

Targeted Molecular Therapies in Allergy and Rhinology

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Abstract

Biologic agents, monoclonal antibodies that target highly-specific molecular pathways of inflammation, are becoming integrated into care pathways for multiple disorders that are relevant in otolaryngology and allergy. These conditions share common inflammatory mechanisms of so-called Type 2 inflammation with dysregulation of immunoglobulin E production and eosinophil and mast cell degranulation leading to tissue damage. Biologic agents are now available for the treatment of chronic rhinosinusitis with nasal polyps (CRSwNP), asthma, eosinophilic granulomatosis with polyangiitis (EGPA), atopic dermatitis (AD), and chronic spontaneous urticaria (CSU). This paper summarizes the diagnosis and management of these conditions and critically reviews the clinical trial data that has led to regulatory approval of biologic agents for these conditions.

Keywords

biologics, biologic agent, anti-IgE, anti-IL-5, anti-IL-4, anti-IL-13, anti-TSLP, omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab, tezepelumab, T2 inflammation, asthma, allergic asthma, eosinophilic asthma, chronic rhinosinusitis with nasal polyposis, atopic dermatitis, chronic spontaneous urticaria, eosinophilic granulomatosis with polyangiitis, aspirin-exacerbated respiratory disease, eosinophilia, unified airway

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New biologic agents are now available for a variety of inflammatory diseases that are relevant to the otolaryngologist and allergist. The biologics discussed in this review are monoclonal antibodies that target highly specific and critical pathways that are essential in the pathogenesis of allergic and respiratory disorders. These agents are changing the treatment paradigms for chronic rhinosinusitis with nasal polyps (CRSwNP), aspirin-exacerbated respiratory disease (AERD), asthma, eosinophilic granulomatosis with polyangiitis (EGPA), atopic dermatitis (AD), and chronic spontaneous urticaria (CSU).

There is a rapidly expanding scientific literature on the role of biologics in these disorders, and recognizing a need to educate otolaryngologists and allergists on the current state of knowledge concerning these treatments, the American Academy of Otolaryngic Allergy convened a multidisciplinary panel of experts for a Biologics Roundtable discussion in May 2019. Panelists were assigned specific content areas for presentation to the group, summarized pivotal trials that led to the current indications for use of these treatments, and critically reviewed current treatment paradigms. The panel also offered insight on a variety of practical issues concerning the use of biologics and where more research is needed to support informed decision making. In addition to analyzing evidence that underpins the approved indications for these agents, the panel considered the relative clinical benefit of biologics as compared with standard or traditional treatment approaches. This article summarizes the discussion that occurred at the May 2019 Biologics Roundtable regarding diseases relevant to allergy and rhinology for which biologic agents are a treatment option. Panelists did not receive any compensation for their participation.

Type 2 Inflammation

While CRSwNP, AERD, asthma, EGPA, AD, and CSU are heterogeneous in nature and have multiple phenotypes, most are characterized by type 2 inflammation (**Figure 1**). In type

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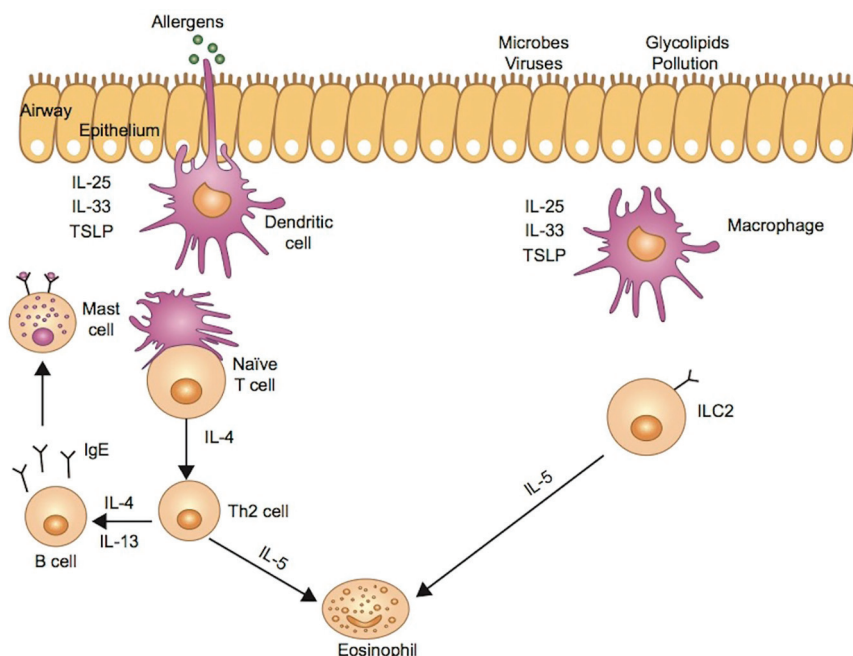


Figure 1. T2 inflammation. Type 2 immune responses involve accumulation of eosinophils, mast cells, Th2 cells, ILC2s, and IgE-producing B cells, and type 2 mediators and cytokines (IL-4, IL-5, and IL-13). IgE, immunoglobulin E; IL-4, interleukin 4; IL-5, interleukin 5; IL-13, interleukin 13; IL-25, interleukin 25; IL-33, interleukin 33; ILC2, type 2 innate lymphoid cell; Th2 cell, T helper type 2 cell; TSLP, thymic stromal lymphopoietin.

2 inflammation, antigens interact with dendritic cells, leading to T-cell activation and differentiation. In allergic disease, type 2 differentiated T-helper (Th2) cells drive the formation of allergen-specific immunoglobulin E (IgE) via IL-4 and IL-13. This IgE binds to mast cells and basophils and functions as the receptor that triggers allergen-induced degranulation. Released mediators as well as IL-4 and IL-13 lead to tissue eosinophilia.¹ In nonallergic type 2 inflammation, type 2 differentiated innate lymphoid (ILC2) cells drive the same cell types and mediators to produce eosinophilic inflammation. This eosinophilic inflammation is sustained by IL-5. The recruitment, activation, and secretion of these inflammatory cells lead to tissue damage and a cycle of chronic inflammation.²⁻⁴

Targeting the Molecules of Type 2 Inflammation

Immunoglobulin E

IgE is the basis for atopy and plays a central role in allergic inflammatory disorders. IgE is secreted by B cells and plasma cells, found in serum, and bound to high- and low-affinity IgE cell surface receptors¹ (**Figure 2**). IgE-receptor interactions are involved in multiple aspects of the allergic response, making IgE a long-standing target for therapeutic intervention.²⁻⁴

The immediate allergic response is triggered by allergen-induced cross-linking of receptor-bound IgE on mast cells and basophils, resulting in the release of a variety of inflammatory mediators, such as histamine. Omalizumab is a

humanized monoclonal anti-IgE antibody that forms complexes with circulating free IgE, inhibiting binding of the IgE molecules to high-affinity and CD23 receptors. Omalizumab cannot complex with or displace bound IgE, nor can it bind to IgE receptors. This is important because omalizumab does not activate mast cells or basophils.

By binding to free IgE and forming small complexes, omalizumab prevents the IgE from binding to receptors on mast cells. This prevents mast cell-bound IgE-antigen interaction and IgE cross-linking, effectively preventing mast cell degranulation and subsequent release of mediators. In turn, this prevents the allergic symptoms normally caused by these events. When IgE levels remain at low levels with omalizumab treatment, high-affinity cell surface receptors are also downregulated, further inhibiting the development of allergic symptoms by reducing the potential for basophil and mast cell activation by uncomplexed free IgE molecules.⁵⁻⁸ Similar downregulation of receptors occurs in mast cells and basophils, but downregulation is faster in basophils.^{8,9} Omalizumab also blocks binding of IgE to low-affinity IgE receptors, although the therapeutic relevance of this action is less clear.¹⁰

IL-5

Interleukin 5 (IL-5) is a potent proeosinophilic cytokine that controls cellular differentiation and maturation of eosinophils in the bone marrow, as well as the survival and activation of eosinophils at peripheral sites. Eosinophils are central to the pathogenesis and severity of chronic inflammatory disorders of the airway, including asthma and nasal

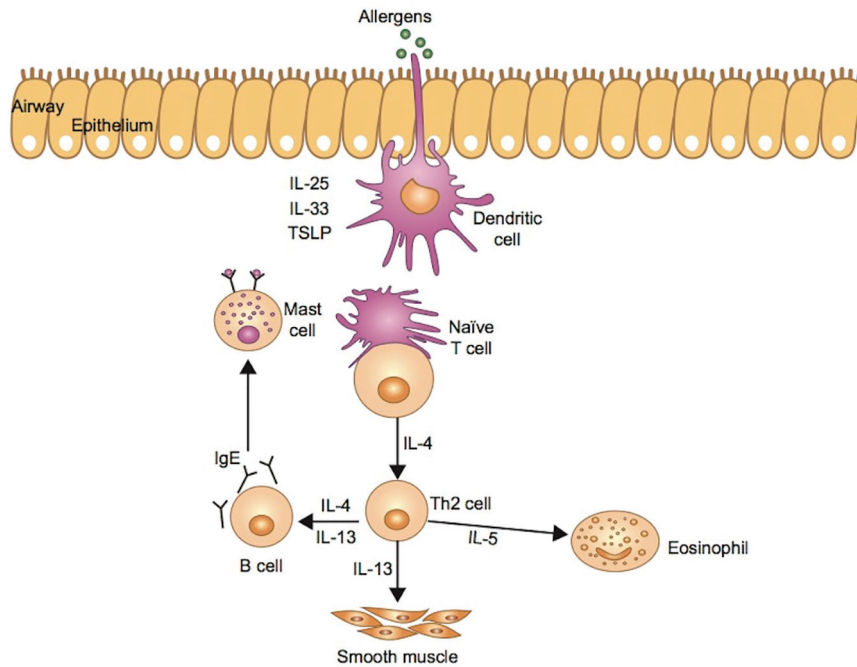


Figure 2. IgE-mediated allergic/inflammatory pathway. Allergens are taken up by dendritic cells and presented to naïve T-helper cells. A cascade of events leads to production of the type 2 cytokines IL-4, IL-5, and IL-13; secretions of IgE by B cells; and chemoattraction of mast cells and eosinophils. IgE, immunoglobulin E; IL-4, interleukin 4; IL-5, interleukin 5; IL-13, interleukin 13; IL-25, interleukin 25; IL-33, interleukin 33; Th2 cell, T helper type 2 cell; TSLP, thymic stromal lymphopoietin.

