Evolving Treatment Strategies in Type 2 Inflammatory Disease

TREATMENT OF ATOPIC CONDITIONS, such as atopic dermatitis (AD), asthma, and chronic rhinosinusitis with nasal polyps (CRSwNP), has traditionally encompassed several treatment modalities and delivery mechanisms to reduce inflammatory response. In recent years, increased knowledge regarding the role of type 2 inflammation in these conditions has coincided with the development of therapies that target specific inflammatory mediators and pathways. These targeted therapies provide new opportunities to optimize care and reduce adverse events (AEs). Specifically, agents targeting various interleukin (IL) pathways offer the potential to halt the type 2 inflammatory process. This article reviews the current treatment paradigms for AD, asthma, and CRSwNP, with an emphasis on the role of IL-based therapies in their management.

Atopic Dermatitis

AD is a skin disease defined by chronic and pruritic inflammation; it follows a relapsing course. It is associated with elevated serum immunoglobulin (IgE) levels and a genetic and environmental history of type I allergies, allergic rhinitis, and asthma.[1,2] AD occurs most frequently in children, with a prevalence of 10% to 20% in the United States. Children with AD often present with symptoms within the first year of life.[1]

Treatment Overview

Multiple guidelines are available for the treatment of atopic dermatitis, the broader goals of which are to provide symptom relief and decrease the severity of itching.[1-3] In addition to potentially improving quality of life, appropriate therapy can also help prevent significant complications, such as infection, sleep disturbance, behavioral problems, and growth impairment.[1-3]

Topical Agents

Topical agents are used frequently in the treatment of AD, even in severe cases, in which they are used in combination with systemic therapy or phototherapy.[2] Topical corticosteroids are recommended in adult and pediatric patients with AD who have not responded to proper skin care regimens and regular use of emollients.[2] Topical corticosteroids act on different immune cells, including T lymphocytes, monocytes, macrophages, and dendritic cells. Moreover, these agents have been employed to manage active inflammatory disease and prevent relapse in AD for 60 years.[2]

Topical calcineurin inhibitors (TCIs) are second-line antiinflammatory therapies used to treat AD. TCIs can be used in more sensitive areas or as an alternative to steroids, such as in situations of steroid recalcitrance or steroid-induced atrophy. TCIs inhibit calcineurin-dependent T-cell activation and block the production of proinflammatory cytokines and of mediators of the AD inflammatory reaction. Topical tacrolimus ointment (0.03% and 0.1% strengths) and pimecrolimus cream (1% strength) have shown to be effective in adults and children with active disease in the short term (3-12 weeks) and long term (up to 12 months).[2]

Patients with AD have a compromised physical barrier on the skin and thus are prone to infections. If an infection is present, the use of topical antimicrobials may be warranted. For instance, bleach baths and intranasal mupirocin may be used in patients with moderate to severe disease who have signs of a secondary bacterial infection to reduce the severity of the AD.[2]

Phototherapy and Systemic Immunomodulatory Agents

According to guidelines from the American Academy of Dermatology, phototherapy is a second-line treatment and can be used in maintenance therapy of chronic disease.[4] Several factors affect the utility of phototherapy as a viable modality in AD, such as availability, cost, patient skin type, skin cancer history, and patient use of photosensitizing medications.[4] Phototherapy treatments must be administered under the guidance of a physician who has knowledge of phototherapy.

Systemic immunomodulatory agents are reserved for the subset of adult and pediatric patients who have uncontrolled disease that is having a significant negative physical, emotional, or social impact. These agents are best used for limited time periods, such as for acute, severe exacerbations of the disease, or as short-term bridge therapy to other systemic, steroid-free therapy.[4]

IL Inhibitors

Many of the available treatment options for AD offer symptom relief rather than addressing the core pathways through which the inflammatory cascade takes place. The FDA approval of the IL-4/IL-13 inhibitor dupilumab in 2017 for the treatment of adults with AD represented a new step in the management of AD, prompting the development of multidisciplinary consensus

recommendations focused on novel therapies for the diagnosis and treatment of disease.[3]

Dupilumab binds to the α subunit of the IL-4 receptor, which modifies the signaling of both the IL-4 and IL-13 pathways.[5-7] It is currently the only monoclonal antibody approved for the treatment of AD. The initial approval of dupilumab in adults with moderate to severe AD was based on findings from three phase 3 trials: SOLO 1, SOLO 2, and CHRONOS.[5,6] SOLO 1 and SOLO 2 were identical in design and enrolled adults with moderate to severe AD whose disease was inadequately controlled by topical treatment. Patients with AD were randomized 1:1:1 and received 300 mg doses of weekly dupilumab subcutaneously, placebo weekly, or a 300-mg dose of dupilumab every other week alternating with placebo for 16 weeks. The proportion of patients who had both an Investigator's Global Assessment (IGA) score of 0 or 1 (clear or almost clear) and a score that had gone down at least 2 points between baseline and week 16 was the primary outcome of the study.[5]

Totals of 671 and 708 patients were enrolled in SOLO 1 and SOLO 2, respectively. At 16 weeks, 38% of patients in SOLO 1 and 36% in SOLO 2 who received dupilumab 300 mg every 2 weeks achieved clear or almost clear skin.[5] Among patients who received either regimen of dupilumab, 51% and 44% in SOLO 1 and SOLO 2, respectively, achieved 75% or greater reduction in the Eczema Area and Severity Index (EASI) score. Patients who received dupilumab saw such improvements as reduction in pruritus, decreased symptoms of anxiety or depression, and improvement in quality of life. However, patients in the dupilumab group saw more injection-site reactions and conjunctivitis than those in the placebo group.[5]

The CHRONOS study examined the use of dupilumab with topical steroids in patients with AD.[6] At 16 weeks, 39% of patients receiving dupilumab 300 mg every 2 weeks, along with topical corticosteroids, achieved clear or almost clear skin, and 69% of patients receiving that combination achieved EASI-75. Additionally, 59% of patients receiving the dupilumab/topical corticosteroid combination achieved a ≥4-point improvement in patient-reported daily itch intensity. At 52 weeks, 36% of patients receiving the dupilumab/topical corticosteroid combination every 2 weeks achieved clear or almost clear skin.

