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Therapeutic Class Overview
Respiratory and Allergy Biologics

INTRODUCTION

- Asthma is a chronic lung disease that inflames and narrows the airways, making it difficult to breathe. Asthma causes recurring periods of wheezing, chest tightness, shortness of breath, and coughing. Asthma affects people of all ages but most often starts during childhood. In 2019, asthma affected an estimated 20 million adults and 5.1 million children in the United States (U.S.). The exact causes of asthma are unknown. A combination of factors such as genetics, certain respiratory infections during childhood, and contact with airborne allergens can contribute to its development. Most patients with asthma have allergies (*Centers for Disease Control and Prevention [CDC] 2021, National Heart, Lung, and Blood Institute [NHLBI] Web site*).
- Current pharmacologic options for asthma management are categorized as: (1) control medications to achieve and maintain control of persistent asthma or prevent exacerbations, and (2) quick-relief medications used to treat acute symptoms and exacerbations (*Cloutier et al 2020, NHLBI 2007, Global Initiative for Asthma [GINA] 2021*).
  - Control medications include:
    - Corticosteroids (inhaled corticosteroids [ICSs], or oral corticosteroids for severe exacerbations)
    - Long-acting beta$_2$-agonists (LABAs)
    - Leukotriene receptor antagonists (LTRAs) in select patients
    - Methylxanthines (ie, theophylline) in select patients
    - Add-on immunomodulators (ie, omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab) in patients with severe asthma
    - Add-on tiotropium in patients whose asthma is not well-controlled with ICS/LABA
    - Add-on azithromycin in patients whose asthma is not well-controlled with high dose ICS/LABA
  - Quick-relief/reliever medications include:
    - Short-acting beta$_2$-agonists (SABAs) for relief of acute symptoms and prevention of exercise-induced bronchospasm
    - ICS-formoterol for relief of acute symptoms and if needed before exercise
    - Anticholinergics (ie, ipratropium bromide) as an alternative bronchodilator for those not tolerating a SABA
    - Systemic corticosteroids, although not short-acting, are used for moderate and severe exacerbations as part of initial treatment.
- Approximately 3.7% of asthma patients have severe disease and 17% have difficult-to-treat asthma. Severe asthma is defined as asthma that is uncontrolled despite adherence to maximal optimized high dose ICS/LABA treatment or asthma that requires high doses of ICS/LABA to remain controlled (*GINA 2021*).
- While there are currently no widely accepted definitions of specific asthma phenotypes, several strategies have been proposed to categorize severe asthma phenotypes based on characteristics such as patient age, disease onset, corticosteroid resistance, chronic airflow obstruction, or type of cellular infiltrate in the airway lumen or lung tissue (*Walford et al 2014*). The most recent GINA guideline on severe or difficult-to-treat asthma recommends assessing for Type 2 inflammation through blood and sputum eosinophil levels, exhaled nitric oxide level, and allergic triggers to asthma (*GINA 2021*).
- Chronic idiopathic urticaria (CIU), also called chronic spontaneous urticaria, is defined by the presence of hives on most days of the week for 6 weeks or longer, with or without angioedema. The hives are circumscribed, raised, erythematous plaques, often with central pallor and variable in size. No external allergic cause or contributing disease process can be identified in 80 to 90% of adults and children with CIU (*Khan 2021, Saini 2021*).
- CIU affects up to 1% of the general population in the U.S., and the prevalence is believed to be similar in other countries. The condition is more common in adults than children and typically begins in the third to fifth decades of life. CIU is a self-limited disorder in most patients although the condition generally has a prolonged duration of 2 to 5 years (*Saini 2021*).
- Non-sedating H$_1$-antihistamines are the cornerstone of therapy for CIU. Limited courses of oral glucocorticoids are often used in combination with antihistamines for refractory symptoms. Other pharmacologic options for patients who do not

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respond to H_1-antihistamines include the use of H_2-antihistamines, leukotriene modifiers, cyclosporine, tacrolimus, mycophenolate, hydroxychloroquine, sulfasalazine, dapsone, and omalizumab (*Khan 2021, Maurer et al 2013*).

- Eosinophilic granulomatosis with polyangiitis (EGPA), previously called Churg-Strauss syndrome, is a systemic necrotizing vasculitis that affects small-to-medium-sized vessels. It is typically associated with eosinophilia and severe asthma (*Groh et al 2015, Padmanabhan et al 2019).*
- EGPA is a rare condition with a prevalence of approximately 13 cases per 1 million persons and an annual incidence of approximately 7 new cases per 1 million persons. It has a higher incidence in patients with asthma (*Groh et al 2015*).
- Systemic glucocorticoids are the mainstay of treatment for EGPA. For refractory EGPA, the addition of cyclophosphamide, azathioprine, methotrexate, rituximab, or intravenous immunoglobulins (IVIG) can be considered *(Groh et al 2015).* In more than 85% of patients with EGPA, remission can be achieved with glucocorticoids with or without an immunosuppressant; however, relapses occur in more than 33% of patients (*Pagnoux and Groh 2016*).
- Chronic rhinosinusitis with nasal polyposis (CRSwNP) has a prevalence of approximately 2.7% in adults, and peaks in the sixth decade of life. Symptoms include nasal obstruction, reduced sense of smell, and sleep disturbance, all of which can substantially impact the quality of life. The majority of cases are idiopathic, but may be due to genetic, metabolic, or immunologic causes, resulting in inflammation characterized by eosinophilia and elevated levels of IL-4, IL-5, and IL-13 *(Hopkins 2019)*.
- Common treatment options for CRSwNP include saline irrigation and intranasal glucocorticoids in patients with mild symptoms, and short-term systemic glucocorticoids, surgery, and biologic agents in patients with severe symptoms *(Hopkins 2019)*.
- Hypereosinophilic syndromes (HES) are disorders characterized by overproduction of eosinophils which causes organ damage (*Roufosse et al 2020a*). Treatment for idiopathic HES may include systemic glucocorticoids, imatinib, hydroxyurea, interferon alfa, alemtuzumab, and Janus kinase inhibitors (eg, tofacitinib and ruxolitinib). Additionally, mepolizumab was Food and Drug Administration (FDA)-approved for HES in 2020.
- This monograph describes the use of Cinqair (reslizumab), Dupixent (dupilumab), Fasenra (benralizumab), Nucala (mepolizumab), and Xolair (omalizumab).
  - Cinqair, Fasenra, and Nucala are humanized monoclonal antibody interleukin-5 (IL-5) antagonists. The mechanism of action of Fasenra is slightly different, in that it binds to the IL-5 receptor on immune effector cells, whereas Cinqair and Nucala bind to the IL-5 cytokine. Eosinophils play a key role in the pathobiology of airway disorders by contributing to inflammation through the release of leukotrienes and pro-inflammatory cytokines. Increases in eosinophils are often correlated with greater asthma severity. IL-5, a cytokine critical to eosinophil differentiation and survival, has been isolated as a potential target in eosinophilic asthma.
    - Nucala is also approved for the treatment of adult patients with EGPA, patients ≥ 12 years of age with HES, and as add-on therapy for inadequately controlled CRSwNP.
  - Xolair is a recombinant DNA-derived monoclonal antibody that selectively binds to human IgE. Xolair, which reduces the allergic response mediators, is useful in a subset of patients with allergic asthma. In addition, Xolair has been shown to improve symptoms in patients with CIU and is indicated for add-on maintenance treatment of nasal polyps in adult patients with inadequate response to nasal corticosteroids.
  - Dupixent is a human monoclonal antibody that inhibits signaling of IL-4 and IL-13. This results in a reduction of the release of inflammatory mediators including cytokines, chemokines, nitric oxide, and IgE. These actions are useful for eosinophilic asthma and add-on therapy for inadequately controlled CRSwNP. Dupixent is also approved to treat moderate to severe atopic dermatitis; this indication is not discussed further in this review.
- Medispan class: Antiasthmatic – Monoclonal Antibodies