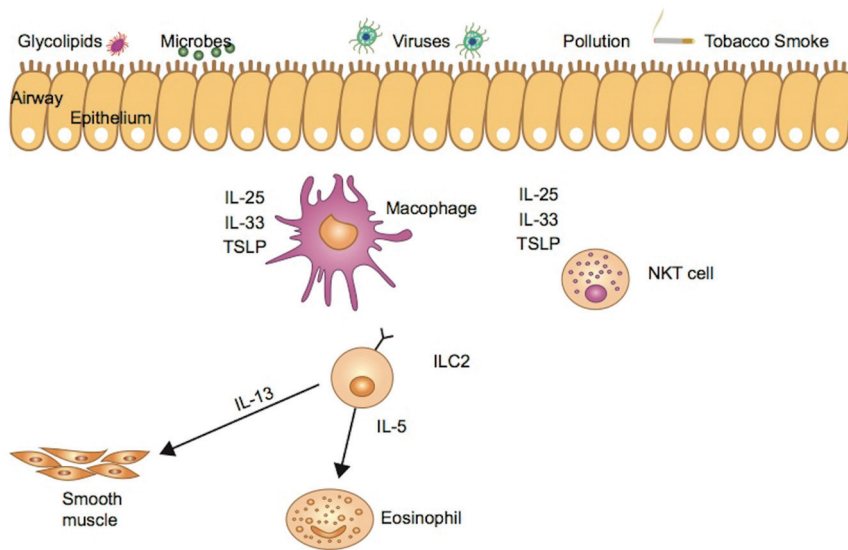


Figure 3. ILC2-mediated type 2 responses. The interaction of environmental exposures with the airway epithelium leads to the release of the mediators IL-33, IL-25, and TSLP. Type 2 cytokines can be produced by ILC2s. ILC2 can be activated by proteases, pathogens, pollution, and other stimuli. IL-5, interleukin 5; IL-13, interleukin 13; IL-25, interleukin 25; IL-33, interleukin 33; ILC2, type 2 innate lymphoid cell; NKT cell, natural killer cell; TSLP, thymic stromal lymphopoietin.

polyposis, and patients with asthma and eosinophilia have more frequent exacerbations.¹¹

IL-5 is produced by Th2 lymphocytes and ILC2 cells (**Figure 3**). Th2 cells synthesize and release IL-5 when they are activated by antigen-presenting dendritic cells in the presence of IL-4. This process occurs via stimulation of STAT6 (signal transducer and activator of transcription 6)

and GATA3 (GATA binding protein 3). ILC2 cells also produce IL-5 upon activation by epithelium-derived alarmins, such as IL-25, IL-33, and thymic stromal lymphopoietin, which can also activate GATA3.^{12,13} Elevated levels of IL-5 mRNA are observed in bronchial biopsies of patients with asthma, and elevated IL-5 levels correlate with asthma severity.^{14,15}

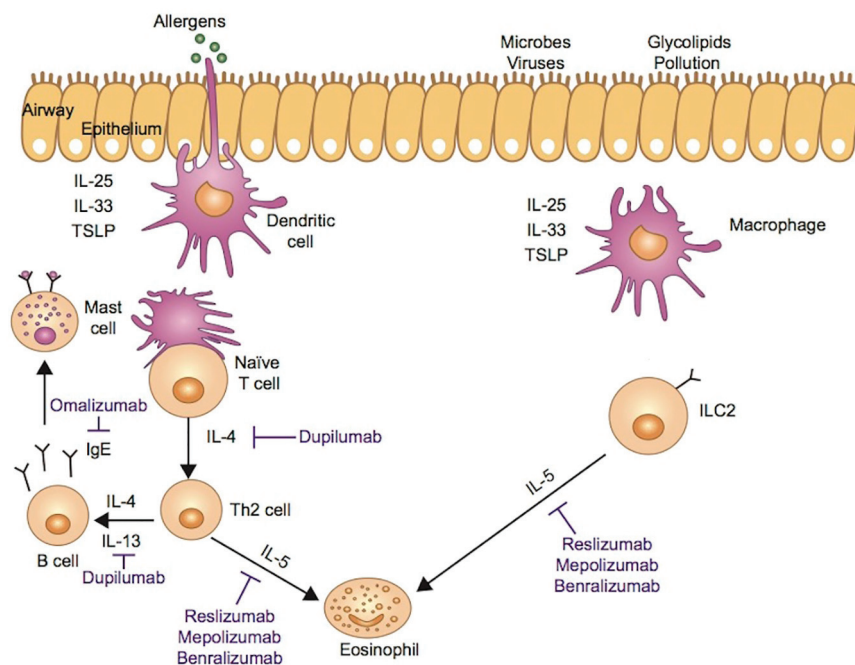


Figure 4. Molecular targets for biologic therapies. The schematic includes sites of targeted treatments with approved monoclonal antibodies. The interaction of genetic susceptibility and environmental exposures, such as allergens, viruses, pollutants, and irritants, creates airway inflammation. This process lends itself to numerous therapeutic targets that have been approved by the US Food and Drug Administration. IgE, immunoglobulin E; IL-4, interleukin 4; IL-5, interleukin 5; IL-13, interleukin 13; IL-25, interleukin 25; IL-33, interleukin 33; ILC2, type 2 innate lymphoid cell; TSLP, thymic stromal lymphopoietin.

Since IL-5 is critical for eosinophil growth, differentiation, and migration to the airways, it is an appropriate therapeutic target in eosinophilic asthma.

There are 2 ways that monoclonal antibodies can block the effects of IL-5. One approach is to bind to IL-5 itself. Mepolizumab and reslizumab are 2 humanized monoclonal antibodies that bind directly to IL-5, preventing it from binding to the IL-5 receptor. Mepolizumab and reslizumab bind to IL-5, blocking its binding to the alpha chain of the IL-5 receptor complex on the eosinophil cell surface.¹⁶ By inhibiting IL-5 signaling through blockade, mepolizumab and reslizumab reduce the production and survival of eosinophils.

Another approach to IL-5 blockade is to bind to a component of the IL-5 receptor. Benralizumab targets the IL-5 receptor α on eosinophils and basophils, which prevents IL-5 binding.¹⁶ As with the other monoclonal antibodies that target IL-5, benralizumab depletes blood and airway eosinophils. However, unlike mepolizumab and reslizumab, benralizumab induces antibody-dependent, cell-mediated cytotoxicity. An active immune response against benralizumab-tagged eosinophils and basophils, via natural killer cells, leads to apoptosis and further depletion of eosinophil numbers.^{16,17}

IL-4/13

IL-4 and IL-13 fuel eosinophilic and allergic inflammatory processes in type 2 inflammatory diseases via a variety of mechanisms, including IgE synthesis, induction of airway hyperresponsiveness, proliferation of bronchial fibroblasts, enhanced mucus production, and recruitment of basophils

and eosinophils. IL-4 and IL-13 function upstream of IL-5 and affect more cell types beyond eosinophils, including airway smooth muscle cells, fibroblasts, macrophages, mast cells, and basophils. Beyond their ability to promote a multimodal inflammatory response, IL-4 and IL-13 also appear to downregulate important components of barrier function in AD, such as filaggrin, ceramides, and antimicrobial peptides, in the skin and airways.¹⁸⁻²²

Blockade of IL-4 and IL-13 can be achieved via receptor inhibition or neutralizing antibodies. Dupilumab binds to the IL-4R α subunit, inhibiting IL-13 and IL-4 signaling and decreasing IgE production by about 40%.²³ The IL-4 α receptor is a common receptor domain for IL-4 and IL-13.

Figure 4 presents sites of the targeted treatments with approved monoclonal antibodies.

Chronic Rhinosinusitis With Nasal Polyps

Definition and Diagnosis

CRSwNP is an inflammatory condition of the nose and paranasal sinuses that lasts >12 weeks.²⁴ Symptoms include nasal obstruction/congestion, anterior or posterior nasal discharge, and loss of the sense of smell. The diagnosis of CRSwNP is confirmed by the finding of nasal polyps (usually bilateral) on anterior rhinoscopy or nasal endoscopy. Phenotyping of chronic rhinosinusitis (CRS) into CRSwNP and CRS without nasal polyps does not adequately reflect the pathophysiologic diversity²⁵ of these conditions; nevertheless, most CRSwNP is characterized by type 2

eosinophilic inflammation, and CRSwNP is closely linked to atopy/allergy and asthma.²⁶

Management

In general, corticosteroids are the most effective treatments for nasal polyp inflammation. Patients with mild symptoms or minimal polyp burden can be adequately treated with long-term topical corticosteroids.^{27,28} When control of this inflammation is insufficient, short courses of oral corticosteroids (OCSs) are often added. The optimal duration of OCS treatment is not established, but randomized controlled trials of a 2-week flat course or 3-week tapering course of oral steroid, beginning at a prednisone equivalent dose of 40 to 50 mg, achieved significant reduction of polyp size with a concomitant improvement in CRS symptoms.²⁹ The long-term efficacy of such as a course of oral steroids, in conjunction with daily topical intranasal steroids, is likely 8 to 12 weeks.³⁰ Short courses of antibiotics (<3 weeks), especially if concomitant bacterial infection is present, and longer-term courses of macrolide antibiotics (>3 months) may provide subjective benefit in select patients.³¹ Aspirin desensitization is an option in patients with AERD.²⁷

Sinus surgery is useful when appropriate medical therapy fails to alleviate symptoms or eliminate polyps and sinus inflammation or when recurrent polyps necessitate the use of oral steroids ≥ 2 times a year. Complete sinus surgery creates access to improve the effectiveness of topical intranasal steroids. “High dose” topical steroids administered via saline irrigation, head-down positioning, or specialized applicator devices have been shown to be beneficial in these patients.³²

Some nasal polyp disease is so severe that complications arise from excessive steroid use.³⁰ For these patients, the emerging biologic therapies hold great promise as an add-on treatment approach that will control disease without repeated surgery or repeated requirements for systemic steroids.