Findings from the LIBERTY AD SOLO trials, presented in March 2018, indicated that dupilumab was effective for adults with AD, even those with comorbid asthma.[8] Results from a 16-week study showed that more patients with comorbid asthma receiving dupilumab 300 mg once or twice weekly achieved IGA 0/1 versus placebo (34.1%/31.9% vs 9.3%), EASI-75 (50.0%/47.4% vs 13.7%), and Peak Pruritus Numerical Rating Scale (NRS) improvement ≥4 (37.9%/37.8% vs 9.3%; $P<.0001$ for all). Patients without comorbid asthma showed similar results. The investigators noted that dupilumab-treated patients with and without comorbid asthma had comparable and significant improvements in AD signs and symptoms. More studies are needed to evaluate the benefits of dupilumab in patients with severe AD with comorbid type 2 inflammatory conditions.

Although the 2017 FDA approval of dupilumab for adults with moderate to severe AD was significant, an unmet need for new monotherapies in the pediatric population persisted until March 2019, when dupilumab was approved to treat children aged 12 to 17 years with moderate to severe AD.[7] Prior to that approval, a multicenter, randomized, double-blind, placebo-controlled, phase 3 trial included patients of those ages with moderate to severe AD. Eligible patients also had an Eczema Area Severity Index score of at least 16 (on a scale of 0 to 72), a minimum of 10% body surface area involvement, and previous inadequate response to topical medication. Patients in the study with a baseline weight of less than 60 kg received an initial dose of 400 mg followed by doses of 200 mg for 16 weeks. Those with a baseline weight of at least 60 kg received an initial dose of 600 mg, followed by weekly doses of 300 mg for 16 weeks. Patients were considered nonresponders if they received rescue treatment at the discretion of the investigator. The primary outcome was the proportion of participants with an IGA score of clear or almost clear and at least a 2-point improvement from baseline to week 16. Other end points were the proportion of subjects with EASI-75 or EASI-90 and a reduction in itch as measured by the Peak Pruritus NRS (≥4-point improvement).

After 16 weeks, results were similar to those evaluating dupilumab in adults with AD. Average improvement in EASI was 66% in those treated with dupilumab, compared with 24% for placebo.[7] Additionally, 42% of patients treated with dupilumab achieved at least a 75% improvement in skin improvement, compared with 8% of those receiving placebo. Also of note, 24% of patients with an IGA score of clear or almost clear who received dupilumab based on their weight reached the primary outcome, compared with 2% of the placebo arm. Dupilumab was also shown to significantly reduce itch in 37% of those treated, compared with 5% for placebo.

Long-term safety and efficacy of the drug in adolescents was assessed in an open-label extension study. These results were consistent through 52 weeks, with common AEs being injection-site reactions, eye and eyelid inflammation, throat pain, and cold sores in or on the mouth and lips.[7]

The new indication for dupilumab for adolescents aged 12 to 17 years represents a significant step in

the trajectory of AD care. Additionally, investigations continue for a potential indication in patients aged 6 to 11 years with severe AD not well controlled by topical medications[9]; in 2016, dupilumab was granted breakthrough designation by the FDA for this indication. See **Table 1** lists ongoing clinical trials evaluating dupilumab in atopic dermatitis.[9-13]

Investigational IL Inhibitors for Atopic Dermatitis

Several IL inhibitors are in development for the treatment of AD. Lebrikizumab, which targets the IL-13 pathway, has shown promising results in a phase 2, randomized, placebo-controlled, double-blind study.[14] Eligible adults with AD were required to use topical corticosteroids for 2 weeks and were then randomized 1:1:1:1 into 4 arms: a single 125-mg lebrikizumab dose; a single 250-mg lebrikizumab dose; 125-mg doses of lebrikizumab every 4 weeks for 12 weeks; or placebo every 4 weeks for 12 weeks. The primary end point was achievement of an EASI-50 score. Of the patients who received lebrikizumab, 82.4% achieved the primary end point with 125 mg doses every 4 weeks ($P = .026$). In the placebo arm, 62.3% of patients reached the primary end point. Patients who received a single dose of the drug experienced no significant improvement.[14]

In March 2019, lebrikizumab manufacturer Dermira revealed results of a 16-week phase 2b trial showing that 33.7% of patients treated with lebrikizumab every 4 weeks achieved clear or near-clear skin, compared with 15.3% of those receiving placebo. Additionally, 56.1% of patients in this group achieved a reduction of at least 75% from baseline in EASI score, while 36.1% of patients achieved a 90% reduction. Safety data were consistent with those of previous studies. The company is expected to initiate its phase 3 clinical trial program by the end of 2019.[15]

Tralokinumab is another agent in development that targets IL-13. In a phase 2b study, adults (N = 204) with moderate to severe AD were randomized 1:1:1:1 to receive 45 mg, 150 mg, or 300 mg of subcutaneous tralokinumab, or placebo, every 2 weeks for 12 weeks, along with topical glucocorticoids.[16] The primary end point was the percentage of participants with a reduction of >2 grades from the baseline in the EASI score and with an IGA response (0/1 score) at week 12. At 12 weeks, patients receiving 300 mg of tralokinumab were significantly improved from baseline in EASI score versus placebo (adjusted mean difference, –4.94; 95% CI, –8.76 to –1.13; $P = .01$), and a greater percentage of participants achieved an IGA response (26.7% vs 11.8%). Those with increased IL-13 activity experienced greater responses.[16] Phase 3 trials for tralokinumab are currently underway.