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Cinqair (reslizumab)	--
Dupixent (dupilumab)	--
Fasenra (benralizumab)	--
Nucala (mepolizumab)	--
Xolair (omalizumab)	--

(*Drugs@FDA 2021, Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations 2021*)

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INDICATIONS

Table 2: Food and Drug Administration Approved Indications*

Indication	Cinqair† (reslizumab)	Dupixent (dupilumab)	Fasenra† (benralizumab)	Nucala (mepolizumab)	Xolair‡ (omalizumab)
Moderate to severe persistent asthma in patients ≥ 6 years of age with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with ICS					✔
Add-on maintenance treatment for patients ≥ 12 years of age with severe asthma with an eosinophilic phenotype			✔		
Add-on maintenance treatment for patients ≥ 6 years of age with severe asthma with an eosinophilic phenotype				✔	
Add-on maintenance treatment for patients ≥ 6 years of age with moderate-to-severe asthma with an eosinophilic phenotype or with oral corticosteroid dependent asthma		✔			
Add-on maintenance treatment for patients ≥ 18 years of age with severe asthma with an eosinophilic phenotype	✔				
Treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA)				✔	
Add-on maintenance treatment of nasal polyps for patients ≥ 18 years of age with an inadequate response to nasal corticosteroids					✔
The treatment of adults and adolescents ≥ 12 years of age with chronic idiopathic urticaria (CIU) who remain					✔

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Indication	Cinqair[†] (reslizumab)	Dupixent (dupilumab)	Fasenra[†] (benralizumab)	Nucala (mepolizumab)	Xolair[‡] (omalizumab)
symptomatic despite H_1-antihistamine treatment.					
Add-on maintenance treatment in adult patients with inadequately controlled CRSwNP		✔		✔	
Treatment of adult and pediatric patients ≥ 12 years of age with hypereosinophilic syndrome (HES) for ≥ 6 months without an identifiable non-hematologic secondary cause				✔	

* None of the agents are indicated for the relief of acute bronchospasm or status asthmaticus.
† Not indicated for the treatment of other eosinophilic conditions.
‡ Not indicated for other allergic conditions or other forms of urticaria.

(*Prescribing information: Cinqair 2020, Dupixent 2021, Fasenra 2021, Nucala 2021, Xolair 2021*)

Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

OMALIZUMAB

Asthma

- The original FDA approval of omalizumab was based on the results of 3 randomized, double-blind, placebo-controlled, multicenter trials conducted in patients ≥ 12 years of age with moderate to severe asthma for ≥ 1 year and a positive skin test reaction to a perennial aeroallergen. All patients were required to have a baseline IgE between 30 and 700 international unit (IU)/mL and body weight not more than 150 kg. Patients were treated according to a dosing table to administer at least 0.016 mg/kg/IU (IgE/mL) of omalizumab or placebo over each 4-week period.
  - Each study was comprised of a run-in period to achieve a stable conversion to a common ICS, followed by randomization to omalizumab or placebo. Patients received omalizumab for 16 weeks with an unchanged ICS dose unless an acute exacerbation necessitated an increase. Patients then entered an ICS reduction phase of 12 (*Busse et al 2001, Solèr et al 2001*) and 16 weeks (*Holgate et al 2004*) during which ICS dose reduction was attempted in a stepwise manner.
  - In the 28-week study by Busse et al (N = 525), during the steroid stable phase, patients treated with omalizumab had fewer mean exacerbations/subject (0.28 vs 0.54; p = 0.006) and decreased mean duration of exacerbations (7.8 vs 12.7 days; p < 0.001) compared with placebo-treated patients. Similarly, during the steroid reduction phase, omalizumab was associated with fewer exacerbations/subject (0.39 vs 0.66; p = 0.003), and a shorter mean duration of exacerbations (9.4 vs 12.6 days; p = 0.021) (*Busse et al 2001*).
  - In the 28-week study by Solèr et al (N = 546), asthma exacerbations/patient, the primary endpoint, decreased more in the omalizumab group compared to placebo during both the stable steroid (0.28 vs 0.66; p < 0.001) and steroid reduction phases (0.36 vs 0.75; p < 0.001) (*Solèr et al 2001*).
  - In the 32-week study by Holgate et al (N = 246), the percentage reduction in ICS dose, the primary endpoint, was greater among patients treated with omalizumab than among patients treated with placebo (median, 60 vs 50%; p = 0.003). The percentages of patients with ≥ 1 asthma exacerbation were similar between omalizumab and placebo groups during both the stable steroid and steroid reduction phases (p-value not reported). The absence of an observed treatment effect may be related to differences in the patient population compared with the first 2 studies, study sample size, or other factors (*Holgate et al 2004*).

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- A meta-analysis of 3 of the previously mentioned trials (*Busse et al 2001, Holgate et al 2004, Solèr et al 2001*) and their extension studies assessed the efficacy of omalizumab in a subgroup of 254 patients at high risk of serious asthma-related mortality and morbidity. Patients were defined as high-risk due to asthma histories that included the following: intubation history, emergency room visit within the last year, overnight hospitalization, or intensive care unit treatment. The primary outcome was an annualized rate of acute exacerbation episodes based on data from the initial 16-week stable steroid phase for high-risk patients. Two kinds of acute exacerbation episodes were considered as endpoints: significant acute exacerbation episodes and all acute exacerbation episodes (ie, all episodes recorded by the investigator). Significant acute exacerbation episodes were defined as those requiring a doubling of baseline ICS dose (*Busse et al 2001, Solèr et al 2001*) or use of systemic steroids (all 3 studies). During the stable steroid phase, mean significant acute exacerbation episode rates were 1.56 and 0.69/patient-year, respectively, a reduction of 56% with omalizumab ($p = 0.007$). Similar reductions in exacerbations in favor of omalizumab were observed for the whole study period and for all acute exacerbation episodes. The authors concluded that 113 significant acute exacerbation episodes were prevented for every 100 patients treated with omalizumab for 1 year (*Holgate et al 2001*).
- A Cochrane Review conducted in 2014 evaluated the efficacy of omalizumab in patients with allergic asthma. Treatment with omalizumab was associated with a significant reduction in the odds of a patient having an asthma exacerbation (odds ratio [OR], 0.55; 95% confidence interval [CI], 0.42 to 0.6; 10 studies; 3261 participants). This represents an absolute reduction from 26% for participants suffering an exacerbation on placebo to 16% on omalizumab, over 16 to 60 weeks. Additionally, in patients with moderate to severe asthma and in those who were receiving background ICS therapy, treatment with omalizumab resulted in a significant reduction in the odds of having an asthma exacerbation (OR, 0.50; 95% CI, 0.42 to 0.6; 7 studies; 1889 participants). A significant benefit was noted for subcutaneous (SC) omalizumab vs placebo with regard to reducing hospitalizations (OR, 0.16, 95% CI, 0.06 to 0.42; 4 studies; 1824 participants), representing an absolute reduction in risk from 3% with placebo to 0.5% with omalizumab over 28 to 60 weeks. The authors concluded that omalizumab was effective in reducing asthma exacerbations and hospitalizations as an adjunctive therapy to ICS and significantly more effective than placebo in increasing the numbers of participants who were able to reduce or withdraw their ICS. Omalizumab was generally well tolerated, although there were more injection site reactions with omalizumab. However, the clinical value of the reduction in steroid consumption has to be considered in light of the high cost of omalizumab (*Normansell et al 2014*).
- A systematic review of 8 randomized, placebo-controlled trials (N = 3429) evaluated the efficacy and safety of SC omalizumab as add-on therapy to corticosteroids in children and adults with moderate to severe allergic asthma. At the end of the steroid reduction phase, patients taking omalizumab were more likely to be able to withdraw corticosteroids completely compared with placebo (relative risk [RR], 1.8; 95% CI, 1.42 to 2.28; $p = 0.00001$). Omalizumab patients showed a decreased risk for asthma exacerbations at the end of the stable (RR, 0.57; 95% CI, 0.48 to 0.66; $p = 0.0001$) and adjustable-steroid phases (RR, 0.55; 95% CI, 0.47 to 0.64; $p = 0.0001$); post-hoc analysis suggests this effect was independent of duration of treatment, age, severity of asthma, and risk of bias. The frequency of serious adverse effects was similar between omalizumab (3.8%) and placebo (5.3%). However, injection site reactions were more frequent in the omalizumab patients (19.9 vs 13.2%). Omalizumab was not associated with an increased risk of hypersensitivity reactions, cardiovascular effects, or malignant neoplasms (*Rodrigo et al 2011*).
- In July 2016, the FDA expanded the indication of omalizumab to patients 6 to 11 years of age with moderate to severe persistent asthma. The approval was based primarily on a 52-week, randomized, double-blind, placebo-controlled, multicenter trial. The study evaluated the safety and efficacy of omalizumab as add-on therapy in 628 pediatric patients 6 to < 12 years of age with moderate to severe asthma inadequately controlled despite the use of an ICS (*Lanier et al 2009*).
  - Over the 24-week fixed-steroid phase, omalizumab reduced the rate of clinically significant asthma exacerbations (worsening symptoms requiring doubling of baseline ICS dose and/or systemic steroids) by 31% vs placebo (0.45 vs 0.64; RR, 0.69; $p = 0.007$). Over a period of 52 weeks, the exacerbation rate was reduced by 43% ($p < 0.001$). Other efficacy variables such as nocturnal symptom scores, beta-agonist use, and forced expiratory volume in 1 second (FEV_1) were not significantly different in omalizumab-treated patients compared to placebo.
- A 2017 systematic review of 3 randomized, placebo-controlled trials and 5 observational studies evaluated the safety and efficacy of omalizumab in children and adolescents. Omalizumab reduced exacerbations compared with placebo or baseline in all studies that included this outcome. The randomized controlled trials did not identify significant differences in FEV_1; however, 3 of the 4 observational studies that included this outcome did find significant FEV_1 improvement with omalizumab. Generally, ICS and rescue medication use were reduced with omalizumab in the studies. The authors