CRSwNP Treatment With Biologics

Dupilumab. At present, the only biologic approved by the US Food and Drug Administration (FDA) for treatment of nasal polyp disease is dupilumab. Dupilumab is approved for add-on maintenance treatment for adults with inadequately controlled CRSwNP. A phase II study was conducted to determine if dupilumab would improve clinical measures of disease when added to intranasal corticosteroids (INCSs) in patients with CRSwNP. The primary endpoint was change in endoscopic nasal polyp score (NPS) after 16 weeks. Secondary endpoints included sinus computed tomography (CT) scores, olfaction, validated symptom scores, biomarkers, and safety assessments. The trial enrolled 60 adults with CRSwNP, of whom 35 had asthma. All had failed ≥ 8 weeks of INCS, had ≥ 2 symptoms of CRSwNP, and had bilateral nasal polyps on endoscopy. Participants were treated with a subcutaneous (SC) 600-mg loading dose of dupilumab, followed by SC 300 mg weekly plus mometasone furoate (MF) nasal spray for 16 weeks. All clinical outcomes—including NPS, Lund-McKay CT score, Sino-

Nasal Outcome Score (SNOT-22), and measures of olfaction—improved significantly in the group treated with dupilumab as compared with control. NPS was reduced by 1.6 relative to placebo in the actively treated group (mean baseline NPS of 5.9 in the active treatment group). Lund-Mackay CT score³³ significantly improved by 8.9 points relative to placebo (baseline in active group, 18.6). Sino-nasal quality of life significantly improved in participants treated with dupilumab (26-point reduction relative to placebo; baseline score of 41 in active treatment arm). Olfaction, as assessed by the University of Pennsylvania Smell Identification Test (UPSIT), significantly improved with dupilumab treatment. The baseline UPSIT score was 13 of 40 in the active treatment group, and the mean UPSIT score increased by 13 relative to placebo. In patients with asthma, dupilumab improved FEV1 percentage predicted (forced expiratory volume in 1 second; 7.1% increase relative to placebo) and asthma control (1.1-unit reduction on Asthma Control Questionnaire-5 score). The Asthma Control Questionnaire minimal clinically important difference has been well established and accepted as 0.5 points for within-person change.^{34,35} Biomarkers associated with Th2 cells, such as serum IgE and plasma eotaxin 3, decreased with treatment, but peripheral eosinophil count did not significantly decrease.³⁶

SINUS-24 was a phase III trial of dupilumab versus placebo in 276 participants with severe CRSwNP with and without comorbid asthma who had been treated with systemic corticosteroids and/or surgery and were being treated with daily intranasal MF. Patients were randomized to SC dupilumab (300 mg) or placebo every 2 weeks for 24 weeks.

Dupilumab significantly improved the NPS (baseline score of 5.6 on a 0-8 scale, with a mean improvement of 2), nasal congestion, Lund-Mackay CT score (baseline score of 19, with a mean improvement of 7.4), olfaction (UPSIT, with a mean improvement of 10.6), and SNOT-22 (baseline score of 48, with a mean improvement of 21.1 points). The proportion requiring systemic corticosteroids or nasal polyp surgery (surgery for nasal polyp disease) during the 24-week treatment period was 7.2% in the dupilumab group versus 23.3% in the placebo group (16% absolute risk reduction).³⁷

Epistaxis occurred more frequently in the dupilumab group versus the control group (7.7% vs 3.0% placebo). Treatment discontinuation due to adverse events occurred in 2% in the dupilumab group. Dupilumab-treated participants had a greater initial increase from baseline in blood eosinophil count as compared with those treated with placebo, which is likely related to its underlying mechanism of action in blocking IL-4-mediated eosinophil migration out of the bloodstream. The clinical significance of the transient increase in eosinophils is unknown.

SINUS-52 was a 3-arm phase III trial that randomized 448 participants into 3 treatment groups: SC dupilumab (300 mg) every 2 weeks for 52 weeks; SC dupilumab (300 mg) every 2 weeks for 24 weeks, then every 4 weeks for an additional 28 weeks; and placebo. SINUS-52 enrolled

participants with baseline disease characteristics similar to those enrolled in SINUS-24. Seventy-two percent of those in SINUS-24 had prior sinus surgery, and 58% of those in SINUS-52 had prior surgery with a mean number of 2.0 prior procedures in both groups. Both groups had an average of 1.6 systemic corticosteroid courses in the 2 years prior to enrollment. The average NPS was 5.8 in SINUS-24 and 6.1 in SINUS-52. Fifty-eight percent of the SINUS-24 group and 60% in the SINUS-52 group had comorbid asthma, with 30% in SINUS-24 and 27% in SINUS-52 having AERD. Both groups had baseline eosinophils >300 cells/ μ L and a total IgE >200 IU/mL.

Dupilumab significantly improved the NPS (baseline score of 6.1 on a 0-8 scale, with a mean improvement of 1.80), nasal congestion, Lund-Mackay CT score (baseline score of 18, with a mean improvement of 6.94), olfaction (UPSIT, with a mean improvement of 10.30), and SNOT-22 (baseline score of 52, with a mean improvement of 20.96 points). Dupilumab reduced systemic corticosteroid use and need for sinus surgery versus placebo, and in those with comorbid asthma, dupilumab improved lung function (FEV1) and asthma control (Asthma Control Questionnaire–5). Results showed that nasal polyp, SNOT-22, and olfaction scores improved significantly in both dupilumab arms starting at week 4, and effects continued for 1 year during treatment in SINUS-52. In SINUS-24, symptoms returned after cessation of treatment, as soon as 12 weeks after cessation.

Injection site reactions were the most common treatment-associated adverse event, which occurred at a higher frequency in the dupilumab-treated group, and nasopharyngitis was the most common treatment-emergent adverse event across all treatment groups. Overall, as compared with dupilumab administered every 2 weeks followed by every 4 weeks, the 300-mg dose administered every 2 weeks yielded better sustained improvements in the objective measures of the NPS and Lund-Mackay CT score and fewer breakthrough treatment-emergent adverse events of worsening of nasal polyps, asthma, and sinusitis; the drug was also well tolerated.³⁸

In the pooled safety population, the incidence of adverse events emerging during the 24-week treatment period was lower in the dupilumab-treated group than in the placebo group. The most commonly reported adverse events were nasopharyngitis, nasal polyps, headache, asthma, epistaxis, and injection site erythema; these events were more frequent with placebo. In both studies, and consistent with previous dupilumab studies, there was a transient increase in mean blood eosinophil counts in those treated with dupilumab. In SINUS-52, eosinophil counts returned to baseline levels by the end of the 52-week treatment period.³⁹

There is an ongoing single-center, single-blinded study being conducted in adult patients with AERD that is assessing the efficacy and safety of dupilumab in treating symptoms of CRS. All participants are being treated with SC dupilumab (300 mg) every 2 weeks for 7 months and will continue their background medications for CRS with nasal

polyposis and asthma. The primary outcome of this trial is SNOT-22 score.⁴⁰ Of note, all studies have excluded patients with suspected allergic fungal rhinosinusitis.

Omalizumab. Several trials have demonstrated that omalizumab is effective in allergic and nonallergic participants with nasal polyps and asthma. A pilot study by Penn and Mikula examined whether anti-IgE therapy was efficacious in the treatment of nasal polyposis. Data were retrospectively collected on 2 groups of patients with atopic asthma and nasal polyposis who underwent endoscopic sinus surgery (ESS), including a control group ($n = 4$) and an anti-IgE treatment group ($n = 4$), who received omalizumab postoperatively. Both groups were evaluated by sinus CT and nasal endoscopic examination, and comparisons were made between the groups with respect to differences in the recurrence of nasal polyposis after ESS. Collectively, the participants showed a direct relationship between nasal polyposis severity and pretreatment total serum IgE levels. Relative to preoperative values, the NPSs significantly improved in the omalizumab group, whereas the control group showed no significant improvement. This pilot study established that endoscopic nasal polyposis severity directly correlates to total serum IgE levels and that inclusion of anti-IgE therapy in the postpolypectomy management of atopic asthma may reduce the severity of nasal polyposis recurrence.⁴¹

A later trial of 24 allergic and nonallergic patients with CRSwNP and asthma focused on change in polyp score at 16 weeks. There was a significant decrease in total nasal endoscopic polyp scores after 16 weeks in the omalizumab-treated group (improvement of 2.67), and secondary endpoints demonstrated Lund-Mackay CT score improvement from 17.6 to 13.6 after 16 weeks in the omalizumab-treated group. The omalizumab-treated group also had improvement in quality-of-life scores based on the Short-Form Health Questionnaire, 31-item Rhinosinusitis Outcome Measuring Instrument, and Asthma Quality of Life Questionnaire, irrespective of the presence of allergy. Study patients were selected by the presence of nasal polyps and asthma, irrespective of the presence of allergy. Nevertheless, omalizumab was equally efficacious in allergic and nonallergic patients with nasal polyps and asthma in this study.⁴²

In a small randomized double-blind placebo-controlled clinical trial by Pinto et al, participants with CRS despite treatment—including surgery, intranasal steroids, and systemic steroids—were randomized to receive omalizumab or placebo for 6 months. The primary outcome was quantitative measurement of sinus inflammation on imaging (Lund-Kennedy Scoring System). Secondary outcome measures included quality of life, symptoms, cellular inflammation, nasal airflow (nasal peak inspiratory flow), and olfactory testing (UPSIT). Patients diagnosed with CRS with total IgE levels between 30 and 700 IU/mL were dosed by weight and IgE levels every 4 weeks for a 6-month study duration. The omalizumab-treated group showed reduced inflammation with no such change in the placebo-treated group; also, the

omalizumab-treated group used significantly fewer courses of steroids over the length of the study as compared with the placebo group, with a trend toward less antibiotic use.⁴³

Two multicenter double-blind randomized placebo-controlled trials of omalizumab in participants with CRSwNP completed enrollment in March 2019.^{44,45} POLYP 1 and POLYP 2 are replicate phase III studies designed to determine the efficacy and safety of omalizumab as compared with placebo in adults with CRSwNP who had an inadequate response to standard-of-care treatment. Both were multicenter randomized double-blind placebo-controlled trials, with POLYP 1 enrolling 138 participants and POLYP 2 enrolling 127 with NPS scores ≥ 5 (pooled average, 6.3) and baseline SNOT-22 scores ≥ 20 (pooled average, 59.8). Other baseline characteristics for the studies included blood eosinophils >250 cells/ μ L and total serum IgE >100 IU/mL for both studies. The primary outcomes for both trials were change from baseline in average daily nasal congestion score at week 24 and change from baseline in NPS at week 24. Participants in the studies were administered omalizumab or placebo by SC injection every 2 to 4 weeks based on IgE levels and weight. These trials also included a considerable number of secondary outcomes, such as change in total nasal symptom score, olfaction as assessed by UPSIT, quality of life, and need for surgery.