Several other agents are being evaluated that target IL pathways in AD, including IL-12, IL-23, IL-17A, IL-31/31R, TLSP, and anti-OX40. Additional areas of research, beyond IL pathways, may involve various immune and nonimmune mediated responses.[17]

Asthma

Asthma is typically characterized by airway inflammation, structural changes to the bronchial wall, and bronchial hyperresponsiveness with clinical episodes of wheeze, shortness of breath, chest tightness, and cough.[18]

Treatment Overview

Guidelines from the National Asthma Education and Prevention Program for initial diagnosis and treatment of asthma involve controlling the disease with appropriate medication for long-term management and making

Table 1. Current Ongoing US Clinical Trials for Dupilumab for the Treatment of Atopic Dermatitis[9-13a]

Name	NCT#	Status	Estimated Completion Date
Immunogenetic Profiling of Dupilumab for the Treatment of Atopic Dermatitis	NCT03293030	Recruiting	October 2019
Study to Investigate the Efficacy and Safety of Dupilumab Administered With Topical Corticosteroids (TCS) in Participants ≥6 to <12 Years With Severe Atopic Dermatitis (AD)	NCT003345914	Active, not recruiting	June 2020
The Impact of Dupilumab on Quality of Life in Moderate to Severe Atopic Dermatitis Patients	NCT03667014	Recruiting	October 2020
A Study to Compare Safety and Efficacy of Upadacitinib to Dupilumab in Adult Participants With Moderate to Severe Atopic Dermatitis	NCT03738397	Recruiting	September 2020
Study to Assess the Long-Term Safety of Dupilumab Administered in Participants ≥6 Months to <18 years of Age With Atopic Dermatitis (AD)	NCT02612454	Enrolling by invitation	November 2023

[a]Not a complete list of trials.

therapy adjustments as necessary on an individual basis. Initial visits consist of diagnosis, assessment of severity, initiating and demonstrating medication use, developing a treatment plan, and scheduling a follow-up visit. Follow-up appointments are recommended to assess how the patient is responding to treatment and to determine whether adjustments are needed to the asthma therapy plan and/or medication.[19]

The existing goal of asthma therapy is to provide long-term management and improve overall symptom control. To successfully achieve disease control, it is essential to do the following to reduce impairment and risk[19]:

- Avoid exacerbations.
- Prevent chronic symptoms.
- Decrease use of short-acting β2 agonists.
- Maintain lung function and normal activities.
- Minimize the need for emergency department visits and hospitalizations.
- Reduce AEs.
- Prevent loss of lung function.

Additionally, patient education, environmental control, and management of comorbidities play an important role in asthma management.[19]

Several therapeutic options are available to help control disease symptoms and reduce exacerbations. Often, treatment selection is dependent on disease severity.[20]

Corticosteroids

Two types of corticosteroids are indicated for the treatment of asthma. Inhaled corticosteroids (ICS) provide the most effective long-term control for persistent asthma, because they reduce inflammation and prevent symptoms when administered daily (recommended use).[19] ICS have shown activity on multiple inflammatory cell types, including mast cells, eosinophils, neutrophils, macrophages, and lymphocytes, as well as inflammatory mediators (eg, histamines, eicosanoids, leukotrienes, cytokines). The benefits of ICS are not immediate; it may take 1 to 2 weeks or longer for benefits to be completely present.[21] Oral corticosteroids may be given as a short-course treatment if a patient is having an acute exacerbation or in cases of uncontrolled severe disease. Regardless of delivery mechanism, chronic use of systemic oral corticosteroids is associated with a significant occurrence of AEs.[22]

β2 Agonists and Leukotriene-Receptor Antagonists

Short-acting β2 agonists (SABAs) are used for quick relief of asthma symptoms to manage acute exacerbations. This medication class is indicated for the treatment of bronchospasms in patients with obstructive airway disease and exercise-induced bronchospasms.[23] Long-acting β2 agonists (LABAs) may be added to the treatment plan for patients who are not well controlled on ICS or for those whose disease calls for both an ICS and a LABA. As SABAs do, LABAs exert their effects by agonizing β2 receptors, leading to the relaxation of bronchial smooth muscle.[24] LABAs should not be used as monotherapy for long-term control.[19]

Leukotriene-receptor antagonists (LTRAs) are indicated for the treatment of chronic asthma and for prophylaxis. The most commonly used LTRAs for asthma treatment are montelukast and zafirlukast. Zafirlukast was the first LTRA to receive FDA approval to prevent exercise-induced bronchospasms in both adults and children with asthma.[25-27]

Monoclonal Antibodies

Not all cases of asthma can be appropriately treated with ICS, β2 agonists, and LTRAs. For patients with severe asthma, monoclonal antibodies can reduce airway inflammation and address underlying type 2 inflammation.[28] One agent that targets this pathway is omalizumab, an anti-IgE antibody that has been shown to slow airway responses to inhaled allergens. Approved by the FDA in 2003, omalizumab has also been shown to reduce exacerbation rates and maintenance doses of oral corticosteroids.[29]

Targeting Type 2 Inflammation With Interleukin Inhibitors

For subgroups of patients who have severe asthma, in whom standard treatment options are not successful, treatment may be needed to target specific inflammation pathways.[30] Targeting various IL pathways and receptors directly has been shown to offer important benefits.

IL-5

The first IL-based agents approved for the treatment of asthma were IL-5 inhibitors. As described in the previous article (p. 4), IL-5 is a crucial cytokine in multiple asthma phenotypes and places selective action on eosinophils, which in turn worsens asthma symptoms, inflammation, and overall severity of the disease. As add-on maintenance therapies, drugs that target IL-5 or IL-5Ra (the IL-5 subunit) have shown benefits in patients with refractory asthma with an eosinophilic phenotype who continue to have inadequate asthma control or exacerbations despite corticosteroid use. Three IL-5 inhibitors have been approved for asthma.[31]