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concluded that the evidence strongly supports omalizumab safety and efficacy in patients 6 to 11 years *(Corren et al 2017)*.

- The EXCELS study was a multicenter, observational cohort study to evaluate the clinical effectiveness and long-term safety of omalizumab in patients with moderate-to-severe allergic asthma. Patients were evaluated as part of 3 groups: non-omalizumab users, those newly starting omalizumab, and those who have established users at study initiation.
  - Interim efficacy results demonstrated that at month 24, the ACT score increased in all 3 patient groups: from 18.4 to 20 in non-omalizumab users, from 15.2 to 19.4 in those newly starting on omalizumab, and from 18.2 to 19.4 in established omalizumab users. For patients newly starting omalizumab treatment, 54% achieved at least a minimally important difference, defined as a ≥ 3 point increase from baseline in ACT. The study demonstrated that established users of omalizumab maintained asthma control during the study period (*Eisner et al 2012*).
  - To investigate the relationship between omalizumab and malignant neoplasms, safety information from the EXCELS trial was analyzed. Similar rates of primary malignancies in omalizumab- and non-omalizumab-treated patients were found. However, study limitations preclude definitively ruling out a malignancy risk with omalizumab (*Long et al 2014*).
  - A higher incidence of overall cardiovascular and cerebrovascular serious adverse events was observed in omalizumab-treated patients compared to non-omalizumab-treated patients (*Iribarren et al 2017*). To further evaluate the risk, a pooled analysis of 25 randomized controlled trials was conducted. An increased risk of cardiovascular and cerebrovascular serious adverse events was not noted, but the low number of events, the young patient population, and the short duration of follow-up prevent a definite conclusion about the absence of a risk (*FDA 2014*).
  - Patients from the EXCELS study were eligible for the XPORT trial, a 52-week, randomized, placebo-controlled trial evaluating the persistence of response to omalizumab in patients who discontinued omalizumab therapy after long-term use. Patients were randomized to continue their omalizumab therapy or to omalizumab discontinuation. More patients who continued omalizumab did not have an exacerbation compared to those who discontinued therapy (67.0% vs 47.7%; absolute difference, 19.3%; 95% CI, 5.0 to 33.6). The authors concluded that continuation of omalizumab after long-term use results in sustained benefit (*Ledford et al 2017*).

Chronic idiopathic urticaria (CIU)

- The safety and efficacy of omalizumab for the treatment of CIU was assessed in 2 placebo-controlled, multiple-dose clinical studies. Patients received omalizumab 75, 150, or 300 mg or placebo by SC injection every 4 weeks in addition to their baseline level of H_1 antihistamine therapy for 24 or 12 weeks, followed by a 16-week washout observation period. In both studies, patients who received omalizumab 150 mg or 300 mg had greater decreases from baseline in weekly itch severity scores and weekly hive count scores than placebo at week 12. The 75 mg dose did not demonstrate consistent evidence of efficacy and is not approved for use (*Kaplan et al 2013, Maurer et al 2013*).
- Another randomized, double-blind, placebo-controlled study evaluated omalizumab as add-on therapy for 24 weeks in patients with CIU who remained symptomatic despite H_1 antihistamine therapy. Similar to previous studies, patients treated with omalizumab had significantly greater reductions in weekly itch severity score from baseline to week 12 compared to placebo ($p \leq 0.001$) (*Saini et al 2015*).
- A meta-analysis of randomized clinical trials evaluating omalizumab for the treatment of CIU was published in 2016. The analysis included 7 randomized, placebo-controlled studies with 1312 patients with CIU. Patients treated with omalizumab (75 to 600 mg every 4 weeks) had significantly reduced weekly itch and weekly wheal scores compared with the placebo group. The effects of omalizumab were dose-dependent, with the strongest reduction in weekly itch and weekly wheal scores observed with 300 mg. Rates of complete response were significantly higher in the omalizumab group ($p < 0.00001$) and dose-dependent, with the highest rates in the 300 mg group. Rates of patients with adverse events were similar in the omalizumab and placebo groups (*Zhao et al 2016*). Similar results were identified in a 2019 meta-analysis of 6 trials and a 2020 meta-analysis of 9 trials, both comparing omalizumab with placebo (*Jia and He 2020, Rubini et al 2019*).
- A Phase 4 randomized clinical trial evaluated the effect of omalizumab in 205 patients with antihistamine-resistant CIU/chronic spontaneous urticaria. After an initial 24-week period of open-label treatment with omalizumab 300 mg every 4 weeks, patients randomized to continue omalizumab for another 24 weeks of double-blind therapy experienced a significantly lower rate of clinical worsening compared with patients randomized to double-blind placebo (21.0% vs 60.4%; $p < 0.0001$). No new safety signals were detected over the 48-week omalizumab treatment period *(Maurer et al 2018)*.

Nasal Polyps

- The efficacy and safety of omalizumab for the treatment of nasal polyps in adult patients with an inadequate response to intranasal corticosteroids were based on results from 2 randomized, multicenter, double-blind, placebo-controlled,

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Phase 3 studies, POLYP 1 (n = 138) and POLYP 2 (n = 127) (*Gevaert et al 2020*). Patients were randomly assigned to omalizumab 75 to 600 mg SC every 2 or 4 weeks (based upon pretreatment serum total IgE level and body weight) or placebo for 24 weeks. All patients received background intranasal mometasone therapy. Results from both studies revealed that omalizumab was associated with a significantly greater improvement from baseline at week 24 in Nasal Polyp Score (NPS) and weekly average Nasal Congestion Score (NCS) as compared to placebo. In POLYP 1 and POLYP 2, the mean changes in NPS from baseline to week 24 for omalizumab compared to placebo were -1.08 vs 0.06 ($p < 0.0001$) and -0.9 vs -0.31 ($p = 0.014$), respectively, and mean changed in NCS from baseline were -0.89 vs -0.35 ($p = 0.0004$) and -0.7 vs -0.2 ($p = 0.0017$), respectively. Adverse events were similar between treatment groups.