Results from these 2 important trials were published⁴⁶ after the roundtable meeting. In these 2 phase III studies, omalizumab met co-primary endpoints and multiple key secondary endpoints. Omalizumab significantly improved health-related quality of life, smell, congestion, endoscopic nasal polyp size, postnasal drip (posterior rhinorrhea score), and runny nose (anterior rhinorrhea score). Positive therapeutic effects were observed as early as week 4. There were no new or unexpected safety signals identified, and the safety profile in these studies was consistent with the known safety profile for omalizumab. The data suggest that omalizumab may be a promising new therapy for the treatment of CRSwNP in patients refractory to first-line therapies.⁴⁷ It is speculated that omalizumab may also gain FDA approval for the indication of CRSwNP in 2020 (fourth quarter) or 2021 (first quarter).

An open-label crossover extension of these omalizumab trials is ongoing. Specifically, the extension is evaluating the safety, efficacy, and durability of response of omalizumab in an open-label setting in adult participants with CRSwNP who completed the 2 double-blind placebo-controlled phase III studies described earlier (POLYP 1 and POLYP 2). After enrollment into the open-label crossover extension, participants will receive 28 weeks of omalizumab dosing before entering a 24-week off-treatment observation phase.⁴⁸

A real-life small study by Bidder et al examined omalizumab as a treatment for coexistent CRSwNP and asthma. Adult patients with CRSwNP and severe allergic asthma with total IgE levels between 30 and 1500 kU/mL ($n = 13$) received omalizumab every 2 or 4 weeks based on weight and IgE levels and were matched with a surgery group ($n = 24$), who did not receive omalizumab. Assessment of SNOT-

22 and the Asthma Control Questionnaire-7 scores was performed at 4 and 16 weeks of treatment in those treated with omalizumab and compared with those in the postsurgery group.

Both groups had baseline eosinophils >500 cells/ μ L and total serum IgE median >250 IU/L, with 77% in the omalizumab-treated group and 63% in the surgery group having aspirin sensitivity. The median SNOT-22 at baseline was 52 (range, 27-78) in the omalizumab group and 70 (range, 26-104) in the surgery-only group. Omalizumab led to a rapid improvement in the SNOT-22 in patients with CRSwNP. This improvement was seen early postomalizumab and sustained with continued treatment. There was no statistical difference in the median SNOT-22 between the omalizumab- and surgery-treated groups. Rapid asthma improvement occurred alongside as reflected in the significantly decreased Asthma Control Questionnaire-7 at 4 and 16 weeks of treatment.⁴⁹

Mepolizumab. Three studies have examined the impact of mepolizumab on severe CRSwNP. The first assessed 30 participants with severe CRSwNP with grade 3 or 4 polyps or recurrent polyps following sinus surgery. Participants were randomized to receive 2 single doses of intravenous (IV) mepolizumab (750 mg) or placebo 28 days apart. The primary outcome was change in NPS; secondary outcomes included symptoms and molecular markers of eosinophilic inflammation in serum and nasal secretions. At 48 weeks, polyp scores were significantly lower in the mepolizumab group as compared with placebo. Although CT scan scores and clinical symptoms showed trends toward improvement, neither reached statistical significance. Serum markers of eosinophilic inflammation were significantly lower in the mepolizumab-treated group, but nasal secretions demonstrated mixed results in the treatment arm. Side effects were mild and not significantly different between groups. Overall, this small trial demonstrated a favorable improvement in nasal polyp burden among patients with CRSwNP who were treated with mepolizumab.⁵⁰

In a subsequent mepolizumab trial, 103 patients with CRSwNP who failed treatment with daily INCS and were deemed to be surgical candidates (defined by an NPS of at least 2 on one side and 3 on the other, as well as symptoms >7 on a visual analog scale) were randomized to receive 6 doses of IV mepolizumab (750 mg) 28 days apart or placebo. Both arms received daily INCS. The primary outcome in this study was the need for nasal polyp surgery. At enrollment, 100% of patients were candidates for surgery. However, at completion of the 25-week treatment period, 70% in the mepolizumab group met criteria for surgery versus 90% in the placebo group. Secondary outcome measures showed significant improvements with mepolizumab treatment. These included improved symptom severity as measured by visual analog scale score, endoscopic NPS, and SNOT-22 scores. However, there was no difference between groups in olfaction, pulmonary function, or non-disease-specific quality of life. The safety profile of mepolizumab was comparable

to placebo. Overall, this study demonstrated a favorable improvement in nasal polyp treatment for some patients with CRSwNP.⁵¹

There is an active randomized double-blind parallel-group phase III study, SYNAPSE, investigating SC mepolizumab (100 mg) every 4 weeks for 52 weeks as an add-on to maintenance treatment in 413 adults with severe bilateral nasal polyposis. In this study, the study group and the placebo group are receiving a standard of care for nasal polyposis, which consists of daily MF nasal spray and, if required, saline nasal douching, occasional short courses of high-dose OCS, and/or antibiotics. In addition, up to the first 200 randomized participants will be followed monthly for up to 6 months after the last dose, to assess maintenance of response and to validate a physiologic model derived from a previous phase II study. The primary outcomes include a change from baseline in total endoscopic NPS at week 52 and change from baseline in mean nasal obstruction visual analog scale score during the 4 weeks prior to week 52. This trial was scheduled to be completed in December 2019.⁵²

Reslizumab. A small 3-arm phase I study of reslizumab randomized 24 participants with CRSwNP to receive placebo or a single infusion of reslizumab at 3 mg/kg or 1 mg/kg. NPSs decreased in half the treated patients for up to 4 weeks, but these differences were not statistically significant. However, pretreatment IL-5 levels in nasal secretions predicted response to reslizumab treatment, a promising finding in the search for biomarkers that could help select appropriate patients for treatment with this biologic therapy. In this early-phase study, 96% of patients had at least 1 non-severe adverse event, most commonly an upper respiratory tract infection, with no significant difference between the study groups and placebo group. Overall, the intervention was safe and well tolerated.⁵³

Benralizumab. A phase II study of benralizumab in 63 participants with eosinophilic CRS was completed in 2017. The primary outcome of this trial was change in NPS at week 12, and secondary outcomes included change in CT scores, treatment discontinuation, change in eosinophil count, and change in nasal airway resistance.⁵⁴ The results of this trial have not been published.

An ongoing single-center phase II trial of 32 patients CRS and eosinophilic polyposis is examining the effect of SC benralizumab (30 mg) versus placebo on NPS after 6 months of treatment. Secondary outcomes include nasal polyp size by CT, SNOT-22, olfaction, eosinophil count, time to surgery, and dropout rate. This trial was scheduled to be completed in June 2020.⁵⁵ OSTRO, a phase III trial of benralizumab in patients with severe nasal polyposis, is also ongoing. This study comprised 400 patients who were still symptomatic despite standard-of-care therapy, including current use of INCS and prior surgery and/or use of systemic corticosteroids. Patients were randomized to receive SC benralizumab (30 mg) plus MF or placebo plus MF over 56 weeks of treatment. The primary outcome measures in this trial are the effect of benralizumab on nasal polyp burden, as

measured by the NPS and patient-reported nasal blockage score, the latter of which is assessed in a daily diary by asking patients to rate the severity of their worst nasal blockage over the past 24 hours. Secondary outcomes include quality of life, nasal polyp surgery, systemic corticosteroid use for relief of nasal symptoms, and nasal symptom scores. In addition, the first 200 participants who complete the 56-week treatment will have a 6-month follow-up period without dosing. The trial was scheduled to be completed in September 2020.⁵⁶

Where Do Biologics Fit in the Treatment Paradigm of CRSwNP?

Current guidelines recommend topical corticosteroids, short-term systemic corticosteroids, antibiotics, and nasal saline irrigations as potential medical treatment options for CRS.^{29,32} In general, patients whose CRS is inadequately controlled with medical therapy should be treated with surgery.

There is a high recurrence of nasal polyposis following ESS: a recent multicenter study revealed 35% recurrence at 6 months and 40% at 18 months.⁵⁷ Several potential risk factors for polyp recurrence, including AERD, atopy, eosinophilia, and asthma, have also been associated with worse outcomes.⁵⁸ These clinical factors exhibit a type 2 endotype that is amenable to treatment directed at T2 cytokines.

Endotyping of CRS could help identify which patients exhibit T2 inflammation and would likely respond to current biologic therapies targeting cytokines IL-4/IL-13 and IL-5 as well as IgE. The presence of other type 2 inflammatory diseases may be suggestive of an endotype, but optimally, serum or tissue markers for biologic therapy targets could help select the appropriate candidates for treatment. For the currently available biologic therapies targeting type 2 inflammation, patients should exhibit a type 2 endotype.

The role of biologic therapies in the treatment of medically and surgically refractory CRSwNP is promising given the favorable data in clinical trials. Dupilumab demonstrated a reduction in NPS and improvement in nasal congestion and olfaction in clinical trials. Other biologics are currently being studied and are expected to gain FDA approval. Comparative studies with medical and surgical therapies will be needed to ultimately determine the appropriate place for biologics in treatment algorithms.

Current trials investigated use for 24 or 52 weeks; however, with a chronic disease that fluctuates over the course of years, it is presumed that longer-term treatment will be needed to achieve sustained outcomes. Recurrence of CRS symptoms and polyps was seen within a few months of stopping these agents, confirming that continuous treatment will be needed to achieve long-term improvement with these interventions alone. As with any chronic treatment regimen, concerns about long-term safety profiles and costs are significant factors in deciding to undergo treatment.