Mepolizumab, approved by the FDA in 2015, is an IL-5 receptor antagonist indicated as an add-on maintenance treatment for patients aged ≥12 years with severe asthma and eosinophilic phenotype.[32] MUSCA, a randomized,

double-blind, placebo-controlled, parallel-group, multicenter phase 3b trial evaluated mepolizumab and its effect on health-related quality of life (HRQoL) in patients aged ≥12 years with severe eosinophilic asthma, with a history of ≥2 exacerbations that required treatment within the year prior to the study.[33] Enrolled patients received 100 mg mepolizumab (n = 274) or placebo (n = 277). The mepolizumab group had significant improvements, versus the placebo arm, from baseline to week 24 in St George's Respiratory Questionnaire total scores (mean least squares change –156 [1.0] vs –7.9 [1.0]). More patients who received placebo reported 1 or more on-treatment AEs compared with those who received mepolizumab (74% vs 70%). Investigators also found that mepolizumab contributed to significant HRQoL improvements in patients with severe eosinophilic asthma.[33]

In 2016, the FDA approved the IL-5 inhibitor reslizumab as an add-on maintenance treatment for use in patients aged ≥18 years who have severe asthma with an eosinophil phenotype.[34] Results from a phase 3 study testing reslizumab in patients with poorly controlled asthma and eosinophils demonstrated efficacy and good tolerability in patients with high eosinophils, and the agent was well tolerated.[35] In patients who had baseline eosinophils <400 cells/μL, there was no significant improvement in forced expiratory volume in 1 second (FEV_1) in either patient population. However, those with eosinophils ≥400 cells/μL who were treated with reslizumab, compared with placebo, experienced considerable improvements in FEV_1, Asthma Control Questionnaire-7 responses, SABAs used, and forced vital capacity. The reslizumab cohort also experienced fewer AEs than the placebo group.[35]

Benralizumab, FDA approved in 2017, is indicated as an add-on maintenance treatment for patients aged ≥12 years with severe asthma and eosinophilic phenotype.[36] In SIROCCO, a randomized, double-blind, parallel-group, placebo-controlled phase 3 study, researchers assessed the safety and efficacy of benralizumab at 374 sites in 17 countries.[37] Of 2681 recruited patients aged 12 to 75 years, 1205 participants met the study criteria. Patients were randomized to receive either placebo, benralizumab 30 mg every 4 weeks, or benralizumab 30 mg every 8 weeks (n = 398). Results showed that when given every 4 or 8 weeks, benralizumab reduced the annual asthma exacerbation rate. At week 48, both benralizumab dosing regimens considerably improved prebronchodilator FEV_1 compared with placebo. Common AEs were worsening asthma (observed in 13% and 19% of patients receiving benralizumab and placebo, respectively) and nasopharyngitis (observed in 12% of patients treated in the 2 benralizumab groups and the placebo group).[37]

In CALIMA, a randomized, double-blind, placebo-controlled phase 3 trial, investigators evaluated benralizumab as an add-on treatment in patients with severe, uncontrolled asthma and high eosinophil counts.[38] The trial was conducted at 303 sites in 11 countries with patients aged 12 to 75 years; each had severe asthma, uncontrolled on medium-to-high ICS plus LABA, and a history of ≥2 exacerbations within the year prior to randomization. Of 2505 patients who were enrolled, 1306 were randomized; 425 were assigned to 30 mg benralizumab every 4 weeks, 441 to 30 mg benralizumab every 8 weeks, and 440 to placebo. The primary analysis population consisted of 728 patients. Annual exacerbation rate ratio for benralizumab versus placebo was the study's primary end point. Patients administered benralizumab every 4 or 8 weeks experienced significantly lower exacerbation rates compared with those on placebo. Also, benralizumub was found to be a well-tolerated medication for patients with uncontrolled asthma with blood eosinophils ≥300 cells per μL.[38]

IL-4/13

Although the IL-5 pathway plays a significant role in asthma, the utility of the currently available IL-5 inhibitors is limited to a particular subset of patients with severe disease and high eosinophil counts. IL-13, another active pathway in the type 2 inflammatory process that contributes to multiple aspects of asthma, has also been the focus of therapeutic development in recent years.[39] Lebrikizumab and tralokinumab, both IL-13 inhibitors, were evaluated for potential indications for asthma. Lebrikizumab met its primary end point in 1 of 2 phase 3 trials,[40] and tralokinumab missed its phase 3 trial end points.[41] Despite the challenges in targeting IL-13 in asthma, however, IL-13 was revealed to be a more promising pathway when targeted together with IL-4 via dupilumab.

In a phase 2 trial, the safety and efficacy of dupilumab was evaluated in patients with moderate to severe asthma with a blood eosinophil count of ≥300 cells/μL or sputum eosinophil level of ≥3% who had used medium-to-high doses of ICS plus LABAs. Patients were either administered 300 mg dupilumab (n = 52) or placebo (n = 52) once weekly. They were also given instructions to discontinue LABAs starting at week 4 and ICS from weeks 6 to 9. The primary end point was occurrence of asthma exacerbation. An 87% reduction in asthma exacerbation occurred with dupilimab (odds ratio, 0.08; 95% CI, 0.02-0.28; *P* <.001) and significant improvements were found in multiple measures of lung function and asthma control. Twenty-three patients (44%) with placebo and 3 patients (6%) with dupilumab experienced asthma exacerbation. AEs were more frequent in patients given dupilmab

compared with placebo (eg injection-site reactions, nasopharyngitis, nausea, and headache).[42]

In 2018, the FDA approved dupilumab as an add-on maintenance treatment in patients aged ≥12 years with moderate to severe asthma and eosinophilic phenotype or corticosteroid-dependent asthma.[7] The approval was based on results from 3 clinical trials showing that dupilumab reduced severe exacerbations and ICS use for improved lung function. It is the only FDA-approved biologic agent for patients with moderate to severe asthma.