BENRALIZUMAB

Asthma

- The safety and efficacy of benralizumab were evaluated in a 52-week dose-ranging exacerbation trial, 4 confirmatory trials, and a 12-week lung function trial (*Bleecker et al 2016, Castro et al 2014, Ferguson et al 2017, Fitzgerald et al 2016, Nair et al 2017, Harrison et al 2021*).
  - In a randomized, controlled, double-blind, dose-ranging Phase 2b study, 324 adults with uncontrolled eosinophilic asthma were randomly assigned to placebo (n = 80), benralizumab 2 mg (n = 81), benralizumab 20 mg (n = 81), or benralizumab 100 mg (n = 82) and 285 adults with non-eosinophilic asthma were randomized to benralizumab 100 mg (n = 142) or placebo (n = 143) (*Castro et al 2014*). Treatments were given as 2 SC injections every 4 weeks for the first 3 doses, then every 8 weeks, for 1 year. Among adults with eosinophilic asthma, benralizumab 100 mg reduced exacerbation rates as compared to placebo (0.34 vs 0.57; rate reduction, 41%; 80% CI, 11 to 60; $p = 0.096$). A significant reduction in exacerbation rates was not seen with benralizumab 2 mg or 20 mg as compared to placebo in these patients. In patients with a baseline blood eosinophil count of ≥ 300 cells/μL, exacerbation rates were lower than in the placebo group for the benralizumab 20 mg (0.30 vs 0.68; rate reduction, 57%; 80% CI, 33 to 72; $p = 0.015$) and 100 mg (0.38 vs 0.68; rate reduction, 43%; 80% CI, 18 to 60; $p = 0.049$) groups.
  - SIROCCO was a randomized, multicenter, double-blind, placebo-controlled, 48-week, Phase 3 trial (N = 1205) involving patients with severe asthma with eosinophilia uncontrolled with high-dose ICS and LABAs (*Bleecker et al 2016*). Enrolled patients were randomly assigned to placebo (n = 407), benralizumab 30 mg every 4 weeks (n = 400), or benralizumab 30 mg every 8 weeks (n = 398). Compared with placebo, benralizumab reduced the annual asthma exacerbation rate over 48 weeks when administered every 4 weeks (RR, 0.55; 95% CI, 0.42 to 0.71; $p < 0.0001$) or every 8 weeks (RR, 0.49; 95% CI, 0.37 to 0.64; $p < 0.0001$). Both doses of benralizumab also significantly improved pre-bronchodilator FEV_1 in patients at week 48 vs placebo. Asthma symptoms were improved with benralizumab every 8 weeks, but not every 4 weeks, as compared to placebo.
  - CALIMA was a randomized, multicenter, double-blind, placebo-controlled, 56-week, Phase 3 trial that assessed benralizumab as add-on therapy (to high-dose ICS and LABA) for patients with severe, uncontrolled asthma and elevated blood eosinophil counts (*Fitzgerald et al 2016*). A total of 1306 patients were randomly assigned to benralizumab 30 mg every 4 weeks (n = 425), benralizumab 30 mg every 8 weeks (n = 441) or placebo (n = 440). When compared to placebo, significant reductions in annual exacerbation rates were seen with benralizumab every 4 weeks (RR, 0.64; 95% CI, 0.49 to 0.85; $p = 0.0018$) and every 8 weeks (RR, 0.72; 95% CI, 0.54 to 0.95; $p = 0.0188$). Benralizumab was also associated with significantly improved pre-bronchodilator FEV_1 and total asthma symptom scores vs placebo.
  - Patients enrolled in the SIROCCO and CALIMA trials who completed treatment were eligible for the BORA Phase 3 safety extension trial. This was a randomized, double-blind study that randomized patients to received benralizumab 30 mg every 4 or 8 weeks. Adult patients received treatment for 52 weeks and adolescents (12 to 17 years of age) were treated for 108 weeks. A total of 1576 patients were included in the full-analysis set with safety assessed at 56 weeks. Treatment discontinuation due to any adverse event occurred in approximately 2% of patients in each group. The most common adverse events were viral upper respiratory tract infections and worsening asthma. Serious adverse events included worsening asthma (3% in the every-8-week dosing group and 4% in the every-4-week dosing group), pneumonia (< 1% in both groups) and pneumonia caused by bacterial infection (< 1% in the every-4-week dosing group and 1% in the every-8-week dosing group). New malignancy occurred in 12 (1%) of the 1,576 patients. Hypersensitivity related to treatment occurred in 3 patients. For the secondary efficacy outcome, patients with elevated blood eosinophil levels had similar exacerbation rates to that observed during the first year of treatment in the SIROCCO and CALIMA trials (*Busse et al 2019a*).

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- BISE was a randomized, multicenter, double-blind, placebo-controlled, 12-week, Phase 3 trial that evaluated benralizumab therapy for patients with mild to moderate persistent asthma (*Ferguson et al 2017*). Patients (N = 211) had been receiving either low- to medium-dose ICS or low-dose ICS plus LABA therapy and were randomized to benralizumab 30 mg every 4 weeks (n = 106) or placebo (n = 105). Benralizumab resulted in an 80 mL (95% CI, 0 to 150; p = 0.04) greater improvement in pre-bronchodilator FEV_1 after 12 weeks as compared to placebo. Despite this improvement, this lung function result does not warrant the use of benralizumab in mild to moderate asthma because it did not reach the minimum clinically important improvement of 10%.
- ZONDA was a randomized, multicenter, double-blind, placebo-controlled, 28-week trial that primarily assessed whether or not benralizumab was effective as an oral glucocorticoid-sparing therapy in patients on oral steroids to manage severe asthma associated with eosinophilia (*Nair et al 2017*). Of the enrolled patients, 220 were randomly assigned to benralizumab 30 mg every 4 weeks (n = 72), benralizumab 30 mg every 8 weeks (n = 73), or placebo (n = 75). Results revealed that the 2 benralizumab dosing regimens significantly reduced the median final oral glucocorticoid doses from baseline by 75% vs a 25% reduction seen with placebo (p < 0.001 for both comparisons). Additionally, benralizumab administered every 4 weeks resulted in an annual exacerbation rate that was 55% lower than that seen with placebo (marginal rate, 0.83 vs 1.83; p = 0.003) and benralizumab administered every 8 weeks resulted in a 70% lower rate than that seen with placebo (marginal rate, 0.54 to 1.83; p < 0.001).
- ANDHI was a randomized, multicenter, double-blind, placebo-controlled, Phase 3b study that assessed the effect of benralizumab in adults with severe eosinophilic asthma and at least 2 exacerbations in the previous year despite use of medium- to high-dose ICS plus another asthma controller (*Harrison et al 2021*). Patients were randomized to receive benralizumab 30 mg every 8 weeks (with the first 3 doses given 4 weeks apart; n = 427) or placebo (n = 229). Benralizumab significantly reduced annualized asthma exacerbation rate over the 24-week treatment period compared to placebo (RR, 0.51; 95% CI, 0.39 to 0.65; p < 0.0001).