There are many unanswered questions regarding the place for biologics in the treatment algorithms for CRSwNP: Which patients should be considered appropriate candidates

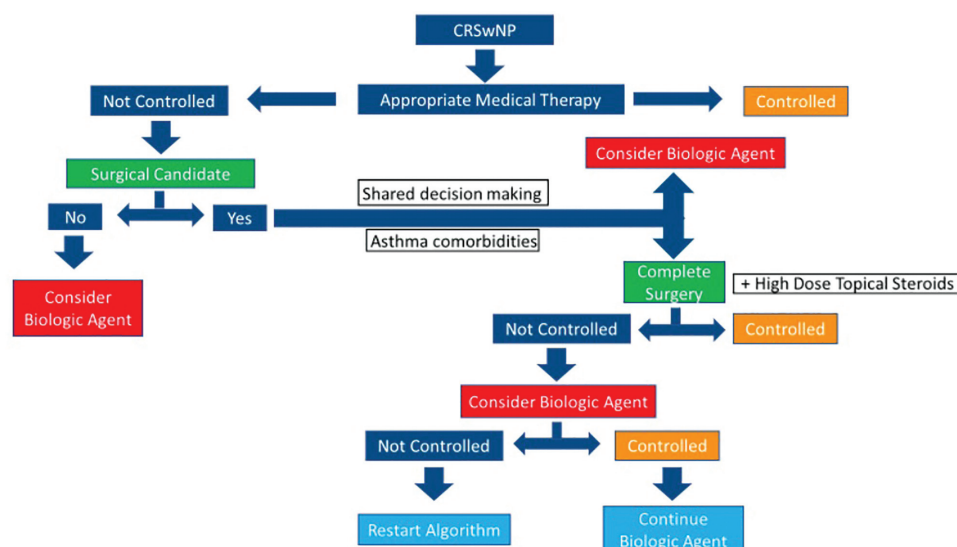


Figure 5. Proposed pathway for the treatment of chronic rhinosinusitis with nasal polyps (CRSwNP).

for treatment with biologics? Which patients will respond to biologics? Should biologics be considered before considering surgical therapies?

The current ICAR recommendation for revision surgery for patients with refractory CRSwNP includes failure of appropriate medical therapy for 3 to 4 weeks.³² This recommendation is also a reasonable consideration for use of a biologic agent in refractory CRSwNP. A proposed pathway for treatment of CRSwNP with biologic agents (**Figure 5**) includes appropriate medical therapy for a minimum of 3 to 4 weeks prior to initiation of a biologic agent. Comorbidities, suitability for surgery, and a shared decision-making approach are all factors included in the proposed algorithm.

The decision to use a biologic agent should include consideration of other comorbid conditions for which these agents have known benefit. For example, a patient with severe persistent asthma and CRSwNP would be an ideal candidate. This would also include patients who have risk factors for severe recurrent nasal polyp disease, such as those with severe AERD or numerous prior surgical procedures with rapid polyp recurrence.

For patients who are considered poor surgical candidates, biologics may be an ideal treatment option. Patients with endotypes that have worse treatment outcomes, such as severe AERD, might be considered candidates for biologic use post- or preoperatively.

With all the uncertainty remaining in this new and promising treatment option, a shared decision-making approach is essential for clinicians to allow patients to make informed decisions with the best available evidence and accepted uncertainty regarding long-term outcomes and risks. The patient's decision to undergo sinus surgery, as opposed to continuing with medical therapy, was demonstrated to be based on the severity of baseline disease-specific quality of life, as measured by the SNOT-22.⁵⁹ Patients with more severe quality-of-life index self-selected to undergo surgery

in studies. Patients may self-select biologics rather than surgery if presented the option in an shared decision-making approach with consideration of the efficacy, risks, and financial implications for long-term treatment. There is a need for development of biomarkers for CRSwNP that will help predict patient-specific treatments and to monitor response to such treatments.

The Unified Airway

CRSwNP is often associated with asthma. The upper and lower airways share similar histology and inflammatory infiltrates.⁶⁰ The immunopathologic features of CRSwNP, allergic rhinitis, and asthma share similar T2 immune response features,⁶¹ and there is a well-documented epidemiologic link between allergic rhinitis and asthma.⁶² There is also significant clinical evidence that treatment of rhinosinusitis results in improved outcomes for concurrent lower airway disease.⁶³⁻⁶⁵ Thus, in treating upper respiratory disease such as nasal polyposis, the lower airways should also be considered.

Moderate to Severe Asthma

Definition and Treatment

Asthma is a heterogeneous disease characterized by chronic airway inflammation. Asthma severity is determined by pulmonary function and the level of treatment that is required to control symptoms and exacerbations. In general, patients with moderate to severe persistent asthma require daily treatment with medium- or high-dose inhaled corticosteroid in conjunction with a long-acting bronchodilator. Poor symptom control and/or frequent exacerbations (≥ 2 /year) requiring oral steroids or serious exacerbations (≥ 1 /year) requiring hospitalization, despite appropriate daily inhaled medications, warrant consideration of adding a biologic to the treatment regimen.

Table 1. Pivotal Trials Supporting Approved Indications for Asthma.

Biologic agent	Inclusion criteria	Effects and outcomes	Notable findings
Omalizumab: IgE	12-75 y old, asthma inadequately controlled with ICS. Positive SPT to DF, DP, cockroach, dog, or cat. Total IgE 30-700 IU/mL	Reduced exacerbations (40% overall / 60% if EOS >300 cells/ μ L). Improved QOL. Decreased ICS use. Decreased asthma symptoms	Improved responses with $\uparrow$ FeNO and EOS >300 cell/ μ L. Improvement in FEV1 less consistent
Reslizumab: IL-5	18-75 y old, asthma inadequately controlled with ICS + LABA, LTRA, or cromolyn. ACQ $\geq$ 1.5. Sputum EOS >3%	Reduced exacerbations (approximately 50%-60%). Improved FEV1 (0.100-0.160 L)	Greatest improvement in FEV1 of all 3 anti-IL-5 agents
Mepolizumab: IL-5	18-82 y old, asthma inadequately controlled with ICS + 1 additional controller. $\geq$ 2 exacerbations in past year treated with OCS. EOS >150 cells/ μ L at screening; >300 cells/ μ L within past year	Reduced exacerbations (47%-53% overall / 79% if EOS >500 cells/ μ L). Improved FEV1 (0.100 L overall / 0.122 L if EOS >500 cell/ μ L)	Most efficacious with EOS >500 cell/ μ L
Benralizumab: IL-5	12-75 y old, asthma inadequately controlled with ICS + LABA. $\geq$ 2 exacerbations in past year	Reduced exacerbations (28%-51%). Improved FEV1 (0.100-0.160 L)	Efficacy correlates with increased EOS
Dupilumab: IL-4/13	>18 y old, asthma inadequately controlled on medium to high dose with ICS + LABA. $\geq$ 1 exacerbation in past year	Reduced exacerbations (60%-80%). Improved FEV1 (0.150-0.160 L)	Most effective if EOS >300 cell/ μ L

Abbreviations: ACQ, Asthma Control Questionnaire; DF, *Dermatophagoides farinae*; DP, *Dermatophagoides pteronyssinus*; EOS, eosinophils; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; IgE, immunoglobulin E; IL, interleukin; LABA, long-acting beta-agonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; QOL, quality of life; SPT, skin prick test.

Several biomarkers can be used to help guide patient management. Peripheral eosinophil count is used as a criterion for several biologic therapies for asthma. Blood eosinophils >150 to 400 cells/ μ L are associated with response to treatment with omalizumab, mepolizumab, benralizumab, reslizumab, and dupilumab.⁶⁶ Fractional exhaled nitric oxide (FeNO) >25 to 50 ppb is another biomarker that is associated with steroid responsiveness and T2 airway inflammation.⁶⁷ Sputum eosinophils have the strongest correlation with T2-high asthma, but this marker is more difficult to assess from a technical standpoint.⁶⁸ Specific IgE identifies the presence of atopy, and it is measured with a skin prick test or serum-specific IgE. Total IgE is easily measured and provides additional phenotypic information that is different from peripheral eosinophil count.⁶⁹

In patients with severe asthma, specific comorbidities can influence the choice of biologic therapy. For example, CRS with or without polyposis is common in moderate to severe asthma, and AD occurs frequently in people with allergic asthma. Allergic sensitization to allergens such as pets, dust mites, grass, and pollen should also be noted and their relevance established.⁷⁰

Approved Indications for Asthma Treatment With Biologics

Currently, various biologics are available for the add-on treatment of moderate and severe persistent asthma (**Table 1**). These include the anti-IgE agent omalizumab; the anti-IL-5

agents reslizumab, mepolizumab, and benralizumab; and the anti-IL4/13 agent dupilumab. Clinical trials for these agents enrolled patients with moderate and/or severe persistent asthma who were already being treated with inhaled corticosteroids and other adjuncts. Some studies enrolled patients with OCS-dependent asthma. While the clinical trials varied in design, consistent findings in the actively treated groups included a reduction in asthma exacerbations and improvement in pulmonary function. Studies of omalizumab showed that it could improve asthma symptoms and reduce overall inhaled steroid requirements.^{71,72} Omalizumab had a favorable impact on quality of life, pulmonary function, unscheduled outpatient visits, and hospitalizations.^{73,74}

Studies of reslizumab on patients with asthma⁷⁵⁻⁷⁹ showed that IV reslizumab significantly relieved asthma symptoms and improved asthma-related quality of life.

Studies of mepolizumab showed that it significantly reduced eosinophil counts.⁸⁰ Mepolizumab treatment also resulted in a significantly lower rate of exacerbations requiring hospitalization or an emergency department visit,⁸¹ improved disease-specific quality of life,⁸² reduced oral glucocorticoid dose requirements,⁸³ and demonstrated long-term safety.⁸⁴

Studies of benralizumab⁸⁵⁻⁸⁹ showed that patients with noneosinophilic disease did not improve with treatment. However, reduction in exacerbations and improved FEV1 and asthma symptom score are seen in patients with eosinophils $\geq$ 300 cells/ μ L.⁹⁰ Improvements can be maintained over an 8-week dosing interval,⁹¹ including a reduction in OCS use for patients with severe, uncontrolled OCS-dependent

Table 2. Monoclonal Antibodies for Use in Asthma.