In the first trial that led to FDA approval, patients were randomly assigned to receive subcutaneous dupilumab 200 mg, dupilumab 300 mg, or placebo every 2 or 4 weeks for 24 weeks. The trial had 2 subsets of patients: those with eosinophils >300 cells/μL and those with eosinophils <300 cells/μL. Increases in FEV_1 were seen across all groups. Patients receiving dupilumab every 2 weeks experienced reductions in annualized rates of exacerbation of 71.2%-80.7% (patients with eosinophils >300 cells/μL) and 59.9%-67.6% (patients with eosinophils <300 cells/μL).[43]

In the second trial, lasting 52 weeks, participants received add-on subcutaneous dupilumab at doses of 200 mg or 300 mg, or placebo, every 2 weeks.[44] Annual severe exacerbation rates and FEV_1 change from baseline to week 12 were the primary end points. In the 200-mg group, there was a 47.7% lower rate of exacerbations with dupilumab compared with placebo (P <.001). The total rate of severe asthma exacerbations in patients who received 200 mg of dupilumab every 2 weeks was 0.46 (95% CI, 0.39-0.53); it was 0.87 in the placebo group (95% CI, 0.72-1.05). In patients with eosinophils >300 cells/μL, dupilumab reduced severe exacerbations 65.8% and 67.4% more than with placebo, in the lower- and higher-dose groups, respectively. In patients with eosinophil counts <300 cells/μL, dupilumab reduced severe exacerbations 35.6% and 44.3% more than with placebo, in the lower- and higher-dose groups, respectively. Across groups, dupilumab also improved FEV_1 by 29% to 33%, compared with 14% to 16% for placebo.[44] Post intervention, 52 patients who were administered dupilumab experienced blood eosinophilia, compared with 4 patients who were given placebo. Participants who were given dupilumab compared with placebo had overall better lung function and asthma control and considerably lower rates of severe asthma exacerbation.[44]

The third trial that led to dupilumab's approval evaluated the effect of dupilumab in patients dependent on oral corticosteroids.[45] Findings indicated that dupilumab reduced average daily oral corticosteroid use by 70%, compared with 42% for placebo. In the overall population, dupilumab resulted in a 59% reduction in severe exacerbations compared with the placebo group.[45] **Table 2** includes more information about ongoing trials evaluating dupilumab in asthma.[46-49]

Investigational IL Inhibitors for Asthma

Given the promise of therapeutic inhibition of IL pathways in asthma, research into inhibition of additional inflammatory pathways is underway. IL-17, for instance, has shown promise. Patients with severe asthma have been found to have IL-17A/F in their bronchoalveolar lavage fluid and airway tissue, correlating with disease severity and neutrophil inflammation.[50] Several drugs have been tested to target this pathway, including brodalumab and secukinumab. Both of these agents have been approved for the treatment of psoriasis, but in these asthma investigations, both were found to either lead to severe mental health issues or did not demonstrate significant changes in Asthma Control Questionnaire Scores.[50] Currently, CJM112, an anti–IL-17A agent, is being evaluated in a phase 2 clinical trial in patients with

Table 2. Current Ongoing US Clinical Trials for Dupilumab for the Treatment of Asthma[46-49]

Name	NCT#	Status	Estimated Completion Date
Assessment of the Safety and Efficacy of Dupilumab in Children With Asthma (Liberty Asthma Excursion)	NCT03560466	Recruiting	April 2026
Evaluation of Dupilumab in Children With Uncontrolled Asthma (VOYAGE)	NCT02948959	Recruiting	July 2021
Long-Term Safety Evaluation of Dupilumab in Patients With Asthma (LIBERTY ASTHMA TRAVERSE)	NCT02134028	Active, not recruiting	November 2019
Effect of IL-4R R576 Polymorphism on Response to Dupilumab in Adolescents and Adults With Asthma (I-DAG)	NCT03694158	Not yet recruiting	October 2023

inadequately controlled moderate to severe asthma who have low IgE and blood eosinophil levels. Results are expected in July 2019.[51]

Predicting patient response to therapy remains a challenge for type 2 inflammation in asthma.[52] Nevertheless, significant opportunity remains for the utilization of IL inhibitors as monotherapies and potentially in combination with other agents, to target type 2 inflammatory pathways and offer relief to patients with asthma.

Chronic Rhinosinusitis With Nasal Polyps

Traditional treatment options for CRSwNP include topical corticosteroids, nasal saline, short-term antibiotics (if infection is present), oral corticosteroids (for acute exacerbations), and surgery (after all other options have been attempted).[53,54] Currently, no monoclonal antibodies are FDA approved for the treatment of CRSwNP, but several have been evaluated. For example, trial results have shown potential benefit for omalizumab in patients with CRSwNP and comorbid asthma.[55] Additionally, drugs with a higher affinity for and increased ability to suppress free IgE are currently being developed.[56]

Treating Type 2 Inflammation With Interleukin Agents

Among other monoclonal antibodies, IL inhibitors have shown efficacy in the treatment of CRSwNP.[54] In March 2019, dupilumab was granted Priority Review by the FDA for a Supplemental Biologics Application as add-on maintenance treatment for adults with severe, inadequately controlled CRSwNP. Data from the phase 3 SINUS-24 and SINUS-52 trials were presented at the 2019 American Academy of Allergy, Asthma & Immunology annual meeting in San Francisco.[57] Results showed 42% and 27% improvement in sinus opacification at 24 weeks among dupilumab-treated patients with CRSwNP in SINUS-24 and SINUS-52, respectively, versus 4% and 0% with placebo. Treatment with dupilumab was also associated with 146% and 108% improvement in the ability to identify different smells at 24 weeks in SINUS-24 and SINUS-52, respectively, versus 19% and 7% with placebo. With dupilumab, improvements in HRQoL of 60% and 51% in SINUS-24 and SINUS-52, respectively, were also observed, along with improvements in lung function. Moreover, both trials showed reductions of 73% and 76% in rescue treatment with systemic corticosteroids and in nasal polyp surgery, in SINUS-24 and SINUS-52, respectively. The reduction in the use of corticosteroids extended to patients with comorbid asthma, as well (58.3% and 59.6% in SINUS-24 and SINUS-52, respectively).