- Fitzgerald et al conducted a study exploring the efficacy of benralizumab for patients with different baseline blood eosinophil thresholds and exacerbation histories. This study was a pooled analysis (n = 2295 patients) of the results from the SIROCCO and CALIMA Phase 3 studies. The annual exacerbation rate among patients with baseline blood eosinophil counts of ≥ 0 cells/μL was 1.16 (95% CI, 1.05 to 1.28) in patients who received placebo vs 0.75 (0.66 to 0.84) in patients who received benralizumab every 8 weeks (RR, 0.64; 0.55 to 0.75; p < 0.0001). In patients who received benralizumab every 4 weeks who had eosinophil counts of ≥ 0 cells/μL, the annual exacerbation rate was 0.73 (0.65 to 0.82); RR vs placebo was 0.63 (0.54 to 0.74; p < 0.0001). The extent to which exacerbation rates were reduced increased with increasing blood eosinophil thresholds and with greater exacerbation history in patients in the every-4-week and every-8-week benralizumab groups. Greater improvements in the annual exacerbation rate were seen with benralizumab compared with placebo for patients with a combination of high blood eosinophil thresholds and a history of more frequent exacerbations *(FitzGerald et al 2018).*
- A 2017 meta-analysis evaluated the therapeutic efficacy and safety of benralizumab in patients with eosinophilic asthma. A total of 7 articles (n = 2321) met the inclusion criteria of the systematic review. The pooled analysis found that benralizumab significantly reduced exacerbations (RR, 0.63; 95% CI, 0.52 to 0.76; p < 0.00001) compared to placebo. There was no statistical trend for improvement in FEV_1 or asthma control indices such as Quality of Life Assessment (AQLQ) and Asthma Control Questionnaire score in benralizumab-treated patients. In addition, safety data indicated that benralizumab administration did not result in an increased incidence of adverse events and was well tolerated (RR, 1.00; 95% CI, 0.95 to 1.05; p = 0.96) *(Tien et al 2017)*.

MEPOLIZUMAB

Asthma

- The safety and efficacy of mepolizumab were evaluated in 3 double-blind, placebo-controlled, multicenter, randomized controlled trials in adolescent and adult patients with severe refractory asthma and signs of eosinophilic inflammation. Generally, patients were eligible for enrollment in the trials if they had eosinophils ≥ 150 cells/μL in the peripheral blood at screening or ≥ 300 cells/μL at some time during the previous year. Patients also were required to be on a high-dose ICS as well as another controller medication (*Bel et al 2014, Ortega et al 2014, Pavord et al 2012*).
  - DREAM was a dose-ranging, 52-week, Phase 2b/3 study (N = 621) that compared annual asthma exacerbation frequency and improvements in clinical symptoms between patients receiving 75 mg, 250 mg, and 750 mg intravenous (IV) mepolizumab and placebo. Mepolizumab decreased clinically significant exacerbation rates across all doses compared to placebo, at a rate of 2.40 per patient per year in the placebo group, 1.24 in the 75 mg mepolizumab group (p < 0.0001), 1.46 in the 250 mg mepolizumab group (p = 0.0005), and 1.15 in the 750 mg

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mepolizumab group ($p < 0.0001$). No significant improvements were found for secondary clinical symptom measures, which included change in pre-bronchodilator FEV_1 from baseline, or change in Asthma Control Questionnaire (ACQ) scores *(Pavord et al 2012)*.
  - MENSA was a 32-week Phase 3 trial (N = 576) that compared annual asthma exacerbation frequency and improvements in clinical symptoms between patients receiving SC and IV mepolizumab vs placebo. Patients were selected on the basis of frequent exacerbations, treatment with high doses of ICS, and a defined blood eosinophil count. Both SC and IV mepolizumab significantly decreased clinically significant exacerbation rates compared to placebo, at a rate of 1.74 per patient per year in the placebo group, 0.93 per patient per year in the IV mepolizumab group ($p < 0.001$), and 0.83 per patient per year in the SC mepolizumab group ($p < 0.001$). In both the SC and IV mepolizumab-treated groups, the ACQ scores met thresholds for minimal clinically important change and were significantly improved compared to placebo ($p < 0.001$) *(Ortega et al 2014)*.
  - SIRIUS was a 24-week Phase 3 trial (N = 135) that compared oral corticosteroid requirements between patients receiving SC mepolizumab and placebo. The likelihood of a reduction in the daily oral glucocorticoid dose was 2.39 times higher in the mepolizumab group (95% CI, 1.25 to 4.56; p = 0.008). The median reduction in daily oral corticosteroid dose was 50% (95% CI, 20 to 75) in the mepolizumab-treated group compared to 0% (95% CI, -20 to 33.3) in the placebo group (p = 0.007) *(Bel et al 2014)*.
- A post-hoc analysis of data from DREAM and MENSA was conducted to assess the relationship between baseline blood eosinophil counts and efficacy of mepolizumab. Of 1192 patients, 846 received mepolizumab and 346 received placebo. The overall rate of mean exacerbations per person per year was reduced from 1.91 with placebo to 1.01 with mepolizumab (47% reduction; RR, 0.53; 95% CI, 0.44 to 0.62; $p < 0.0001$). The exacerbation rate reduction with mepolizumab vs placebo increased progressively from 52% (RR, 0.48; 95% CI, 0.39 to 0.58) in patients with a baseline blood eosinophil count of ≥ 150 cells/μL to 70% (RR, 0.30; 95% CI, 0.23 to 0.40) in patients with a baseline count of ≥ 500 cells/μL. At a baseline count < 150 cells/μL, predicted efficacy of mepolizumab was reduced. The authors concluded that the use of a baseline blood eosinophil count will help to select patients who are likely to achieve important asthma outcomes with mepolizumab (*Ortega et al 2016*).
- COSMOS was a 52-week, open-label extension study in patients who received mepolizumab or placebo in MENSA or SIRIUS. Patients received SC mepolizumab regardless of prior treatment allocation and continued to receive appropriate standard-of-care asthma therapy throughout. In total, 558 (86%; previous mepolizumab: 358; previous placebo: 200) and 94 (14%; previous mepolizumab: 58; previous placebo: 36) patients experienced on-treatment adverse events and serious adverse events, respectively. No fatal adverse events or instances of mepolizumab-related anaphylaxis were reported. Mepolizumab treatment was shown to exert a durable response, with patients who previously received mepolizumab in MENSA or SIRIUS maintaining reductions in exacerbation rate and oral corticosteroid dosing throughout COSMOS. Patients who previously received placebo in MENSA or SIRIUS demonstrated improvements in these endpoints following treatment with mepolizumab (*Lugogo et al 2016*).
- COLUMBA was an open-label extension study of patients enrolled in the DREAM trial who received mepolizumab 100 mg every 4 weeks plus standard of care until criterion for discontinuation was met (safety profile not positive for patient, patient withdrawn by their physician, patient withdrew consent, or drug became commercially available). There were 347 patients enrolled who received treatment for a mean of 3.5 years. Adverse events most frequently reported were respiratory tract infection (67%), headache (29%), bronchitis (21%), and worsening asthma (27%). Although 6 deaths occurred, none were considered related to study treatment. No anaphylaxis reactions were reported. Malignancy was reported in 2% (n = 6) of patients. The exacerbation rate for patients on treatment for 156 weeks or longer was 0.74 events/year, which was a 56% reduction from the off-treatment period between the 2 studies (*Khatri et al 2018*).
- A pharmacokinetic study of SC mepolizumab 40 and 100 mg (for bodyweight < 40 and ≥ 40 kg, respectively) every 4 weeks in 36 children 6 to 11 years of age with severe eosinophilic asthma and ≥ 2 exacerbations in the prior year demonstrated reductions in blood eosinophil count by 89% at week 12 *(Gupta et al 2019a)*. A 52-week safety extension study of 30 children demonstrated no safety or immunogenicity concerns, as well as improvements in blood eosinophil counts and asthma control from baseline *(Gupta et al 2019b)*. Findings of these studies supported FDA approval of mepolizumab for the treatment of severe eosinophilic asthma in children (*GlaxoSmithKline 2019*).
- A systematic review and meta-analysis compared hospitalization or hospitalization and/or emergency room visit rates in patients with severe eosinophilic asthma treated with mepolizumab or placebo in addition to standard of care for ≥ 24 weeks. Four studies (N = 1388) were eligible for inclusion. Mepolizumab significantly reduced the rate of exacerbations requiring hospitalization (relative rate, 0.49; 95% CI, 0.30 to 0.80; p = 0.004) and hospitalization/emergency room visit (relative rate, 0.49; 95% CI, 0.33 to 0.73; $p < 0.001$) vs placebo. Significant

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reductions of 45% and 38% were also observed for the proportion of patients experiencing 1 or more hospitalization and hospitalization and/or emergency room visit, respectively (*Yancey et al 2017*).