	Omalizumab ¹	Mepolizumab ²	Reslizumab ³	Benralizumab ⁴	Dupilumab ⁵⁻⁷
Mechanism of action	Anti-IgE	Anti-IL-5	Anti-IL-5	Anti-IL-5R α	Anti-IL-4R α
Biomarker/test requirement	IgE 30-700 IU/mL	Blood EOS $\geq$ 150 cells/ μ L or history of blood EOS $\geq$ 300 cells/ μ L	Blood EOS $\geq$ 400 cells/ μ L	Blood EOS $\geq$ 300 cells/ μ L (phase III data); company messaging, $\geq$ 150 cells/ μ L	Blood EOS $\geq$ 150 cells/ μ L or FeNO $\geq$ 25 ppb
Patient population	$\geq$ 6 y old with moderate to severe asthma	$\geq$ 6 y old with severe asthma	$\geq$ 18 y old with severe asthma	$\geq$ 12 y old with severe asthma	$\geq$ 12 y old with moderate to severe asthma
Administration					
Route	SC-lyo; PFS	SC-lyo; PFS and AI at home	IV (phase III PFS SC trial failed)	PFS in office and AI at home	PFS and PFP at home
Dosing schedule	q2w/q4w	q4w	q4w	q8w (after 3 q4w doses)	q2w

Abbreviations: AI, autoinjector; EOS, eosinophils; FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E; IV, intravenous; PFS, prefilled syringe; PFP, pre-filled pen; q2w, every 2 weeks; q4w, every 4 weeks; q8w, every 8 weeks; SC, subcutaneous; SC-lyo, subcutaneous lyophilized powder.

eosinophilic asthma. Benralizumab studies have also demonstrated long-term safety: no new consequences of long-term eosinophil depletion occurred, and the incidence of other adverse events (including opportunistic infections) was similar during the second year of treatment.

Studies of dupilumab in asthma treatment have shown a beneficial effect on asthma control (Asthma Control Questionnaire-5) and symptoms.⁹² Those with baseline eosinophils $>300/\mu$ L or FeNO >25 ppb showed the greatest benefit in FEV1, but an asthma exacerbation reduction of 37% and 68% was seen among intervention patients with eosinophils <300 .^{93,94} Dupilumab treatment has also been demonstrated to reduce oral steroid requirements.⁹⁵

Which to Choose?

As clinicians start to relate the observable characteristics (phenotypes) present in patients to the mechanisms driving disease (endotypes) through the use of biomarkers, this will allow them to better understand how mechanisms of disease can give rise to many of the characteristic features of severe asthma. Identifying asthmatic patients by phenotype and, ideally, endotype—truly bringing us into the realm of precision medicine—will result in a thoughtful approach to choosing a biologic for patients with moderate to severe asthma. For our patients with T2 asthma, this means that there are now novel, targeted treatment options that have demonstrated reduced asthma exacerbations. Many factors need to be taken into account when creating an individualized treatment plan, particularly the likelihood of treatment responsiveness as well as patient preferences.

As we move into this era of personalized (precision) medicine, patients are playing a larger role in their health care. Shared decision making plays a crucial part in the decision of which biologic to choose.^{96,97} Shared decision making is

an approach where clinicians and patients share the best available evidence when faced with the task of making decisions and where patients are supported to consider options to achieve informed preferences.

Some factors to discuss with patients when choosing their treatment option include the following: patient age (currently, omalizumab and mepolizumab have an indication down to 6 years of age), frequency of dosing (every 2, 4, or 8 weeks), route of administration (SC vs IV), importance of weight-based dosing, and location of administration (dupilumab, the autoinjector form of mepolizumab, and the benralizumab pen can be self-administered at home; the others require treatment in a medical office setting; **Table 2**). Of course, our treatment choices are influenced by other factors, including cost and insurance coverage issues. Existence of poorly controlled comorbidities that can be treated by these agents should also be taken into consideration.

For allergic uncontrolled asthma in patients with a perennial allergen sensitization, omalizumab is currently a good choice for therapy. Choice of anti-IL-5 agent may be limited by peripheral eosinophil count. Although there is no strict eosinophil cut point for dupilumab, studies suggest better therapeutic response with higher eosinophil counts or elevated FeNO. All the biologics demonstrated an improvement in their primary endpoints of asthma exacerbations, but there were differences in their secondary endpoints, including lung function and symptoms. There are currently no approved targeted therapies for non-T2 asthma.

Choosing the right biologic for the right patient is challenging. Comparative head-to-head studies would be ideal; however, these are unlikely to occur. We are left with “real world” studies, meta-analyses, network meta-analyses, and our own clinical experience to help guide us in our decisions in choosing the right biologic.

Aspirin-Exacerbated Respiratory Disease

Definition and Diagnosis

One example of tightly linked upper and lower respiratory inflammatory disease is AERD. AERD (or N-ERD in many European countries) is defined by acute upper and lower respiratory tract reactions triggered by nonsteroidal anti-inflammatory drugs (NSAIDs), and this reaction is contingent on cyclooxygenase 1 inhibition. Patients with AERD typically have CRSwNP and asthma. AERD is considered to be a distinct endotype of asthma and CRSwNP.⁹⁸ Diagnosis of AERD begins with report of respiratory symptoms triggered by NSAID exposure.^{99,100} If the history of respiratory symptoms after NSAID exposure is unconvincing or the presence of chronic airway disease is uncertain, oral aspirin challenge or similar challenge can be performed to establish the diagnosis.¹⁰¹

Management

Treatment of AERD includes the use of oral and topical/inhaled corticosteroids, leukotriene modifiers, ASA desensitization, and ESS.¹⁰²

Biologics and AERD

Monoclonal antibodies are potential therapies in the treatment of AERD because these cases are so difficult to control with current treatment approaches. In a prospective cohort study of 21 patients, Hayashi et al noted that omalizumab administration produced a significant decrease in concentration of urinary LTE4 and a PGD2 metabolite in a postsurgical AERD population and helped to ameliorate upper and lower respiratory tract symptoms.¹⁰³

A small retrospective study of mepolizumab for patients with AERD demonstrated positive results. Fourteen participants who received at least 3 doses of mepolizumab were included, and outcomes such as absolute eosinophil count, SNOT-22 and ACT scores, and FEV1 were investigated. After receipt of at least 3 doses of mepolizumab, the absolute eosinophil count decreased significantly; SNOT-22 decreased by 17.7 points; and the ACT score significantly increased by 5.1. FEV1 percentage predicted increased by 6.3%. During this time, no patients required sinus surgery, and none needed to start or increase their dose of oral corticosteroids. This is the first study to show the efficacy of mepolizumab in patients with AERD.¹⁰⁴ However, this retrospective analysis of mepolizumab in AERD has limitations: it was not randomized, blinded, or placebo controlled, and it involved patient-reported data.

A substudy on AERD from a phase II trial of dupilumab was conducted by Laidlaw et al. Results for 19 patients with self-reported AERD were analyzed (8 in the dupilumab-treated group and 11 in the placebo group). At baseline, those with AERD had significantly higher Lund-Mackay CT scores than those without AERD (21.2 vs 17.5). Patients with AERD had worse olfactory function as measured by UPSIT score. This substudy by Laidlaw et al demonstrated that treatment with dupilumab improved UPSIT score by 10,

led to a 30-point reduction in the SNOT-22 score, and reduced the NPS by 2.5 points.¹⁰⁵

Eosinophilic Granulomatosis With Polyangiitis

Definition and Diagnosis

EGPA is defined by eosinophil-rich and necrotizing granulomatous inflammation/vasculitis that often involves the respiratory tract and other organ systems.¹⁰⁶ EGPA is distinguished from other small-vessel vasculitides by the presence of severe asthma and blood and tissue eosinophilia.¹⁰⁷ EGPA onset typically occurs in middle age among patients with asthma and eosinophilia, who go on to develop vasculitis. Laboratory findings for patients with EGPA generally include eosinophilia >10% or >1000 cells/ μ L, increased erythrocyte sedimentation rate, C-reactive protein, IgE, rheumatoid factor, and antinuclear antibody. There is perinuclear antineutrophil cytoplasmic antibody positivity in 30% to 40% of patients with EGPA, and this is associated with renal involvement, neuropathy, and biopsy-proven vasculitis.¹⁰⁸

The diagnosis of EGPA relies primarily on clinical parameters.^{109,110} The following criteria have been suggested for diagnosing and documenting EGPA:

- A history or presence of asthma
- Blood eosinophil level of 10% or an absolute eosinophil count >1000 cells/ μ L
- The presence of ≥ 2 of the following features:
 - Biopsy: eosinophilic vasculitis
 - Biopsy: perivascular eosinophilic infiltration or eosinophil-rich granulomatous inflammation
 - Neuropathy (mono- or polyneuropathy via motor deficit or nerve conduction abnormality)
 - Pulmonary infiltrates
 - Sinonasal abnormality
 - Cardiomyopathy
 - Glomerulonephritis (hematuria, red cell casts, proteinuria)
 - Alveolar hemorrhage (by bronchoalveolar lavage)
 - Palpable purpura
 - Antineutrophil cytoplasmic antibody positivity (anti-MPO [myeloperoxidase], perinuclear antineutrophil cytoplasmic antibody)

Management

Treatment of EGPA should begin as early as possible. Steroids inhibit eosinophil colony growth and survival as well as cytokine production, making these drugs effective in >90% of patients with EGPA. However, some patients do not respond to steroids, and even among patients in whom these drugs are effective, EGPA often recurs with steroid withdrawal. As a result, very few patients with EGPA can fully discontinue steroid treatment. When EGPA affects critical organs, patients are usually treated with corticosteroids

combined with another immunosuppressive drug, such as cyclophosphamide, methotrexate, or azathioprine.

Approved Indications for EGPA Treatment With Biologics

Mepolizumab is indicated for treatment of adults with EGPA. The recommended dose of mepolizumab for patients with EGPA is 300 mg administered once every 4 weeks as 3 separate 100-mg SC injections into the upper arm, thigh, or abdomen.¹¹¹

Pivotal Trials Supporting Approved Indications

Mepolizumab. Mepolizumab's indication for use in treating adults with EGPA was based on findings from the randomized placebo-controlled MIRRA trial.¹¹² This double-blind parallel-group trial enrolled EGPA patients aged ≥ 18 years with a history of relapsing or refractory disease who were taking stable prednisolone/prednisone for ≥ 4 weeks. The 52-week trial included administration of SC mepolizumab (300 mg) plus standard of care ($n = 65$) or placebo plus standard of care ($n = 65$). Primary efficacy endpoints were total accrued weeks of remission (defined as Birmingham Vasculitis Activity Score¹¹³ of 0 and prednisolone/prednisone dose ≤ 4 mg/d) over 52 weeks and the proportion of participants in remission at weeks 36 and 48. Secondary endpoints included time to first relapse of EGPA and average corticosteroid dose during weeks 48 to 52.

During the trial, the mepolizumab arm demonstrated significantly more weeks of accrued remission, a higher remission rate by week 12, and a longer time to first major relapse. Median daily glucocorticoid dosing was lower among patients treated with mepolizumab, starting in week 5 of the trial and continuing for 8 weeks beyond the treatment period. Mepolizumab improved asthma control scores (Asthma Control Questionnaire-6) starting in week 4 of the trial, and these differences were present at 12 of 13 time points over the course of the trial. In contrast, Birmingham Vasculitis Activity Scores differed little between the treatment arms, and findings for SNOT-22 scores were mixed during follow-up.

Chronic Spontaneous Urticaria

Definition and Diagnosis

CSU (or CIU [chronic idiopathic urticaria]) is characterized by hives with or without angioedema for >6 weeks with no apparent external trigger. CSU lesions are typically edematous pink or red wheals of variable size and shape with surrounding erythema, and they are generally pruritic. Individual urticarial lesions usually fade within 24 to 48 hours, but new lesions may develop simultaneously at other sites. The diagnosis of CSU is made thorough history and physical examination; diagnostic testing is not usually warranted.^{114,115}

Management

H₁-antihistamines are the mainstay of treatment for CSU, and nonsedating antihistamines are preferred. In some cases, antihistamine doses up to 4 times the labeled dose are required for adequate symptomatic control.¹¹⁴ Potential add-on treatments include leukotriene receptor antagonists, systemic corticosteroids, cyclosporine, dapsone, and methotrexate; these all lack approval for CSU and have low-quality clinical evidence supporting their use. Long-term use of systemic corticosteroids is not recommended in patients with CSU. In patients unresponsive to antihistamines, current guidelines recommend the use of omalizumab.

Approved Indications for Urticaria Treatment With Biologics

Omalizumab. Omalizumab is an anti-IgE antibody that is FDA approved for treatment of CSU in adults and adolescents ≥ 12 years of age who remain symptomatic despite H₁ antihistamine treatment. In CSU, omalizumab is administered at 150 mg or 300 mg SC every 4 weeks independent of serum IgE and body weight. The appropriate duration of therapy for CSU has not been determined, so patients must be reassessed periodically to determine the need for continued therapy. The pivotal trials that supported the CSU indication are summarized in **Table 3**.¹¹⁶⁻¹¹⁸

Moderate to Severe AD

Definition and Diagnosis

Diagnosis of AD is made clinically on the basis of historical features, distribution and morphology of skin lesions, and associated clinical signs. Laboratory testing is used occasionally to exclude alternate diagnoses. The American Academy of Dermatology clinical guidelines¹¹⁹ require the presence of 4 key features for diagnosis: pruritus, eczema, a chronic or relapsing history, and typical morphology and age-specific distribution patterns. Facial, neck, and extensor eczematous lesions are seen in infants and children; flexural lesions are seen in any age group; and the groin and axillary regions are spared. Additional features that support the diagnosis of AD include early age of onset, presence of atopy, personal and/or family history of AD, IgE reactivity, and xerosis (dry skin).

Management

AD is characterized by a relapsing and remitting nature, with periods of relative improvement interspersed with periods of flares or exacerbations over many years. Management of AD involves maintenance therapy and treatment of exacerbations. Bathing, moisturization, and trigger avoidance strategies are the main nonpharmacologic interventions. Topical prescription medications include topical corticosteroids, topical calcineurin inhibitors, and crisaborole ointment.

Table 3. Pivotal Trials Supporting Approved Indications for Omalizumab for CSU.

Trial	Study design	Inclusion criteria	Primary outcome	Effects
ASTERIA I (N = 329)	Evaluate efficacy and safety of omalizumab (75 mg, 150 mg, 300 mg) or placebo. Double-blind treatment period was 24 wk	12-75 y old with uncontrolled CSU for 8 mo despite approved doses of H ₁ -antihistamines	Change from baseline in a weekly ISS at week 12	Diminished clinical symptoms and signs of CSU
ASTERIA II (N = 323)	Evaluate efficacy and safety of omalizumab (75 mg, 150 mg, 300 mg) or placebo. Double-blind treatment period was 12 wk	≥ 12 y old with uncontrolled CSU for 6 mo despite approved doses of H ₁ -antihistamines	Change from baseline in a weekly ISS at week 12	Diminished clinical symptoms and signs of CSU
GLACIAL (N = 336)	Evaluate efficacy and safety of omalizumab (300 mg) vs placebo	12-75 y old with uncontrolled CSU for 8 mo despite treatment with H ₁ -antihistamines at up to 4 times the approved dose plus H ₂ -antihistamines, LTRAs, or both	Asses safety of omalizumab in those with different add-on therapies. Key efficacy endpoint was change in mean weekly ISS at week 12	Diminished clinical symptoms and signs of CSU. Similar adverse events between omalizumab and placebo groups

Abbreviations: CSU, chronic spontaneous urticaria; ISS, itch severity score; LTRA, leukotriene receptor antagonist.

Approved Indications for AD Treatment With Biologics

Dupilumab is FDA approved for treatment of patients aged ≥6 years with moderate to severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Dupilumab can be used with or without topical corticosteroids. In adults, an initial dose of 600 mg SC is administered as two 300-mg injections in different injection sites, followed by 300 mg SC every 2 weeks. The most common adverse reactions are injection site reactions, conjunctivitis, blepharitis, oral herpes, keratitis, eye pruritus, other herpes simplex virus infection, and dry eye.¹²⁰

Pivotal Trials Supporting Approved Indications

Three clinical trials of dupilumab treatment led to the current indication in patients with AD. These trials are summarized in **Table 4**.^{121,122}

Clinical Practicalities of Using Biologics

Clinicians should ensure that they have the staff, equipment, and knowledge to prepare, store, and administer these treatments; to monitor the effects of treatment; and to recognize and treat adverse effects at the point of administration and over the entire course of treatment. Given the many unknowns of biologic therapies—including optimal patient selection, timing of treatment, costs, and unknown long-term risks—it is important to include a patient-centered decision-making approach when considering treatment. Biologic agents have different dosing schedules, and patient preference may play a role in choosing the agent employed. Insurance coverage and out-of-pocket costs will also factor into whether patients can receive biologic therapies (**Table 5**).

Omalizumab

Although omalizumab is indicated for asthma and CSU, the dosing in these 2 patient populations differs. In asthma, the dose and dosing frequency are determined by body weight and serum total IgE level before the start of treatment. By contrast, in CSU, omalizumab (150 or 300 mg) is administered every 4 weeks, independent of serum IgE or body weight. Omalizumab has 2 formulation options: a prefilled syringe and a powder formulation that requires reconstitution with sterile water.

Omalizumab must be administered in a health care setting by health care providers prepared to manage life-threatening anaphylaxis. Anaphylaxis has been reported in 0.1% to 0.2% of patients, a side effect that resulted in a black box warning. The Omalizumab Joint Task Force recommended that patients be kept under observation for 2 hours for the first 3 injections and 30 minutes for each subsequent injection. However, these observation periods can be modified by a physician's clinical judgment after discussion of risks with the patient.¹²³ Discontinuation of omalizumab is recommended if patients experience a severe hypersensitivity reaction.

Mepolizumab

Mepolizumab dosing for asthma in patients ≥12 years old is SC 100 mg; in patients 6 to 11 years old, it is 40 mg every 4 weeks independent of weight and eosinophil levels. Mepolizumab is available as a lyophilized powder for reconstitution in sterile water, but it is also available in a prefilled syringe or an autoinjector for at-home administration. For patients with EGPA, the 300-mg dose requires three 100-mg injections administered at least 5 cm apart.

Table 4. Pivotal Trials Supporting Approved Indications for Dupilumab for AD.

Trial	Study design	Inclusion criteria	Primary outcome	Effects
SOLO 1 (N = 671)	Evaluate efficacy of dupilumab 300 mg q2w (after 600-mg loading dose), dupilumab 300 mg q1w (after 600-mg loading dose), placebo	≥ 18 y old with moderate to severe AD inadequately controlled with topical treatment; chronic AD for at least 3 y; and IGA score of 3 or 4	Percentage with IGA score of 0 or 1 (clear or almost clear) at 16 wk	38% in q2w arm and 37% in q1w arm had IGA score of 0 to 1. 51% in q2w arm and 52% in q1w arm achieved EASI-75
SOLO 2 (N = 708)	Evaluate efficacy of dupilumab 300 mg q2w (after 600-mg loading dose), dupilumab 300 mg q1w (after 600-mg loading dose), placebo	≥ 18 y old with moderate to severe AD inadequately controlled with topical treatment; chronic AD for at least 3 y; and IGA score of 3 or 4	Percentage with IGA score of 0 or 1 at 16 wk	36% in q2w arm and 36% in q1w arm had IGA score of 0 to 1. 44% in q2w arm and 48% in q1w arm achieved EASI-75
CHRONOS (N = 740)	Evaluate dupilumab treatment and concomitant TCS: dupilumab 300 mg q1w + TCS, dupilumab 300 mg q2w + TCS, placebo + TCS. Determine efficacy and long term safety	≥ 18 y old with moderate to severe AD inadequately controlled with topical treatment; chronic AD for at least 3 y; and IGA score of 3	Percentage with IGA score of 0 or 1	64% in q1w arm + TCS and 65% in q2w + TCS arm sustained EASI-75. 39% in q1w arm had IGA score of 0 to 1 at 26 wk and 39% in q2w arm had IGA score 0 or 1 at 16 wk

Abbreviations: AD, atopic dermatitis; EASI-75, improvement of ≥75% in Eczema Area and Severity Index; IGA, Investigators Global Assessment; q1w, every week; q2w, every 2 weeks; TCS, topical corticosteroid.

Table 5. Monoclonal Antibodies and Their FDA-Approved Indications.

Monoclonal antibody: mechanism of action	Patient type	Dosing
Asthma		
Omalizumab: IgE (at Fcε3)	IgE, 30-700; positive SPT for at least 1 perennial allergen; moderate to severe asthma. Age ≥ 6 y	SC q2w to q4w based on IgE and weight
Mepolizumab: IL-5	Blood EOS >300 within 12 mo or >150 within 6 wk; severe asthma. Age ≥ 6 y	SC q4w
Reslizumab: IL-5	Sputum EOS >3%; blood EOS >400; severe asthma. Age ≥ 18 y	IV q4w
Benralizumab: IL-5Rα	Severe asthma; >1 exacerbation/y; EOS >300. Age ≥ 12 y	SC q8w (first 3 doses monthly)
Dupilumab: IL-4Rα	Moderate to severe asthma with an eosinophilic phenotype or with OCS-dependent asthma regardless of phenotype. Age ≥ 12 y	SC q2w
Atopic dermatitis		
Dupilumab: IL-4Rα	Moderate to severe AD. Age ≥ 6 y	SC q2w
Chronic spontaneous urticaria		
Omalizumab: IgE	Moderate to severe CSU. Age ≥ 12 y	SC q4w
Eosinophilic granulomatosis with polyangiitis		
Mepolizumab: IL-5	EGPA on stable oral steroids. Age ≥ 18 y	SC q4w
CRSwNP		
Dupilumab: IL-4Rα	CRSwNP in adults whose disease is not controlled. Age ≥ 18 y	SC q2w

Abbreviations: AD, atopic dermatitis; CRSwNP, chronic rhinosinusitis with nasal polyposis; CSU, chronic spontaneous urticaria; EGPA, eosinophilic granulomatosis with polyangiitis; EOS, eosinophils; FDA, Food and Drug Administration; IgE, immunoglobulin E; IV, intravenous; OCS, oral corticosteroids; q2w, every 2 weeks; q4w, every 4 weeks; q8w, every 8 weeks; SC, subcutaneous; SPT, skin prick test.

Herpes zoster has occurred in patients receiving mepolizumab in controlled clinical trials, and vaccination should be considered if medically appropriate. Patients with preexisting helminth infections should be treated prior to mepolizumab therapy. Reports of anaphylaxis have been received in postmarketing surveillance.

Reslizumab

Reslizumab is indicated for treatment of patients aged ≥ 18 years with severe asthma and eosinophils ≥ 400 . Reslizumab is administered as an IV infusion over 20 to 50 minutes, and dosing is weight based. Anaphylaxis occurred in 0.3% of treated subjects in placebo-controlled studies; malignancies were noted in 0.6% of treated subjects versus 0.3% of placebo; and helminth and parasitic infections have been observed. Patients with preexisting helminth infections must be treated before initiating reslizumab. If patients become infected while taking reslizumab and do not respond to anti-helminth treatment, reslizumab treatment should be discontinued until the infection resolves.

Benralizumab

Benralizumab is indicated for treatment of severe eosinophilic asthma in patients aged ≥ 12 years. This medication is administered by SC injection, and dosing is independent of weight and eosinophil levels. The recommended dose is 30 mg once every 4 weeks for the first 3 doses, then once every 8 weeks thereafter. Patients with preexisting helminth infections should be treated before initiating therapy with benralizumab. Benralizumab can be administered by a health care professional; however, there is an additional option for at-home administration with a benralizumab pen.

Dupilumab

Dupilumab is indicated for moderate to severe asthma (or OCS-dependent asthma, regardless of phenotype) in patients ≥ 12 years old, moderate to severe AD in patients ≥ 6 years old, and adults with uncontrolled CRSwNP. Dupilumab has different dosing schedules for patients with AD, asthma, and CRSwNP. For adults with AD, dupilumab is not weight or eosinophil based, but in adolescents aged 12 to 17 years with AD, it is dosed above and below 60 kg with 200- and 300-mg doses available. For AD, in the pediatric (6–11 years of age) population, dupilumab is given either every 2 weeks (200 mg) or four weeks (300 mg), based on weight, following an initial loading dose. For patients aged 12 to 17 years with asthma, either dose can be used, but if patients are OCS dependent or if they have comorbid AD, the 300-mg dose is suggested. There is no loading dose for CRSwNP. The medication is delivered in prefilled syringes or prefilled pens for SC administration. Conjunctivitis was the most frequently reported adverse event in trials of this drug, with most patients recovering relatively quickly. For patients with asthma, clinicians should be alert to vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy in patients with eosinophilia, as these may be associated with a reduction of OCSs.

Conclusion

Biologic therapy provides a new and promising modality for patients with severe eosinophilic diseases (asthma, CRSwNP, AERD, EGPA) and other inflammatory conditions, such as AD and CSU. Clinical trials have demonstrated that these biologic agents improve objective and subjective parameters of disease, particularly in severe cases. At the same time, biologic therapy appears to reduce the need for systemic steroid treatment and the attendant risks of these steroids.

The introduction of multiple biologic agents in a relatively short period has resulted in a number of unanswered questions regarding optimal use. The costs of new biologic agents should be balanced against their relative benefits. Costs are a factor in any long-term treatment, and biologic agents are expensive. Cost-utility analysis is a common type of cost-effectiveness analysis in which quality-adjusted life years (QALYs) are used as the measure of benefit. In the United States, therapies are generally considered cost-effective at ceilings of \$50,000 to \$150,000.¹²⁴

A recent report by the Institute for Clinical and Economic Review (ICER)¹²⁵ for the treatment of asthma associated with type 2 inflammation concluded that biologic agents provide gains in quality-adjusted survival over standard care alone; however, they seem to be priced higher than the modeled benefits over a lifetime horizon at commonly accepted cost-effective thresholds. The ICER base case incremental cost-effectiveness ratio analysis found that biologics range from \$325,000 to \$391,000 (2018 dollars) per QALY gained. ICER defines a value-based benchmark for a drug as the price that would achieve incremental cost-effectiveness ratios between \$100,000 to \$150,000 per QALY gained. No biologic agent achieved the likelihood of meeting that threshold. The ICER report recommended that biologic costs would need to be reduced to 62% to 80% from their 2018 wholesale acquisition cost, depending on the biologic to meet this threshold. Biologics do need to become cost-effective for patients to have access to therapy long-term. Scangas et al evaluated the cost-effectiveness of dupilumab versus ESS for patients with CRSwNP and found that the ESS strategy cost \$50,436.99 and produced 9.80 QALYs. The dupilumab treatment strategy cost \$536,420.22 and produced 8.95 QALYs. With 1-way sensitivity analyses, the authors determined that ESS was cost-effective versus dupilumab, regardless of the frequency of revision surgery and at any yearly cost of dupilumab above \$855.¹²⁶

In general, initiation of biologic treatment should depend on a failure of conventional treatments. Thus, medication adherence, frequency of exacerbations, and severity of symptoms need to be thoroughly evaluated before the use of a biologic agent is considered. In nasal polyp disease, the adequacy of previous surgery should also be assessed. Disease phenotype/endotype should be elucidated to the extent possible to help determine the appropriate biologic agent to employ. Therefore, biomarkers are needed to aid in selection of the most appropriate biologic agents for a patient. Ideally, these biomarkers would also be able to

predict response and track improvement. Finally, the identification of new endotypes through biomarkers would allow for new biologic therapies that could target specific pathways beyond those currently available.

The introduction of biologic therapies has led to groundbreaking improvements for patients with severe inflammatory diseases that are important in allergy and rhinology. These biologic agents are finding an important place in our treatment paradigms.

Author Contributions

Cecelia C. Damask, coordination of project, preparation work for roundtable discussion, presentation of assigned topics to the roundtable, participation in roundtable discussion, contributed to creation of manuscript, and editing of manuscript; **Matthew W. Ryan**, preparation work for roundtable discussion, presentation of assigned topics to the roundtable, participation in roundtable discussion, contributed to creation of manuscript, and editing of manuscript; **Thomas B. Casale**, preparation work for roundtable discussion, presentation of assigned topics to the roundtable, participation in roundtable discussion, contributed to creation of manuscript, and editing of manuscript; **Mario Castro**, preparation work for roundtable discussion, presentation of assigned topics to the roundtable, participation in roundtable discussion, and contributed to creation of manuscript; **Christine B. Franzese**, preparation work for roundtable discussion, presentation of assigned topics to the roundtable, participation in roundtable discussion, and contributed to creation of manuscript; **Stella E. Lee**, preparation work for roundtable discussion, presentation of assigned topics to the roundtable, participation in roundtable discussion, and contributed to creation of manuscript; **Joshua M. Levy**, preparation work for roundtable discussion, presentation of assigned topics to the roundtable, participation in roundtable discussion, contributed to creation of manuscript, and editing of manuscript; **Sandra Y. Lin**, preparation work for roundtable discussion, presentation of assigned topics to the roundtable, participation in roundtable discussion, and contributed to creation of manuscript; **Peter A. Lio**, preparation work for roundtable discussion, presentation of assigned topics to the roundtable, participation in roundtable discussion, contributed to creation of manuscript, and editing of manuscript; **Anju T. Peters**, preparation work for roundtable discussion, presentation of assigned topics to the roundtable, participation in roundtable discussion, contributed to creation of manuscript, and editing of manuscript; **Michael P. Platt**, preparation work for roundtable discussion, presentation of assigned topics to the roundtable, participation in roundtable discussion, contributed to creation of manuscript, and editing of manuscript; **Andrew A. White**, preparation work for roundtable discussion, presentation of assigned topics to the roundtable, participation in roundtable discussion, contributed to creation of manuscript, and editing of manuscript.

Disclosures

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