IL-5 inhibitors are also under consideration for the treatment of CRSwNP. For instance, mepolizumab is a targeted anti–IL-5 monoclonal antibody that is currently in phase 3 trials. In the SYNAPSE study, participants are receiving mepolizumab or placebo every 4 weeks for 52 weeks. The patients are receiving standard-of-care treatments consisting of mometasone nasal spray, saline nasal douching, and occasional short courses of antibiotics and/or systemic corticosteroids. The study is ongoing and no results have yet been published.[58]

The IL-5 inhibitor reslizumab is also under consideration for treatment of CRSwNP. Post hoc results from phase 3 trials found that add-on reslizumab treatment reduced frequency of asthma exacerbations by 83% versus placebo.[59]

Future Directions

Significant advances regarding the inhibition of IL-4/13 within the past year alone suggest the broader importance of type 2 inflammation across atopic conditions. In asthma, following the FDA approval of dupilumab as an add-on maintenance treatment in patients aged ≥12 years with moderate to severe asthma and eosinophilic phenotype or corticosteroid-dependent asthma, the Global Initiative for Asthma recognized the role of type 2 inflammation in its April 2019 Pocket Guide for difficult-to-treat and severe asthma. The guidelines provide a blueprint for care that incorporates various IL-based therapies if type 2 inflammation is present.[60] The guidelines also note several factors that should be considered when selecting an appropriate therapy, including local payer eligibility criteria, predictors of response, cost, dosing frequency, deliver route, and patient preference.

In AD, the recent approval of dupilumab in adolescent patients aged between 12 and 18 years with moderate to severe AD, coupled with FDA breakthrough designation and ongoing trials evaluating dupilumab in patients with severe AD as young as 6 years, suggest the potential for dupilumab to offer benefit to patients in various age populations and stages of disease. Also promising is the FDA priority review for dupilumab in adult patients with inadequately controlled severe CRSwNP.

Given the rapid rate of these developments, the broader utility of IL inhibition in atopic diseases is increasingly evident. This may be particularly relevant given the frequency of comorbid conditions in patients with these diseases.[61] Thus, results from the LIBERTY AD SOLO trials showing the benefits of dupilumab in patients with AD and comorbid asthma offer the hope to broadly modify the course of type 2 inflammatory diseases. Ongoing research and development will likely provide greater clarity regarding the etiology of type 2 inflammatory disease, with the possibility of yielding additional efficacious targeted interventions. ◆

REFERENCES

1. Wolter S, Price HN. Atopic dermatitis. *Pediatr Clin North Am*. 2014;61(2):241-260. doi: 10.1016/j.pcl.2013.11.002.
2. Eichenfield LF, Tom WL, Chamlin SL, et al. Guidelines of care for the management of atopic dermatitis: section 1. diagnosis and assessment of atopic dermatitis. *J Am Acad Dermatol*. 2014;70(2):338-351. doi: 10.1016/j.jaad.2013.10.010.
3. Boguniewicz M, Alexis AF, Beck LA, et al. Expert perspectives on management of moderate-to-severe atopic dermatitis: a multidisciplinary consensus addressing current and emerging therapies. *J Allergy Clin Immunol Pract*. 2017;5(6):1519-1531. doi: 10.1016/j.jaip.2017.08.005.
4. Sidbury R, Davis DM, Cohen DE, et al; American Academy of Dermatology. Guidelines of care for the management of atopic dermatitis: section 3. management and treatment with phototherapy and systemic agents. *J Am Acad Dermatol*. 2014;71(2):327-349. doi: 10.1016/j.jaad.2014.03.030.
5. Simpson EL, Bieber T, Guttman-Yassky E, et al; SOLO 1 and SOLO 2 Investigators. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. *N Engl J Med*. 2016;375(24):2335-2348. doi: 10.1056/NEJMoa1610020.
6. Blauvelt A, de Bruin-Weller M, Gooderham M, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. *Lancet*. 2017;389(10086):2287-2303. doi: 10.1016/S0140-6736(17)31191-1.
7. Dupixent [prescribing information]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc; 2019. d1egnxy4jx1q3f.cloudfront.net/Regeneron/Dupixent_FPI.pdf. Accessed June 5, 2019.
8. Deleuran M, Guttman-Yassky E, Kingo K, et al. Dupilumab in moderate-to-severe atopic dermatitis with or without comorbid asthma: pooled analysis of 2 randomized phase 3 trials (LIBERTY AD SOLO 1 & 2). In: AAAAI/WAO Joint Congress; March 2-March 5, 2018; Orlando, FL. Abstract 417. https://aaaai.confex.com/aaaai/wao18/webprogram/Paper35079.html. Accessed June 5, 2019.
9. Study to Investigate the Efficacy and Safety of Dupilumab Administered with Topical Corticosteroids (TCS) in Participants ≥6 to <12 years With Severe Atopic Dermatitis (AD). ClinicalTrials.gov website. clinicaltrials.gov/ct2/show/NCT03345914. Published November 17, 2017. Updated March 25, 2019. Accessed June 5, 2019.
10. The Impact of Dupilumab on Quality of Life in Moderate to Severe Atopic Dermatitis Patients. ClinicalTrials.gov website. clinicaltrials.gov/ct2/show/NCT03667014. Published September 12, 2018. Updated February 15, 2019. Accessed June 5, 2019.
11. A Study to Compare Safety and Efficacy of Upadacitinib to Dupilumab in Adult Participants With Moderate to Severe Atopic Dermatitis (Heads Up). ClinicalTrials.gov website. clinicaltrials.gov/ct2/show/NCT03738397. Published November 12, 2018. Updated May 21, 2019. Accessed June 5, 2019.
12. Study to Assess the Long-term Safety of Dupilumab Administered in Participants ≥6 months to <18 Years of Age with Atopic Dermatitis (AD). ClinicalTrials.gov website. clinicaltrials.gov/ct2/show/NCT02612454. Published November 23, 2015. Updated March 25, 2019. Accessed June 5, 2019.
13. Immunogenetic Profiling of Dupilumab for the Treatment of Atopic Dermatitis. ClinicalTrials.gov website. clinicaltrials.gov/ct2/show/NCT03293030. Published September 26, 2017. Updated February 15, 2019. Accessed June 5, 2019.
14. Simpson EL, Flohr C, Eichenfield LF, et al. Efficacy and safety of lebrikizumab (an anti-IL-13 monoclonal antibody) in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical corticosteroids: a randomized, placebo-controlled phase II trial (TREBLE). *J Am Acad Dermatol*. 2018;78(5):863-871. doi: 10.1016/j.jaad.2018.01.017.
15. Dermira announces positive topline results from phase 2b study of lebrikizumab in patients with atopic dermatitis [news release]. Menlo Park, CA: Dermira; March 18, 2019. investor.dermira.com/news-releases/news-release-details/dermira-announces-positive-topline-results-phase-2b-study?field_nir_news_date_value[min]=. Accessed June 5, 2019.
16. Wollenberg A, Howell MD, Guttman-Yassky E, et al. Treatment of atopic dermatitis with tralokinumab, an anti-IL-13 mAb. *J Allergy Clin Immunol*. 2019;143(1):135-141. doi: 10.1016/j.jaci.2018.05.029.
17. Nygaard U, Vestergaard C, Deleuran M. Emerging treatment options in atopic dermatitis: systemic therapies. *Dermatology*. 2017;233(5):344-357. doi: 10.1159/000484406.
18. Vatrella A, Fabozzi I, Calabrese C, Maselli R, Pelaia G. Dupilumab: a novel treatment for asthma. *J Asthma Allergy*. 2014;7:123-130. doi: 10.2147/JAA.S52387.
19. National Asthma Education and Prevention Program. Asthma care quick reference. National Heart, Lung, and Blood Institute website. nhlbi.nih.gov/files/docs/guidelines/asthma_qrg.pdf. Updated September 2012. Accessed June 5, 2019.
20. Castillo JR, Peters SP, Busse WW. Asthma exacerbations: pathogenesis, prevention, and treatment. *J Allergy Clin Immunol Pract*. 2017;5(4):918-927. doi: 10.1016/j.jaip.2017.05.001.
21. Flovent HFA [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; 2019. gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Flovent_HFA/pdf/FLOVENT-HFA-PI-PIL-IFU.PDF. Accessed June 5, 2019.
22. Oral corticosteroids for asthma. Asthma and Allergy Foundation of America website. aafa.org/asthma-treatment-oral-corticosteroids-prednisone/. Updated September 2018. Accessed June 5, 2019.
23. Proair Respiclick [prescribing information]. Horsham, PA: Teva Respiratory, LLC; 2018. proair.com/respiclick/assets/pdf/PI.pdf. Accessed June 5, 2019.
24. Advair diskus [patient information]. Research Triangle Park, NC: GlaxoSmithKline; 2019. gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Advair_Diskus/pdf/ADVAIR-DISKUS-PI-PIL-IFU.PDF. Accessed June 5, 2019.
25. Singulair [prescribing information]. Whitehouse Station, NJ: Merck & Co, Inc; 2019. merck.com/product/usa/pi_circulars/s/singulair/singulair_pi.pdf. Accessed June 5, 2019.
26. Accolate [prescribing information]. Wilmington, DE: AstraZeneca LP; 2009. http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020547s027lbl.pdf. Accessed June 5, 2019.
27. Kemp JP. Exercise-induced bronchoconstriction: the effects of montelukast, a leukotriene receptor antagonist. *Ther Clin Risk Manag*. 2009;5:923-933.
28. Rubinsztajn R, Chazan R. Monoclonal antibodies for the management of severe asthma. *Adv Exp Med Biol*. 2016;935:35-42. doi: 10.1007/5584_2016_29.
29. Fahy JV. Type 2 inflammation in asthma--present in most, absent in many. *Nat Rev Immunol*. 2015;15(1):57-65. doi: 10.1038/nri3786.
30. Kim AS, Doherty TA. New and emerging therapies for asthma. *Ann Allergy Asthma Immunol*. 2016;116(1):14-17. doi: 10.1016/j.anai.2015.08.001.
31. Bagnasco D, Ferrando M, Varricchi G, Puggioni F, Passalacqua G, Canonica GW. Anti-interleukin 5 (IL-5) and IL-5Ra biological drugs: efficacy, safety, and future perspectives in severe eosinophilic asthma. *Front Med (Lausanne)*. 2017;4:135. doi: 10.3389/fmed.2017.00135.
32. Nucala [prescribing information]. Research Triangle Park NC: GSK; 2017. gsk-

source.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Nucala/pdf/NUCALA-PI-PIL.PDF. Accessed June 5, 2019.

33. Chupp GL, Bradford ES, Albers FC, et al. Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma (MUSCA): a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3b trial. *Lancet Respir Med.* 2017;5(5):390-400. doi: 10.1016/S2213-2600(17)30125-X.
34. Cinqair [prescribing information]. Frazer, PA: Teva Respiratory, LLC; 2019. cinqair.com/globalassets/cinqair/prescribinginformation.pdf. Accessed June 5, 2019.
35. Corren J, Weinstein S, Janka L, Zangrilli J, Garin M. Phase 3 study of reslizumab in patients with poorly controlled asthma: effects across a broad range of eosinophil counts. *Chest.* 2016;150(4):799-810. doi: 10.1016/j.chest.2016.03.018.
36. Fasenra [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals, LP; 2017. azpicentral.com/fasenra/fasenra.pdf. Accessed June 5, 2019.
37. Bleecker ER, FitzGerald JM, Chanez P, et al; SIROCCO Study Investigators. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet.* 2016;388(10056):2115-2127. doi: 10.1016/S0140-6736(16)31324-1.
38. FitzGerald JM, Bleecker ER, Nair P, et al; CALIMA Study Investigators. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet.* 2016;388(10056):2128-2141. doi: 10.1016/S0140-6736(16)31322-8.
39. Korenblat P, Kerwin E, Leshchenko I, et al. Efficacy and safety of lebrikizumab in adult patients with mild-to-moderate asthma not receiving inhaled corticosteroids. *Respir Med.* 2018;134:143-149. doi: 10.1016/j.rmed.2017.12.006.
40. Roche provides update on two identical phase III studies of lebrikizumab in people with severe asthma [news release]. Basel, Switzerland: Roche; February 29, 2016. roche.com/investors/updates/inv-update-2016-02-29.htm. Accessed June 5, 2019.
41. AstraZeneca provides update on tralokinumab phase III programme in severe, uncontrolled asthma [news release]. Gaithersburg, MD: AstraZeneca; November 1, 2017. astrazeneca.com/media-centre/press-releases/2017/astrazeneca-provides-update-on-tralokinumab-phase-iii-programme-in-severe-uncontrolled-asthma-01112017.html. Accessed June 5, 2019.
42. Wenzel S, Ford L, Pearlman D, et al. Dupilumab in persistent asthma with elevated eosinophil levels. *N Engl J Med.* 2013;368(26):2455-2466. doi: 10.1056/NEJMoa1304048.
43. Wenzel S, Castro M, Corren J, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. *Lancet.* 2016;388(10039):31-44. doi: 10.1016/S0140-6736(16)30307-5.
44. Castro M, Corren J, Pavord ID, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med.* 2018;378(26):2486-2496. doi: 10.1056/NEJMoa1804092.
45. Rabe KF, Nair P, Brusselle G, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. *N Engl J Med.* 2018;378(26):2475-2485. doi: 10.1056/NEJMoa1804093.
46. Assessment of the Safety and Efficacy of Dupilumab in Children With Asthma (Liberty Asthma Excursion). ClinicalTrials.gov website. clinicaltrials.gov/ct2/show/NCT03560466. Published June 18, 2018. Updated May 21, 2019. Accessed June 5, 2019.
47. Evaluation of Dupilumab in Children with Uncontrolled Asthma (VOYAGE). ClinicalTrials.gov website. clinicaltrials.gov/ct2/show/NCT02948959. Published October 31, 2016. Updated June 6, 2019. Accessed June 6, 2019.
48. Long-Term Safety Evaluation of Dupilumab in Patients With Asthma (LIBERTY ASTHMA TRAVERSE). ClinicalTrials.gov website. clinicaltrials.gov/ct2/show/NCT02134028. Published May 8, 2014. Updated June 6, 2019. Accessed June 6, 2019.
49. Effect of IL-4RαR576 Polymorphism on Response to Dupilumab in Adolescents and Adults With Asthma (I-DAG). ClinicalTrials.gov website. clinicaltrials.gov/ct2/show/NCT03694158. Published October 3, 2018. Updated May 2, 2019. Accessed June 5, 2019.
50. Zhu L, Ciaccio CE, Casale TB. Potential new targets for drug development in severe asthma. *World Allergy Organ J.* 2018;11(1):30. doi: 10.1186/s40413-018-0208-1.
51. Study to Assess the Efficacy and Safety of CJM112 in Patients With Inadequately Controlled Severe Asthma. clinicaltrials.gov/ct2/show/NCT03299686?term=NCT03299686&rank=1. Published October 3, 2017. Updated January 29, 2019. Accessed June 5, 2019.
52. Godar M, Blanchetot C, de Haard H, Lambrecht BN, Brusselle G. Personalized medicine with biologics for severe type 2 asthma: current status and future prospects. *MAbs.* 2018;10(1):34-45. doi: 10.1080/19420862.2017.1392425.
53. Fokkens WJ, Lund VJ, Mullol J, et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. a summary for otorhinolaryngologists. *Rhinology.* 2012;50(1):1-12. doi: 10.4193/Rhino50E2.
54. Bachert C, Zhang L, Gevaert P. Current and future treatment options for adult chronic rhinosinusitis: focus on nasal polyposis. *J Allergy Clin Immunol.* 2015;136(6):1431-1440. doi: 10.1016/j.jaci.2015.10.010.
55. Brunk D. Omalizumab may help chronic rhinosinusitis symptoms. *CHEST Physician: The Newspaper of the American College of Chest Physicians* website. mdedge.com/chestphysician/article/134672/asthma/omalizumab-may-help-chronic-rhinosinusitis-symptoms. Published March 29, 2017. Accessed May 20, 2019.
56. Avdeeva K, Fokkens W. Precision medicine in chronic rhinosinusitis with nasal polyps. *Curr Allergy Asthma Rep.* 2018;18(4):25. doi: 10.1007/s11882-018-0776-8.
57. Han JK, Bachert C, Desrosiers M, et al. Efficacy and safety of dupilumab in patients with chronic rhinosinusitis with nasal polyps: results from the randomized phase 3 Sinus-24 study. Presented at: 2019 American Academy of Allergy, Asthma & Immunology Annual Meeting; February 22-25, 2019; San Francisco, CA. Abstract L4.
58. GSK starts phase III study with mepolizumab in patients with nasal polyps [news release] London, UK: GSK; June 27, 2017. gsk.com/en-gb/media/press-releases/gsk-starts-phase-iii-study-with-mepolizumab-in-patients-with-nasal-polyps/. Accessed June 5, 2019.
59. Weinstein SF, Katial RK, Bardin P, et al. Effects of reslizumab on asthma outcomes in a subgroup of eosinophilic asthma patients with self-reported chronic rhinosinusitis with nasal polyps. *J Allergy Clin Immunol Pract.* 2019;7(2):589-596.e3. doi: 10.1016/j.jaip.2018.08.021.
60. Difficult-to-treat and severe asthma in adolescent and adult patients: diagnosis and management. Global Initiative for Asthma website. ginasthma.org/wp-content/uploads/2019/04/GINA-Severe-asthma-Pocket-Guide-v2.0-wms-1.pdf. Published April 2019. Accessed June 5, 2019.
61. Brunner PM, Silverberg JI, Guttman-Yassky E, et al; Councilors of the International Eczema Council. Increasing comorbidities suggest that atopic dermatitis is a systemic disorder. *J Invest Dermatol.* 2017;137(1):18-25. doi: 10.1016/j.jid.2016.08.022.