Eosinophilic granulomatosis with polyangiitis (EGPA)

- A 52-week, randomized, placebo-controlled, double-blind, parallel-group, multicenter, Phase 3 trial assessed the efficacy and safety of mepolizumab as add-on therapy (to glucocorticoid treatment, with or without immunosuppressive therapy) for patients with relapsing or refractory EGPA (*Wechsler et al 2017*). A total of 136 patients were randomly assigned to mepolizumab 300 mg every 4 weeks (n = 68) or placebo (n = 68). Results demonstrated the following for the mepolizumab and placebo groups, respectively:
  - Percentage of patients with ≥ 24 weeks of accrued remission: 28% vs 3% (OR, 5.91; 95% CI, 2.68 to 13.03; p < 0.001).
  - Percentage of patients in remission at both week 36 and week 48: 32% vs 3% (OR, 16.74; 95% CI, 3.61 to 77.56; p < 0.001).
  - Annualized relapse rate: 1.14 vs 2.27 (RR, 0.50; 95% CI, 0.36 to 0.70; p < 0.001).
  - Percentage of patients able to reduce their daily dose of concomitant prednisone or prednisolone to 4 mg or less (average of weeks 48 to 52): 44% vs 7% (OR, 0.20; 95% CI, 0.09 to 0.41; p < 0.001).

Hypereosinophilic syndrome (HES)

- A 32-week, double-blind, placebo-controlled, multicenter, randomized controlled trial evaluated the efficacy and safety of mepolizumab in patients ≥ 12 years with HES (without an identifiable nonhematologic secondary cause) for at least 6 months *(Nucala prescribing information 2021, Roufosse et al 2020b)*. A total of 108 patients were assigned to mepolizumab 300 mg every 4 weeks (n = 54) or placebo (n = 54). Results demonstrated the following for mepolizumab and placebo groups, respectively:
  - Proportion of patients with ≥ 1 HES flare or withdrew from the trial: 28% vs 56% (OR, 0.28; 95% CI, 0.12 to 0.64; p = 0.002)
  - Adjusted mean rate of HES flares per year: 0.50 vs 1.46 (rate ratio, 0.34; 95% CI, 0.19 to 0.63; p < 0.001)
  - Probability of first HES flare by week 32: 26.3% vs 52.7% (hazard ratio, 0.34; 95% CI, 0.18 to 0.67; p = 0.002)

CRSwNP

- SYNAPSE, a 52-week, double-blind, randomized, placebo-controlled, multicenter trial, evaluated the efficacy and safety of mepolizumab in adult patients with CRSwNP. A total of 407 patients with recurrent, refractory, severe, bilateral nasal polyp symptoms despite standard care treatment were enrolled. Patients were randomly assigned to receive 100 mg mepolizumab (n = 206) or placebo (n = 201) every 4 weeks. The total endoscopic nasal polyp score significantly improved from baseline with mepolizumab versus placebo (adjusted difference in medians, -0.73; 95% CI, -1.11 to -0.34; p < 0.0001). The nasal obstruction VAS score during weeks 49 to 52 also significantly improved (adjusted difference in medians, -3.14; 95% CI, -4.09 to -2.18; p < 0.0001). Adverse events related to study treatment occurred in 15% of the mepolizumab group and 9% of the placebo group (*Han et al 2021*).

RESLIZUMAB

Asthma

- The safety and efficacy of reslizumab were evaluated in 4 double-blind, placebo-controlled, multicenter, randomized controlled trials. In all 4 studies, patients were required to be on at least a medium-dose ICS with or without additional controller medications (*Bjermer et al 2016, Castro et al 2015, Corren et al 2016*).
  - Studies 3082 and 3083 were 52-week studies (N = 953) in patients with asthma who were required to have a blood eosinophil count ≥ 400 cells/μL, and ≥ 1 asthma exacerbation requiring systemic corticosteroid use over the past 12 months. These studies compared the asthma exacerbation rate and improvements in clinical symptoms between patients receiving reslizumab 3 mg/kg IV administered once every 4 weeks and placebo. In both studies, patients receiving reslizumab had a significant reduction in the frequency of asthma exacerbations (Study 3082: RR, 0.50; 95% CI, 0.37 to 0.67; Study 3083: RR, 0.41; 95% CI, 0.28 to 0.59; both p < 0.0001) compared with those receiving placebo. In both trials, an improvement in FEV_1 was evident for reslizumab vs placebo by the first on-treatment assessment at week 4, which was sustained through week 52. Reslizumab treatment also resulted in significant improvements compared with placebo in AQLQ total score, ACQ-7 score, and Asthma Symptom Utility Index (ASUI) score (*Castro et al 2015*).
  - Study 3081 was a 16-week study (N = 315) in patients who were required to have a blood eosinophil count ≥ 400 cells/μL. The study compared the change from baseline in FEV_1 and improvements in clinical symptoms between reslizumab 3 mg/kg vs placebo. Reslizumab 3 mg/kg significantly improved FEV_1 (difference vs placebo: 160 mL;

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95% CI, 60 to 259; p = 0.0018). Reslizumab also statistically significantly improved ACQ and AQLQ; however, the minimally important difference was only reached for AQLQ (*Bjermer et al 2016*).

    - Study 3084 was a 16-week study in 496 patients unselected for baseline blood eosinophil levels (approximately 80% of patients had a screening blood eosinophil count < 400 cells/µL). Patients were not allowed to be on maintenance oral corticosteroids. The study compared the change from baseline in FEV_1 and improvements in clinical symptoms between reslizumab 3 mg/kg vs placebo. In the subgroup of patients with baseline eosinophils < 400 cells/µL, patients treated with reslizumab showed no significant improvement in FEV_1 compared with placebo. In the subgroup with eosinophils ≥ 400 cells/µL, however, treatment with reslizumab was associated with much larger improvements in FEV_1, ACQ, and rescue SABA use compared with placebo (*Corren et al 2016*).
  - An open-label, non-randomized extension study of these placebo-controlled trials continued treatment of patients with eosinophilic asthma with reslizumab 3 mg/kg every 4 weeks for up to 24 months to assess the drug's safety. Patients initially randomized to placebo also received active drug. A total of 1051 patients were included (n = 480 reslizumab-naive and n = 571 reslizumab-treated patients). Of these, 740 patients received treatment for 12 months or longer, and 249 patients received treatment for 24 months or longer. Worsening asthma and nasopharyngitis were the most common adverse events. Serious adverse events occurred in 7% of patients and treatment discontinuation due to an adverse event occurred in 2% of patients. No deaths (n = 3) were related to treatment. Malignancy occurred in 15 (1%) patients. Patients previously on reslizumab maintained asthma control and those naive to treatment demonstrated improvement in asthma control and lung function. The authors concluded that reslizumab maintained asthma control for up to 2 years in patients with moderate-to-severe eosinophilic asthma (*Murphy et al 2017*).
  - A post hoc analysis of pooled data from 2 randomized, placebo-controlled trials in patients with inadequately controlled asthma and elevated blood eosinophil levels compared the efficacy of reslizumab vs placebo among the subgroup of patients with oral corticosteroid dependent asthma. Reslizumab was associated with a significant improvement in overall asthma exacerbations (RR, 0.32; 95% CI, 0.18 to 0.55) *(Nair et al 2020)*.
- A 2017 meta-analysis of 5 randomized controlled trials comparing reslizumab to placebo (N = 1366) revealed improvements in exacerbations, FEV_1, and ACQ score with reslizumab. Asthma exacerbations occurred less frequently in reslizumab patients vs placebo (OR, 0.46; 95% CI, 0.35 to 0.59; p < 0.00001). FEV_1 also improved with reslizumab compared to placebo (mean difference, 0.16; 95% CI, 0.10 to 0.23; p < 0.00001). Finally, ACQ score improved with reslizumab compared to placebo (mean difference, -0.26; 95% CI, -0.36 to -0.16; p < 0.00001). All studies included in the meta-analysis were of limited duration of 15 or 16 weeks (*Li et al 2017*).
- A 2019 meta-analysis of 6 randomized controlled trials (5 placebo-controlled trials and 1 open-label extension) evaluated the safety of reslizumab (n = 1028) with placebo (n = 730) in adults with uncontrolled asthma. Compared with placebo, reslizumab was associated with lower proportions of patients with ≥ 1 adverse event (67% vs 81%; RR, 0.83; 95% CI, 0.79 to 0.89) and with ≥ 1 serious adverse event (7% vs 10%; RR, 0.65; 95% CI, 0.48 to 0.89) *(Virchow et al 2020)*.

DUPILUMAB

Asthma

- A 52-week randomized, double-blind, placebo-controlled study evaluated the efficacy of dupilumab in patients ≥ 12 years of age with moderate-to-severe asthma uncontrolled with a medium-to-high dose ICS plus up to 2 additional controller medications (LABA and/or leukotriene receptor antagonist). Approximately 1900 patients were randomized to add-on therapy with dupilumab (200 mg or 300 mg every 2 weeks) or matching placebo for 52 weeks. The annual rate of severe exacerbations during the 52-week study period and the absolute change in FEV_1 at week 12 were the primary endpoints. A subgroup analysis of patients with an elevated blood eosinophil count of $300/mm^3$ was also planned. Both doses of dupilumab resulted in a reduced rate (46% and 47.7%, respectively) of asthma exacerbation compared to placebo (p < 0.0001). Patients with higher blood eosinophil levels had greater than 65% reduction in the annual exacerbation rate compared to placebo. The change in FEV_1 was also significantly improved with both doses of dupilumab compared to placebo and even more pronounced in patients with elevated blood eosinophil levels. Adverse events more common with dupilumab compared to placebo included injection-site reactions and eosinophilia (*Castro et al 2018*). In the subgroup of patients with baseline evidence of allergic asthma, dupilumab 200 mg and 300 mg every 2 weeks reduced severe asthma exacerbation rates by 36.9% and 45.5%, respectively (both p < 0.01) and improved FEV_1 at week 12 by 0.13 and 0.16 L, respectively (both p < 0.001) *(Corren et al 2020)*.
- A total of 210 patients ≥ 12 years of age with oral glucocorticoid-dependent severe asthma were randomized to receive add-on therapy with dupilumab 300 mg or placebo every other week for 24 weeks. Glucocorticoid doses were tapered

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from week 4 to week 20 and then maintained at a stable dose for 4 weeks. The percentage in glucocorticoid dose reduction at week 24 was the primary outcome. The percentage change in glucocorticoid dose was -70.1% with dupilumab vs -41.9% with placebo ($p < 0.001$). A dose reduction of ≥ 50% was observed in 80% of dupilumab-treated patients compared to 50% of placebo patients. Almost 70% of patients in the dupilumab group achieved a glucocorticoid dose of less than 5 mg compared to 33% in patients who received placebo. The exacerbation rate was 59% lower with dupilumab compared to placebo. Injection site reactions and eosinophilia were more common with dupilumab compared to placebo (*Rabe et al 2018*).

- A meta-analysis and systematic review of 4 RCTs evaluated the safety and efficacy of dupilumab compared to placebo in approximately 3000 patients with uncontrolled asthma. The rate of severe asthma exacerbation was significantly reduced with dupilumab compared to placebo (RR, 0.44; 95% CI, 0.35 to 0.055; $p < 0.01$). FEV_1 was also significantly increased with dupilumab with a mean difference of 0.14 L (95% CI, 0.12 to 0.17; $p < 0.01$). With respect to adverse events, the risk of injection site reactions was higher with dupilumab compared to placebo (RR, 1.91; 95% CI, 1.14 to 2.59; $p < 0.01$) (*Zayed et al 2018*).
- A randomized, double-blind, placebo-controlled trial evaluated the safety and efficacy of dupilumab in pediatric patients 6 to 11 years of age with moderate-to-severe asthma on a medium- or high-dose ICS and a second controller medication or high-dose ICS alone. In the 52-week trial, patients were randomized to receive dupilumab (n = 273) or placebo (n = 135) every other week. Dosing was dependent on body weight: patients < 30 kg received 100 mg every 2 weeks, those ≥ 30 kg received 200 mg every 2 weeks. The annualized rate of severe asthma exacerbation events during the study period was significantly reduced in the dupilumab group compared to placebo (rate ratio, 0.35; 95% CI, 0.22 to 0.56). Mean change from baseline in percent predicted FEV_1 was also significantly improved in the dupilumab group compared to placebo (least squares mean difference vs placebo, 5.32; 95% CI, 1.76 to 8.88). The efficacy of dupilumab 300 mg every 4 weeks in patients 6 to 11 years of age with body weight 15 to < 30 kg was extrapolated from efficacy of 100 mg every 2 weeks clinical trial with support from population pharmacokinetic analyses. The risk of any adverse event, serious adverse events, and adverse events leading to treatment discontinuation were not significantly different between dupilumab and placebo with the addition of helminth infections (*Dupixent prescribing information 2021*).

CRSwNP

- Two randomized, double-blind, placebo-controlled trials evaluated dupilumab added to standard of care in adults with severe bilateral CRSwNP (*Bachert et al 2019*). Patients had experienced symptoms despite receiving intranasal corticosteroids, systemic corticosteroids in the previous 2 years, or sinonasal surgery. In both the 24- and 52-week trials, dupilumab resulted in significant improvement as measured by least-squares mean differences in NPS (-2.06; 95% CI, -2.43 to -1.69 and -1.80; 95% CI, -2.10 to -1.51, respectively), nasal congestion or obstruction score (-0.89; 95% CI, -1.07 to -0.71 and -0.87; 95% CI, -1.03 to -0.71, respectively), and Lund-Mackay computed tomography score (-7.44; 95% CI, -8.35 to -6.53 and -5.13; 95% CI, -5.80 to -4.46, respectively). The risk of any adverse event, serious adverse events, and adverse events leading to treatment discontinuation were not significantly different between dupilumab and placebo.

COMPARATIVE REVIEWS

Asthma

- In 2017, Cockle et al conducted a systematic review and indirect treatment comparison to assess the comparative effectiveness and tolerability of mepolizumab and omalizumab, as add-on therapy to standard of care, in patients with severe asthma. Studies included in the primary analysis were double-blind, randomized controlled trials, ≥12 weeks' duration enrolling patients with severe asthma with a documented exacerbation history, and receiving a high-dose ICS plus ≥1 additional controller. Two populations were examined: patients potentially eligible for 1) both treatments (overlap population) and 2) either treatment (trial population) (*Cockle et al 2017*).
  - For the overlap population, no difference was found between mepolizumab and omalizumab. However, trends in favor of mepolizumab were observed, with median estimated RRs of 0.66 (95% CI, 0.37 to 1.19) for the rate of clinically significant exacerbations and 0.19 (95% CI, 0.02 to 2.32) for the rate of exacerbations requiring hospitalization.
  - Results of the trial population analysis showed that mepolizumab was associated with an estimated median RR of 0.63 (95% CI, 0.45 to 0.89) corresponding to a reduction of 37% in the rate of clinically significant exacerbations vs omalizumab. No difference between treatments was observed for the rate of exacerbations resulting in hospitalization; however, the median RR of 0.58 (95% CI, 0.16 to 2.13) demonstrated a trend for mepolizumab over omalizumab.

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  - Both treatments had broadly comparable effects on lung function and similar tolerability profiles.
- Another 2017 systematic review was unable to detect differences in efficacy when comparing add-on therapy with mepolizumab or omalizumab in asthma patients who were not well controlled on ICS therapy. The analysis included both randomized controlled trials and cohort studies with duration of ≥12 weeks. A total of 18 omalizumab studies (N = 4854) and 4 mepolizumab studies (N = 1620) were included. Network meta-analysis did not find a significant difference in FEV_1 between groups (mean difference, 9.3 mL in favor of mepolizumab; 95% CI, -67.7 to 86.3). Both omalizumab and mepolizumab reduced the annualized rates of asthma exacerbations by approximately 50% compared with placebo. Although the authors were unable to identify significant differences in efficacy, there was high heterogeneity among the clinical trials and major differences in study inclusion criteria *(Nachef et al 2018)*.
- A systematic review of the IL-5 antagonists, mepolizumab, reslizumab, and benralizumab, included 13 studies (N = 6000) conducted in patients with asthma poorly controlled by ICS. The majority of patients had severe eosinophilic asthma. All of the IL-5 antagonists reduced asthma exacerbations by approximately 50% and improved FEV_1 by 0.08 L to 0.11 L. Overall, there was not an increase in serious adverse events with any IL-5 antagonist; however, more patients discontinued benralizumab (36/1599) than placebo (9/998) due to adverse events *(Farne et al 2017)*.
- A 2019 network meta-analysis of 11 studies aimed to indirectly compare the efficacy (n = 1855) and safety (n = 3462) of reslizumab with benralizumab in patients with eosinophilic asthma. The efficacy analysis compared a benralizumab subgroup with blood eosinophils ≥ 300 cells/μL (n = 1537) to a reslizumab subgroup in GINA step 4/5 with 2 or more previous exacerbations and blood eosinophils ≥ 400 cells/μL. Reslizumab was found to have significantly greater improvement in the ACQ and AQLQ scores compared to benralizumab. No significant difference between the groups was observed in clinical asthma exacerbation, but a sensitivity analysis with the overall study population suggested a significantly greater reduction in exacerbations with reslizumab. There were fewer discontinuations due to adverse events with reslizumab; however, the frequency and types of adverse events were not significantly different between treatment groups (*Casale et al 2019).*
- A 2019 network meta-analysis of 11 studies compared efficacy of licensed doses of mepolizumab, benralizumab, and reslizumab in patients with severe eosinophilic asthma based on eosinophil levels. Mepolizumab reduced clinically significant exacerbations compared to benralizumab for patients with blood eosinophils ≥ 150 cells/μL (RR, 0.66; 95% CI, 0.49 to 0.89), ≥ 300 cells/μL (RR, 0.61; 95% CI, 0.37 to 0.99), and ≥ 400 cells/μL (RR, 0.55; 95% CI, 0.35 to 0.87) and with mepolizumab compared to reslizumab for patients with blood eosinophils ≥ 400 cells/μL (RR, 0.55; 95% CI, 0.36 to 0.85). Additionally, change from baseline in ACQ score was greater with mepolizumab compared to benralizumab in patients with baseline blood eosinophils ≥ 150 cells/μL (difference, -0.33; 95% CI, -0.54 to -0.11), ≥ 300 cells/μL (-0.40; 95% CI, -0.76 to -0.03), and ≥ 400 cells/μL (difference, -0.36; 95% CI, -0.66 to -0.05) and compared to reslizumab with blood eosinophils ≥ 400 cells/μL (difference, -0.39; 95% CI, -0.66 to -0.12). There was no difference between reslizumab and benralizumab in clinically significant exacerbations or ACQ scores in patients with blood eosinophils ≥ 400 cells/μL *(Busse et al 2019b)*.
- A 2019 systematic review and network meta-analysis of 30 randomized controlled trials compared biologic therapies for treatment of type 2 (ie, eosinophilic) asthma. Mepolizumab, reslizumab, and benralizumab significantly reduced the risk of exacerbations compared with placebo; however, network meta-analysis showed no superiority of any biologic therapy for this outcome among benralizumab, dupilumab, mepolizumab, reslizumab, and other biologics not available in the U.S. (lebrikizumab, tralokinumab, and tezepelumab) *(Edris et al 2019)*.
- In a 2020 meta-analysis including data from 3 trials (n = 2640), dupilumab and benralizumab were compared in patients with inadequately controlled asthma. While there were no significant differences in the annual exacerbation rates between both drugs in the overall population (RR, 0.83; 95% CI, 0.62 to 1.09) and in the subgroup with the blood eosinophil count <150 cells/μL (RR, 1.57; 95% CI, 0.73 to 2.82), dupilumab was superior to benralizumab for the subgroup with a blood eosinophil count of ≥ 300 cells/μL (RR, 0.58; 95% CI, 0.39 to 0.84) and ≥ 150 but < 300 cells/μL (RR, 0.51; 95% CI, 0.29 to 0.92). The incidence of adverse events was similar between groups (OR, 1.023; 95% CI, 0.688 to 1.526) (*Ando et al 2020*).
- Additional meta-analyses have not found significant differences in asthma exacerbation rates between mepolizumab and reslizumab or between benralizumab and mepolizumab *(Bourdin et al 2018, Henriksen et al 2018, Yan et al 2019).*
- The magnitude of treatment effect of biologic agents (including benralizumab, reslizumab, dupilumab, mepolizumab, lebrikizumab [investigational], and tralokinumab [investigational]) in patients with eosinophilic asthma was evaluated in a network meta-analysis. The outcomes evaluated were change in FEV_1, ACQ score, and AQLQ score. Event rates for asthma exacerbation and associated RRs were determined for each drug. A total of 26 studies were included in the analysis (n = 7 benralizumab, n = 2 dupilumab, n = 4 lebrikizumab, n = 7 mepolizumab, n = 4 reslizumab, n = 2

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tralokinumab) with a total of 8444 patients (n = 4406 on active treatment, n = 4038 in control groups). The duration of treatment ranged from 12 to 56 weeks. An increase in FEV_1, reduction in ACQ score, and increase in AQLQ score were observed with all treatments except tralokinumab. Compared to placebo, the greatest FEV_1 increase was with dupilumab (0.16 L; 95% CI, 0.08 to 0.24), followed by reslizumab (0.13 L; 95% CI, 0.10 to 0.17), and benralizumab (0.12 L; 95% CI, 0.08 to 0.17). Mepolizumab and lebrikizumab both had an increase of 0.09 L (95% CI, 0.03 to 0.15 with mepolizumab, 0.04 to 0.15 with lebrikizumab). Reduction in ACQ score (indicating better asthma control) in order of greatest to least reduction was mepolizumab, dupilumab, benralizumab, and reslizumab. The investigational agents had the least impact on the ACQ score. Quality of life scores were similarly increased with the 4 agents while the investigational agents had the least impact on quality of life. Compared to placebo, the calculated RR for annualized asthma exacerbation was significant only for dupilumab (RR, 0.37; 95% CI, 0.17 to 0.80) and reslizumab (RR, 0.64; 95% CI, 0.53 to 0.78). Comparisons between treatments did not show any significant difference for change in FEV_1, asthma control or quality of life except for superiority of mepolizumab to the 2 investigational agents in ACQ score reduction (*Iftikhar et al 2018*).

- In a 2020 network meta-analysis including 9 studies, treatment rankings estimated that dupilumab was most effective at reducing the risk of asthma exacerbation, followed by mepolizumab, reslizumab, and benralizumab. Similar to other indirect treatment comparisons, there were no within-group differences as related to the risk for asthma exacerbations (*Ramonell et al 2020*).

CRSwNP

- In a 2021 network meta-analysis including 9 randomized controlled trials, 4 different biologics (dupilumab [n = 3], omalizumab [n = 4], mepolizumab [n = 2]) and placebo were compared in patients with CRSwNP. