design(93) is a more recent approach to build adaptive interventions. These are multi-arm adaptive trials that incorporate biomarkers and provide a mechanism to decide which treatment to start with, and which treatment to provide next to responsive and to non-responsive participants as identified by one or more biomarkers. An interesting approach would be to use a platform design where different treatments get added as new biologics are approved for CRSwNP. A biomarker-guided adaptive treatment strategy for multiple biologics can also be formed using a Bayesian adaptive approach(94). At the end, the study will still need to answer if one treatment regimen is significantly better than another.

If comparing treatments that have different time to onset of action, like surgery and a biologic, the interim analysis must consider time. There are certain additional considerations specific to adaptive trials in which the primary endpoint is the time to occurrence of a certain event. In the case of CRSwNP that event could be the need for rescue treatment with oral steroids, the requirement for surgery or revision surgery. In these trials, power is dependent on the number of events rather than the number of participants. It is therefore common to target a fixed number of events rather than a fixed number of participants. Sample size adjustment in these trials has the purpose of modifying the number of events and, therefore, may take the form of modifying the number of participants, the length of the follow-up period for each participant, or both. In addition, interim analyses in time-to-event settings may utilize information on surrogate or intermediate outcomes satisfying the Prentice criteria for surrogate markers(95). If substituting a biomarker for the interim analysis rather than a primary outcome, the biomarker should be strongly predictive.

Additional Considerations on CRSwNP Study Designs

Studies of dupilumab in CRSwNP have used intranasal mometasone sprays in run-in phase and throughout the trial, but this may no longer be the standard of care for nasal polyposis. For example, off-label usage of high dose, high volume topical nasal irrigations on a once or twice daily basis (mometasone 2mg in 240ml normal saline) are widely used and have been documented to have superior efficacy to mometasone nasal sprays(16). Notably, the safety of this approach has not been established in large datasets(96). Also, an exhalation device system delivering fluticasone(14) has been approved by the FDA although it has not been compared to a conventional nasal spray or to the off-label use of topical irrigation delivered corticosteroids in randomized clinical trials. In future studies, in order to identify “standard-of-care” refractory patients that could be candidates for biologics, failure to respond to these treatments may be required as an inclusion criterion. Also, studies directly comparing biologics to those new topical corticosteroid approaches will be of value.

A trial to consider in the context of the post-operative role of biologics would be to enroll participants at the time the decision for surgical intervention has been made. A wash-out period from standard medical therapy would precede surgery. This would allow tissue samples collected at surgery to reflect the true disease endotype. The surgical procedure should be standardized, so should postoperative medical therapy. Post-surgical randomization to one or more biologics and possibly to one or more newer corticosteroid delivery approaches would occur at the time an oral steroid course is required, or deterioration of endoscopic scores and/or SNOT-22 on 2 successive evaluations is noted. Since it may take years for the need of revision surgery, this endpoint should probably be avoided. If deemed appropriate, this design can be expanded to involve stratification based on tissue biomarkers or well-defined endotypes.

Oral corticosteroids are routinely applied in the clinical management of CRSwNP. Can we use the response to a standard course of oral corticosteroids as a biomarker to predict response to biologics? A trial could be designed where enrolment would take place at the time the clinical decision to treat a patient with a course of oral corticosteroids is made. Careful evaluation (involving both clinical and inflammatory outcomes) before and at the end of the oral

corticosteroid course would be done and study participants would then be randomized to one or more biologics with or without a placebo control arm. Regardless what the endpoints for this are, data analysis would focus on whether the original response to oral corticosteroids has predictive value for the response to a specific biologic. Of course, a preceding study that provides evidence of the reproducibility of the response to oral corticosteroids would be of help in establishing this response as a biomarker.

On the other hand, as discussed earlier, the use of oral corticosteroid therapy can be considered an outcome to assess the efficacy of biologics. Study participants can be primed with a course of oral corticosteroid for a set duration (e.g. one week) or until a predetermined reduction in nasal polyp size score is detected (see outcomes below). Thereafter, participants could be randomised to various study treatments and the time to the next protocol-required course of oral corticosteroids (e.g., when the nasal polyp size score returns to baseline) could be used as an efficacy outcome. The study could involve a cross-over study design which would allow each participant to be his/her own control. However, the duration of the wash-out period from a biologic will need to be considered.

The AERD population is of particular interest for management with biologics because of high disease severity and frequency of revision surgery (up to 28% after a mean follow-up of 7.4 years)(97). These patients have a special therapeutic option, ASA desensitization, or surgery followed by aspirin desensitization, but also appear to respond to dupilumab(19). However, published studies have involved relatively small numbers of patients and follow-up periods are short. Additionally, ASA desensitization is not without its problems. Comparing dupilumab (or another biologic, if theoretically appropriate) to ASA desensitization as a post-operative therapy, is an important clinical question given that the two treatments have advantages and disadvantages. For example, compared to ASA desensitization, dupilumab will probably be better tolerated, and at least as effective, but much more expensive.

Outcomes

The decision about which variables to include is at the heart of a clinical trial design. The choice of variables to assess CRSwNP in the context of a clinical trial is large. The broadest categorization of those variables is based on the level of subjectivity that they contain, whether deriving from the study participant or the study clinician. The terms “soft” and “hard” outcome measures have been used, but it is important to emphasize that these terms do not determine the quality of the outcome(98). The target of a clinical trial should be to include outcomes which reflect real aspects of CRSwNP that are important to patients, both instantaneously and in the long run, and also important to the health system. For example, it is crucial to assess how a patient feels about her/his condition after receiving a particular treatment, but, if how patients feel about this treatment has no impact on long-term care requirements of a chronic condition like CRSwNP, additional outcomes (e.g. biomarkers) that have better predictive value on disease persistence or progression will need to be used. The workshop devoted substantial time in discussing the pros and cons of currently used outcomes/outcome measures with the goal to identify best application in future trials, opportunities for improvement, or need for creation of new outcomes.

Patient Reported Outcomes (PROs) and Patient Reported Outcome Measures (PROMs)

Symptoms

The inclusion of symptom measures in CRSwNP clinical trials improves the interpretation of clinical trial results for two reasons. First, CRSwNP is a clinical condition defined primarily by the type, duration, and frequency of symptoms and symptom severity influences treatment decisions. Second, multiple studies have demonstrated that objective measures, such as computed tomography (CT) scans, do not always reflect patient reported health measures(99, 100).

Among the various individual symptom measures, the following 8 have been used in prior CRSwNP trials. Visual Analog Scale (VAS)(101) measures include the 1) *Rhinorrhea Symptom VAS*, 2) *Mucus in Throat Symptom VAS*, 3) *Nasal Blockage Symptom VAS*, 4) *Loss of Smell Symptom VAS*, and 5) *Nasal Pain/Discomfort Daily VAS*(5). All of these measures ask the patient

to quantify, “How much trouble was caused by your [symptom]?” by marking on a 10 cm VAS. Symptom severity measures include the 6) *Rhinorrhea Daily Symptom Score*, 7) *Nasal Congestion/Obstruction Symptom Severity Score*, and 8) *Decreased/Loss of Smell Severity Score*(19, 102). These measures ask participants to record severity and duration of their symptoms on a 4-point Likert scale in a daily diary. Results are generally reported as the difference in mean values with some measure of dispersion between comparison groups at different time points (i.e., baseline and weeks after intervention).

Standard psychometric and clinimetric criteria for the assessment of the validity and interpretation of PROMs include internal consistency, test-retest reliability, content validity, criterion validity, discriminant validity, responsiveness and, minimally clinically important difference (MCID)(103, 104). Unfortunately, with the exception of content validity, which is met by definition because the presence of such symptoms is necessary for the diagnosis of CRS, no study has comprehensively assessed these properties for any individual symptom measure. Additional challenges to the interpretation of symptom measures include incorporating control groups to limit placebo effects and confounding, selecting measures that are important to the patient, standardized reporting of multiple symptom measures, and defining clinically meaningful effects such as the minimal clinically important difference (MCID).

Individual symptom measures can be considered for Phase II trials, but Phase III trials should utilize validated, composite, patient-reported outcome measures with known psychometric and clinimetric properties, including MCID. In order to estimate the magnitude and precision of change in symptoms, effect size and 95% confidence intervals should be used and the use of p-values should be de-emphasized(105). Confidence intervals convey information regarding the precision of results and whether the results are compatible with clinically meaningful differences. Finally, future trials should ensure that selected symptom measures are important to patients.

Other Patient Reported Outcome Measures

PROMs can measure a condition at a certain point in time (i.e., “static” measure) or change over time, such as after an intervention (i.e., “transition” measure). PROMs can incorporate a variety of output scales or response categories, including Likert scales(106) or visual analog scales (VAS)(101). Several multi-variable, composite indices can be used in CRSwNP trials. These PROMs can be disease-specific such as the *SinoNasal Outcome Tests* or general health status measures, such as *PROMIS-29*(107), the *Short Form(SF)-36*(108) or the *SF-6D*, which is a health state utility value derived from the SF-36(8). General health status measures are overall less responsive to treatment, compared to disease-specific measures, because CRS has limited impact on physical function and mobility, which play important role in general measures(109).

CRSwNP has dramatic impact upon quality of life (QOL) and disease-specific QOL PROMs are in existence with the *SinoNasal Outcome Test-22* (SNOT-22) being the most commonly used(110, 111). A recent evaluation of CRS-specific PROMs also found that, among validated instruments, SNOT-22 had the highest quality data(112).

In addition to QOL, it is important to be able to compare the impact of CRSwNP and its treatments to other disease states and their treatments. Health utility values (HUV) serve this purpose and are another type of commonly used instruments. With the use of these instruments it has been shown that patients with CRSwNP have worse scores than patients with chronic obstructive pulmonary disease or coronary artery disease(8). CRSwNP therapies can impact HUV: one study of 10 year endoscopic sinus surgery outcomes reported long term HUV improvement with scores approaching the normative United States HUV(37).

While studies are ongoing for a number of biologics in CRSwNP, QOL outcomes have been most extensively reported for dupilumab(19). In a prospective, double blinded, randomized, placebo-controlled study, 93.3% of patients receiving dupilumab achieved MCID on SNOT-22 with overall improvement on SNOT-22 of 27.3 points, which was 18.1 points greater than placebo. To place this in the context of other CRSwNP therapies, a meta-analysis of ESS outcomes found a mean SNOT-22 improvement of 22.9 points with mean follow-up of 14.1 months(113).

Nasal Polyp Score

Several nasal polyp endoscopic scoring systems have been described since the early nineties(114-121). They are based on the visualization of the size of nasal polyposis in the nasal cavity, and mostly use the lower borders of middle and inferior turbinates as the main reference lines. Originally, the scores were simple and meant to be used in daily clinical practice. In 1995, Lund and Kennedy, heading the Staging and Therapy Group for Chronic Rhinosinusitis, proposed the Lund-Kennedy (LK) endoscopic scoring system based on the degree of scarring, crusting, edema, polyps, and discharge(118). This has primarily been used for postoperative evaluations, but is sensitive in identifying minor inflammatory changes before frank polyposis becomes evident.

A total nasal polyp score has been recently developed and has served as a co-primary outcome in clinical trials of biologics(19). Great effort has gone into standardizing and validating the scoring procedure. The results are reproducible and responsive to change in severe disease. The score is based on video recordings of the endoscopic evaluations that are made by trained investigators in multicenter trials. The images are interpreted by trained readers who review them in a blinded manner.

The total nasal polyp score is a research tool and was not developed for clinical practice or to be interpreted by a non-blinded observer. Some of its potential shortfalls include the fact that it is a categorical variable, it does not evaluate polyp size in a 3-dimensional manner and that no MCID has been defined. Interestingly, there is no correlation between the nasal polyp score and PROMs underlying the importance of including PROMs in CRSwNP clinical trials. Some optimization of the statistical methodology to analyze the score may be needed. Since the nasal polyp score is ordinal, there is some concern about handling its change in the course of an intervention as a continuous variable. In addition, the approach of using the baseline score as a covariate may be better than simply analyzing the change from baseline.

Measures of Olfaction

Olfactory dysfunction is a key characteristic of CRSwNP(122). Indeed, 60-80% of patients complain of olfactory impairment. Others demonstrate hyposmia on testing but are unaware of this deficit, reflecting the inaccuracy of self-reporting. Studies of CRSwNP that used olfactory testing have shown that patients perform at levels qualifying them as hyposmic or anosmic. Clinical studies have reported that the presence of nasal polyposis is tightly linked to smell loss (for hyposmia, OR 2.4, 95%CI 2.3 - 43.7; for anosmia, OR 13.2, 95%CI 5.7 – 30)(123). Smell loss correlates with objective measures of sinonasal inflammation, such as increased mucosal inflammation on CT scan(124, 125), and worse olfaction correlates with tissue eosinophilia in postoperative patients(126) and is closely tied to Type-2 inflammation(127, 128).

Olfactory dysfunction can respond to intranasal and systemic steroids, aspirin desensitization (in the setting of AERD), and to surgical treatment, both traditional ESS as well as novel interventions (e.g., steroid implants)(14, 15, 129-131). Olfactory response to steroids also predicts surgical outcomes. In a recent study of dupilumab, the sense of smell was the first outcome to show significant improvement, 2 weeks after starting therapy(19).

There are several methods of testing olfaction. The University of Pennsylvania Smell Identification Test(132) is the standard clinical test in the United States, and the Sniffin' Stick is the standard clinical test in Europe(133, 134). Both have high test-retest reliability, normative values by age and sex, and are widely used in research and clinical practice. The UPSIT is a 'scratch and sniff' format, with 40 item and 12 item versions, which require patients to recognize an odor and select a choice from 4 options. The Sniffin' Sticks identification test consists of 16 marker pens with odors embedded in felt tips, with a similar method of forced choice from 4 options. Both are scored as number correctly identified. Currently, there are no validated MCIDs for either test, although it has been suggested that a change of 1 in the 12 item UPSIT is an MCID based on a distribution model, and validated with an anchor based model (SNOT-22)(132). For the full Sniffin' Sticks battery, which includes odor identification, odor threshold, and odor discrimination, a change of ~1.9 points would be consistent with an MCID(135). For clinical trials, these tests could be used as outcomes in several ways: change in absolute score, modeled changes adjusted for age and sex, changes in category (anosmic to hyposmic to normosmic) or changes in percentile, based on normative values for the general the population.

Imaging

CT scans are the gold standard for assessing burden of disease in the paranasal sinuses and planning surgical intervention. Quantifying disease to improve monitoring of outcome measures in CRSwNP has been challenging. Initial imaging systems were designed to compare baseline characteristics of patients entering into surgical clinical trials. The Kennedy staging system, The Harvard staging system and the Levine and May staging systems were mostly qualitative and have not been used extensively(136). The Lund Mackay (LM) system reported in 1993 has been the most commonly utilized and is semi-quantitative(115). It assigns a score to each of the frontal, anterior and posterior ethmoids, sphenoid and maxillary sinuses: 0 (normal), 1(partial opacification) and 2 (complete opacification). It also allows grading of disease of the osteomeatal unit bilaterally as 0 (clear) or 2 (occluded) thus resulting in a maximum possible score of 24. Zinreich proposed a modification that allows a broader range of scoring(136, 137). Although this scoring system allows better assessment of the extent of disease, it has not been used extensively. Similar to the nasal polyp score, the LM CT scoring system does not correlate with patient symptoms(138), but does correlate with measures of Type-2 inflammation(139). In clinical trials that have assessed biologics, LM scores show reductions after therapy in the active arms in concordance with reductions in nasal polyp score(19, 39, 43). Although scanning protocols to minimize exposure are currently in place, radiation exposure should be considered if multiple CT scans were to be used in clinical trials.

A possible improvement to CT scoring may be the development of volumetric evaluations to allow for determination of the volume of the whole sinus cavity and the part of that volume occupied by air. The major advantage is that this approach can derive a continuous assessment of the extent of disease(137, 140). There is also some evidence that volumetric scores may correlate a little better with symptoms. However, to gather volumetric data, time-consuming and labor-intensive outlining of the boney landmarks of the paranasal sinuses is needed. Automating volumetric assessment would overcome this problem, may yield a better measure of inflammation within the sinuses and may provide a more sensitive approach in assessing small treatment-induced changes allowing comparisons between biologics.

MRI can also be used to evaluate the extent of disease in the paranasal sinuses. It involves no radiation, but is less practical to implement in clinical trials, compared to CT. T2 weighted images facilitate volumetric quantification of disease and allow differentiation between actual polyps and accumulated post-obstructive sinus secretions. Hassaria and colleagues used an MRI scoring technique to evaluate responsiveness to systemic steroids in patients with CRSwNP and showed a significant reduction of the MRI score which correlated well with the nasal endoscopy score(141).

Peak Nasal Inspiratory Flow

Airflow is critical for the function of the nose and nasal blockage is a cardinal complaint of patients with CRSwNP. Abnormal airflow contributes to a number of clinical problems that plague these patients, including sleep interruption, reduced olfaction, and overall poor quality of life. Passage of air is impaired due to physical blockage from polyposis and also from secondary vascular engorgement due to nasal inflammation.

Peak nasal inspiratory flow (PNIF) is an objective measure of airflow, closely correlated with nasal airway resistance. Therefore, PNIF is a direct measure on nasal obstruction. PNIF is simple to obtain, and the devices to measure PNIF are inexpensive and can be used for repeated measurements. Patients are asked to inhale sharply through their nose in the upright; three values are taken and the highest is recorded(142).

PNIF is well-validated. It has excellent test-to-test reliability and correlates with other nasal measures, such as the minimal cross-sectional area of the nasal cavity. Normative values are available. In analyzing PNIF results, one can consider adjustments based on age, sex, height, and ethnicity; remaining variability can be further reduced using transformation(143). In CRSwNP, change in PNIF correlates with disease-specific QOL. For example, there is a strong negative correlation between change in PNIF and change in SNOT-22 score following surgery in patients with and without polyps(144). Some studies report high correlation between subjective reporting of nasal obstruction and PNIF, and polyp size shows an inverse correlation with PNIF

and Sniffin' Stick smell identification scores(143). The most recent results on the efficacy of dupilumab on CRSwNP showed significant improvement by dupilumab over placebo in PNIF, which was concordant with reduction in subjective nasal obstruction and in nasal polyp score(19).

Biomarkers

Biomarkers are measures of pathobiological mechanisms and reflect the activity of these mechanisms. Biomarkers can serve two functions in clinical trials of CRSwNP: they can be used as outcome parameters where pre to post treatment effects are compared, or as predictors of which patients would respond best to therapy. Another role for biomarkers is to provide confirmatory evidence that the treatment in question exerts its expected biologic effect (e.g. an anti-IgE antibody should reduce the levels of IgE). As clinical trial outcomes, biomarkers need to be validated in a manner similar to clinical or physiologic outcomes and results need to be considered in the context of all other measures. For example, reductions in the levels of a disease biomarker, in the absence of any changes in validated PROMs, should question the relevance of the biomarker, and consequently of the disease mechanism it represents. To be useful clinically as a predictor of the response to treatment, a biomarker must be highly predictive. It is more likely that indices derived from measuring several biomarkers may be able to attain high levels of predictability, but extensive work is required to advance this field.

Development of biomarkers for clinical trials in CRSwNP is closely linked to studies assessing the pathophysiology of the disease. Molecular and cellular work, more recently complemented with unbiased analytic and clustering approaches, provides a framework to understand and categorize heterogeneous patterns of inflammation in CRS, a concept known as endotyping. For example, based on protein levels in tissues, investigators at Northwestern University were able to identify patients with predominantly Type 1, 2 or 3 inflammation and to confirm that the vast majority of patients with CRSwNP belong to the Type-2 inflammation category(127, 145). These findings were compatible with work by Belgian investigators(38). These sophisticated clustering approaches have yet to be used in clinical trials of CRSwNP, but the severity of Type-2

inflammation has prognostic implications; for example, higher levels of eosinophilic markers predict more rapid polyp recurrence after surgery(146, 147). On the other hand, a recent study demonstrating that dexpropimexole drastically reduces peripheral and tissue eosinophils without improving symptoms or clinical measures of nasal polyposis cautions the field to track Type-2 inflammation more broadly than simply utilizing eosinophil-specific measures(148).

In clinical trials with biologics for CRSwNP, it is difficult to obtain tissue samples before and after the intervention. Small tissue biopsies and/or superficial scrapings could be used in combination with single cell analyses(66), but it is also important to identify and validate nasal secretion biomarkers that may reflect underlying disease endotypes(149). Measures of Type-2 inflammation in nasal mucus collected from the middle meatus, including cytokines, chemokines and eosinophils, modestly correlate with nasal tissue outcomes, and preliminary analysis via a cluster algorithm identifies the Type-2 endotype in nasal secretions(150, 151). However, further work remains to establish a panel of markers that will most accurately predict underlying tissue endotypes. Other secretion-based assays demonstrating promise are microparticle and exosomal measures that have been found in small studies to reflect cellular patterns in the tissue(152).

Biomarkers can also be measured in peripheral blood. For example, eosinophil counts and total IgE are measured routinely and the levels of dozens of serum cytokines can be tracked using very sensitive multiplex assays. It is important, in this context, to note the experience with blood eosinophils as biomarkers of asthma. Peripheral blood eosinophils have recently entered the clinical management of asthma as a predictor of the response to existing biologics. It is not clear whether this will also be the case in CRSwNP, but continued collection of data in clinical trials of CRSwNP is needed, so that the role of the eosinophil as a biomarker can be elucidated. Eosinophils have long been known to be present in allergic asthma, but recently they have been recognized as a practical way to identify patients with severe eosinophilic asthma(153). Blood eosinophils have emerged as a reliable biomarker as they correlate positively with sputum eosinophils, severity of asthma, risk of exacerbation, and negatively with lung function(154). In patients with adult-onset asthma, those with high eosinophils (classified as blood eosinophils greater than 300) were more likely to have higher FeNO levels, more sputum eosinophils, be on oral steroids, have severe fixed airway obstruction, and have a history of CRSwNP. It is clear

from clustering analyses, biologic trials, and animal studies that eosinophils are elevated in at least two subtypes of asthma- those with allergic asthma and a strong adaptive immune response and those with a strong ILC2-driven response. A blood eosinophil count above 150 or 300 cells/ μ l in patients with severe uncontrolled asthma identifies patients most likely to respond to a Type-2 biologic (including, omalizumab, mepolizumab, benralizumab, or dupilumab), but is not useful to track response once a patient has been treated as levels after drug initiation don't correlate with the clinical response(49).

Exacerbations and Control

Acute exacerbations (AE) occur in patients with CRSwNP despite aggressive management and are associated with significant healthcare costs(155), physician visits(156), workplace productivity reduction(31), and decrements in quality of life(157). Consequently, a systematic metric or an operational definition to document and measure AEs would be of significant value to both quantify disease control and determine the relative durability of different therapeutic options. Current guidelines define AE in CRSwNP as an acute and transient worsening of preexisting symptoms(5, 14). However, these definitions rely on empiric clinical findings and cannot be prospectively applied in a clinical trial setting.

There remains a paucity of studies which report on quantifiable clinical metrics of AE in CRSwNP, particularly with respect to PROMs. Divekar et al(158) found that an AE was associated with a 10-point increase in SNOT-22 score in a population of 9 patients with CRSwNP. When assessing a similar metric, Zemke et al(159) reported an increase of 4.9 points from baseline during an AE; however, this study was evaluating a patient group with cystic fibrosis. Other studies examining SNOT-22 changes in the setting of poorly controlled CRS reported a 25% reduction in disease control for every 15 point increase in SNOT-22 score(160) and a doubling of the relative risk of antibiotic use for every 30 point increase(157). These findings underscore the unmet need for further quantification of AE in CRSwNP using PROMs. At the current time however, the Divekar et al(158) data indicate that a patient reported AE is associated with approximately one MICD unit of worsening in the SNOT-22 score; this may be an appropriate start to assess AEs in future CRSwNP studies.

In light of the Type-2 inflammatory skewing of most nasal polyps in the western world, some studies have attempted to correlate AEs with both nasal and serum derived inflammatory biomarkers. Rank et al(161) prospectively collected nasal mucus samples in patients with CRSwNP experiencing a self-reported AE over 8 time points and demonstrated significant increases in IL-6, eosinophil major basic protein (MBP), eosinophil derived neurotoxin (EDN), myeloperoxidase, and uric acid. Divekar et al(158) showed significant increases in nasal mucus IL-6, IL-5, and MBP, as well as serum levels of granulocyte-macrophage colony-stimulating factor (GM-CSF) and vascular endothelial growth factor (VEGF) during an AE of CRSwNP. These studies are notable for several reasons. First, they confirm that AE in CRSwNP, as reported empirically by patients, are associated with statistically significant quantitative changes in inflammatory biomarkers. Second, they confirm that these biomarkers may be sampled serially and prospectively from nasal mucus. This indicates that the development and validation of a non-invasive biomarker of AE in CRSwNP is, in principle, an attainable goal.

The concept of Type-2 inflammatory biomarker sampling endorsed by Rank et al(161) and Divekar et al(158) has recently been extended through the discovery of novel proteins including cystatins 1 and 2 as well as periostin, which appear to participate in the etiopathogenesis of CRSwNP. Xu et al(162) reported that periostin levels were higher in eosinophilic nasal polyps while Ninomiya et al(163) showed that elevated levels were predictive of CRSwNP recalcitrance. Similarly, both Kato et al(164) and Yan et al(165) found that increased tissue cystatin expression was associated with eosinophilic CRSwNP. Mueller et al(166) synthesized these findings in a prospective 2-year study of 66 post-operative patients with CRSwNP and found that elevated nasal mucus levels of both cystatin and periostin not only correlated with disease recalcitrance but could predict an eventual AE up to 5 months in advance.

Complementing the definition of AE is defining control for CRSwNP. In asthma, tests of control are useful outcomes for evaluating treatment regimens(167). However, no such test exists for CRSwNP. A Rhinitis Control Assessment Test (RCAT) has been validated for allergic rhinitis, but is not widely used(168). Whether this can be applied to CRSwNP is unknown.

Surgery

Surgery plays a major role in the management of difficult-to-control CRSwNP. Patients who have failed appropriate medical therapy are offered ESS. Sinus surgery in the setting of CRSwNP is almost always elective and the decision to surgery can be used as an outcome measure in a clinical trial.

Any trial involving surgery as an outcome will need to include strict criteria defining when it is appropriate to recommend surgery, recognizing that a decision for surgery in an individual patient is complex and influenced by many factors. In the future, these factors may involve biomarker-based disease endotyping. Furthermore, it is important to consider the differences between first-time and revision surgery and between revision surgery that is required within a short period vs several years from the original procedure. Since surgery is elective, we must identify the reasons why some patients may elect surgery and others with similar pathology and even symptom burden may not. Finally, it will be important to capture the reasons for the physicians' recommendations for surgery.

For studies that intend to randomize patients to biologics right after the original surgical procedure and use revision surgery as the outcome, it is important to consider the surgical technique that was used. In addition, given that surgical outcomes and revision ESS rates have changed dramatically over the last decade with alterations in the extent of surgery and adjuvant postoperative therapy, including aspirin desensitization or topical steroid therapies(169), such studies need to be of long duration and may not be practically feasible as conventional, randomized trials. A registry design may be more appropriate in this regard.

Health Economics

The cost of treatment will invariably play a role in decision making as to the appropriate use of biologics in CRSwNP, and clinical trials should try to capture treatment costs. Lauren Roland and her colleagues at Emory University used an insurance claims repository to identify patients with nasal polyps between 2009-2015 and track the cost of surgery, CT scans and debridements,

all costs that would accompany a surgical planning route. The approximate mean and median costs of this surgical route were \$7,000 and \$5,000, respectively, over a 6-year time period (unpublished data). In comparison, the wholesale acquisition cost of biologics can be several-fold higher. However, an appropriate comparison will need to include indirect costs and should consider potential reduction of other medication usage and other disease-related costs, particularly in patients with lower airways disease, while on a biologic.

Patient Characteristics

Baseline Characterization of Study Participants

The more information on study participants, the easier it will be to identify predictors of response, compare data across trials, and allow for exploratory subgroup efficacy analyses for the intervention(s) in question.

Baseline information on sinus disease, in addition to disease-specific PROMs, should include a) date(s) of prior sinus surgery(ies), b) number of oral corticosteroid courses and number of antibiotic courses for sinus-related problems in the last year, c) any other treatments received for CRSwNP, d) imaging (probably a CT scan).

Evaluations of the nose could include a) measurements of nasal airflow, b) olfactory function, c) mucociliary clearance, d) samples of nasal secretions, e) nasal mucosal scrapings, f) polyp and/or nasal tissue biopsies. Samples that will allow for future microbiome, fungome and virome analyses should also be obtained and appropriately stored.

Given the predominance of Type-2 immune responses and inflammation in CRSwNP, systemic markers such as blood eosinophil counts and total serum IgE are needed. Furthermore, co-morbidities need to be recorded beginning with the lower airways because at least 30% of participants in CRSwNP studies will have asthma. Lung function should be assessed, FeNO levels recorded, and more specific evaluation of atopy with either a panel of aeroallergen skin tests or a panel of aeroallergen-specific serum IgE antibodies should be considered.

CRSwNP study participants should be queried for ASA or NSAID respiratory reactions. If aspirin-exacerbated respiratory disease is the focus of a trial, a formal ASA challenge may need to be conducted if the history is unclear. Unless it is the study's focus, there is no need for an immunodeficiency evaluation (immunoglobulin isotype levels and vaccine responses).

Inclusion/Exclusion Criteria

In CRSwNP trials, the standard CRS definition should always be used as the most important inclusion criterion: presence of 2 or more of the following symptoms for greater than 12 weeks duration: 1) nasal blockage/obstruction/congestion; 2) nasal discharge; 3) facial pain/pressure; 4) reduction or loss of smell. In addition, nasal polyposis should be visualized with endoscopy in both nasal passages and objective confirmation should be made by sinus CT scan. Other inclusion criteria should be trial-specific.

Additional inclusion as well as exclusion criteria need to be considered very carefully because restricting the trial population can limit the generalizability of the results and may increase recruitment difficulty to the point of trial failure. However, some absolute exclusion criteria should always be applied to avoid contaminating the study population with other conditions. These include EGPA, unilateral nasal polyps, mucocoeles, cystic fibrosis and immunodeficiencies. Also, children should be excluded from studies of CRSwNP because bilateral nasal polyps are rare and most likely reflect another underlying condition. Allergic fungal sinusitis with bilateral polyps can be excluded or studied as a subgroup.

Conclusion

CRSwNP has a major impact on the quality of life of its sufferers and a large financial impact on health care costs. Better understanding of the pathophysiology is leading to new treatments, mostly biologics. How we integrate these treatments into a new and efficient management paradigm with patients' wellness in mind is a major challenge for the years to come. The NIAID Workshop on "Clinical Research Needs for the Management of Chronic Rhinosinusitis in the

1156 New Era of Biologics” examined in great detail various aspects of clinical trial needs and
1157 designs. We hope that this report will pave the way to pivotal trials that will provide the
1158 evidence for appropriate placement of biologics in the management of CRS.

Table 1: Published clinical trials with biologics in CRSwNP

Biologic (reference)	Target	Publication Year	Therapeutic effects	Limitations/Adverse events	Development Status
Omalizumab (39)	IgE	2013	Reduction in polyp and CT scores, improvement of upper and lower airways symptoms and quality of life	No reduction of serum or nasal secretion mediators, frequent rhinopharyngitis	Phase 3 trials conducted – awaiting publication
Mepolizumab (40)	IL-5	2011	Reduction in polyp score, blood eosinophil counts, serum ECP and IL-5R α levels	No significant improvement of symptoms, frequent rhinopharyngitis	Phase 3 trials ongoing
Mepolizumab (41)	IL-5	2017	Reduction in required sinus surgery, improvement in nasal polyp score, symptoms, and QOL (SNOT-22)	Safety profile comparable to placebo	
Reslizumab (42)	IL-5	2006	Reduction in nasal polyp score, blood eosinophil counts, serum ECP levels	No significant improvement of symptoms	No further development
Dupilumab (43)	IL-4R α	2016	Reduction in nasal polyp and CT scores, improvement in	Headache, rhinopharyngitis, and reaction at injection	

			olfaction, symptoms, and QOL (SNOT-22), pulmonary function (FEV ₁) and asthma control test score (ACQ5)	site	Phase 3 trials published, FDA and EMA approval
Dupilumab (19)	IL-4R α	2019	Reduction in nasal polyp and nasal congestion scores, and in all secondary outcomes (symptoms, CT score, UPSIT smell test, SNOT-22, use of systemic glucocorticosteroids, sinus surgery)	The most common adverse events (nasopharyngitis, worsening of nasal polyps and asthma, headache, epistaxis, and injection-site erythema) were more frequent than with placebo	

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1160 *CT*, computerized tomography; *ECP*, eosinophil cationic protein; *IL-5R α* , IL-5 receptor α ; *IL-*1161 *4R α* , IL-4 receptor α ; *QOL*, quality of life; *SNOT-22*, Sino-Nasal Outcome Test; *FEV₁*, forced1162 expiratory volume in the first second; *ACQ5*, Five-item Asthma Control Questionnaire; *UPSIT*

1163 University of Pennsylvania Smell Identification Test.

1164 **Table 2.** EUFOREA criteria (54) for biologics indication in patients with CRSwNP. Patients
1165 who had prior ESS need 3 while those who had not had ESS need 4 of the following criteria:

Evidence of Type-2 inflammation
Significant impairment of quality of life
Reduced smell
Need for (at least 2) courses of systemic corticosteroids in the past year
Asthma

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Table 3. Questions raised by workshop participants that can influence the design of clinical studies in CRSwNP

STUDY CONCEPTS

- Do we need to fully describe CRSwNP phenotypes and endotypes before designing trials or other studies that aim at comparing biologics to each other or to other forms of treatment?
- How stable are the CRSwNP phenotype and its sub-phenotypes/endotypes? (for example, if an AERD patient, who had prior surgery for nasal polyps, presents with pansinusitis without endoscopically detectable nasal polyps should he/she still be considered a CRSwNP patient?)
- Should clinical trial designs aim at testing biologics on the basis of biomarkers such as previous surgical pathology or biomarkers that can be obtained non-invasively and can be eventually be used in clinical practice?
- Can clinical trial designs and outcomes funded by the public or private sector be harmonized, so that the results can be directly compared?

STUDY DESIGNS

- Do comparator clinical trials require a placebo arm if the effectiveness of each treatment has been already determined?
- What are the most important clinical outcomes for comparing the effectiveness of different biologics or of biologics to other forms of treatment?
- For trials designed to assess the effectiveness of biologics post-operatively, how long after surgery should biologic treatment begin and what should the duration of treatment be?
- For trials that require run-in periods to optimize medical management before randomization to biologics or to surgery, what would optimal management constitute of and what should the optimal run-in duration be?

Table 4. Sample size calculations for randomized clinical trials comparing biologics to placebo (superiority design) or biologics to each other (non-inferiority design)

Parallel Arm Study Design	Endpoint: Change at 24 weeks from baseline	Approximate Sample Size (for 90% power)	Estimates based on Bachert et al(19)
Biologic X vs. Placebo (Superiority)	Nasal Congestion	20/arm	Treatment Effect = 0.9 (SD ~ 0.85)
	Nasal Polyp Score	20/arm	Treatment Effect =1.8 (SD ~1.7)
Biologic X vs. Dupilumab (Non-inferiority)	Nasal Congestion	125/arm	Non-inferiority margin* = 0.35
	Nasal Polyp Score	110/arm	Non-inferiority margin* = 0.75

*Non-inferiority margins are based on 50% of lower limit of confidence interval from Liberty

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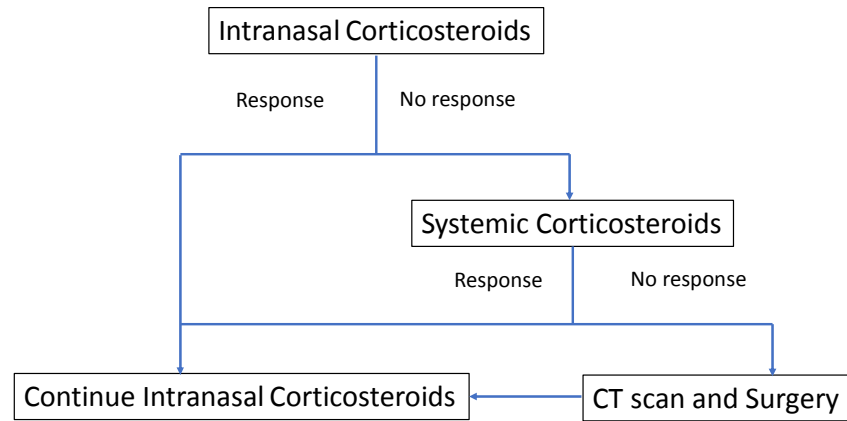
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Figure 1: Basic paradigm for the treatment of CRSwNP before the introduction of biologics

Figure 2: The Type-2 immune cascade in sinonasal mucosa with its inflammatory consequences and with biologic targets and examples of potential therapeutics. Molecules in red represent monoclonal antibodies (biologics). Note that dupilumab has already received approval for CRSwNP, while omalizumab and mepolizumab are currently in Phase 3 development. Parasites are illustrated as another stimulus for Type-2 immune responses, but have not been implicated in the pathogenesis of CRSwNP. Modified from Hulse et al. (170)



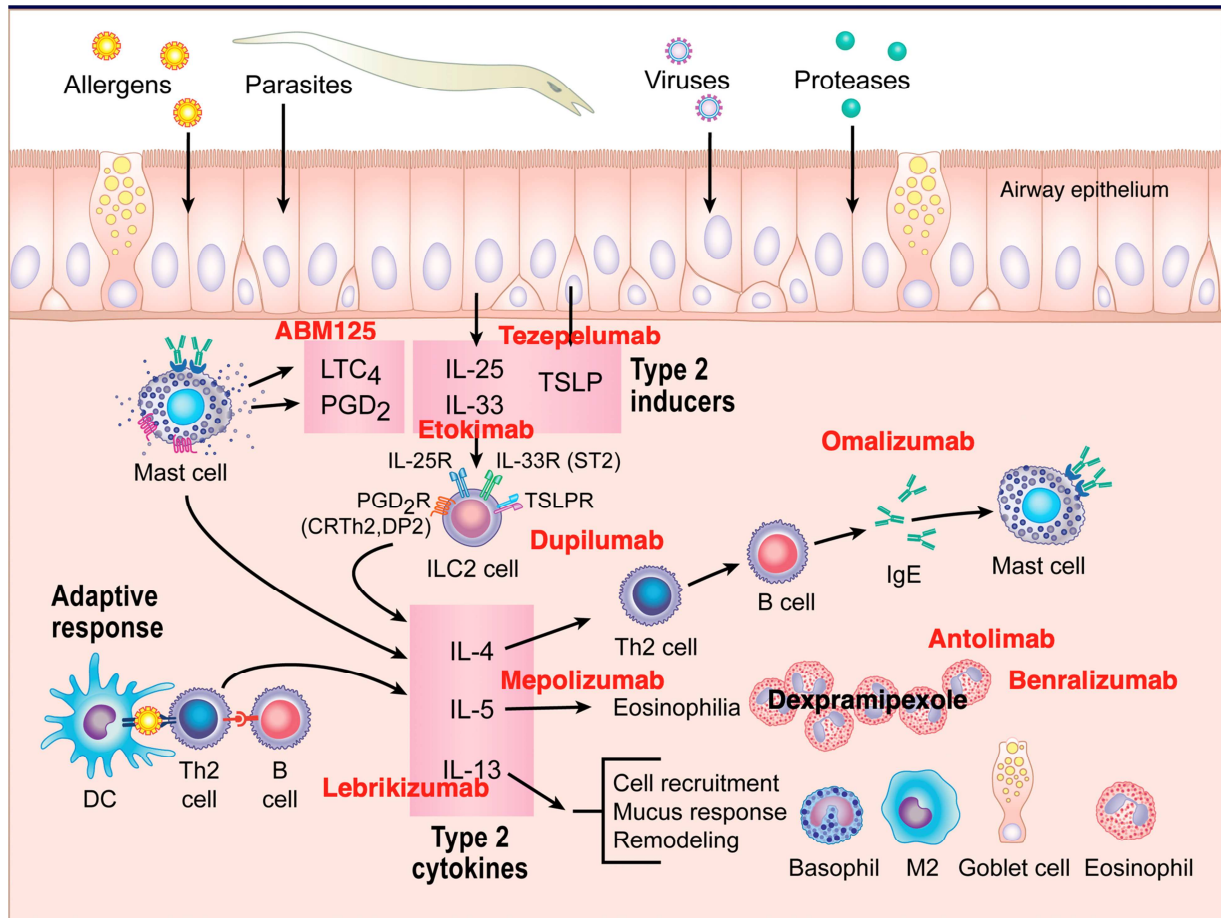


Table S1. Topics and speakers at the NIAID Workshop entitled “Clinical Research Needs for the Management of Chronic Rhinosinusitis with Nasal Polyps in the New Era of Biologics”, November 4-5, 2019

TOPIC	SPEAKER
Defining the Clinical Problem	Robert Naclerio
CRSwNP: Epidemiology	Wyske Fokkens
The Economic Impact of CRSwNP	Timoth L. Smith
Treatment Targets in CRSwNP	Robert P. Schleimer
Current and Upcoming Biologics for the Treatment of CRSwNP	Claus Bachert
Biologics for the Treatment of Asthma: Efficacy and Safety	Sally Wenzel
Biomarkers in Determining Appropriate Treatment with Biologics in Asthma	Geoffrey Chupp
Which Patients will Benefit from Biologics for CRSwNP and Which will Not? Otolaryngologist’s Perspective	David Kennedy
Which Patients will Benefit from Biologics for CRSwNP and Which will Not? Allergist’s Perspective	Tanya Laidlaw
Nasal Polyp Score - How is it Used and Performing; Shortfalls and Suggestions for Improvement	Philippe Gevaert
SNOT-22 and Other QOL Measures in CRSwNP	Rodney J. Schlosser
Symptom Measures for CRSwNP	Jay F. Piccirillo
Imaging in CRSwNP	Fuad Barood
Olfactory Testing and Peak Nasal Inspiratory Flow in CRSwNP	Jayant M. Pinto
Applying Molecular and Cellular Assays or -Omics in Clinical Trials of CRSwNP	Bruce K. Tan
Exacerbations in CRSwNP: How to Define	Benjamin Bleier
Disease Control in CRSwNP: How to Define	Larry Borish
Trial Designs for Comparing Biologics for CRSwNP: Head-to-Head Comparisons	Erica Brittain
Trial Designs for Comparing Biologics for CRSwNP:	Ming Tan

Comparisons Using Adaptive Designs	
Trial Designs for Comparing Biologics for CRSwNP: Registry/Database Comparisons	Anat Fisher
Design of Future Trials (Discussion)	Robert Naclerio (Moderator)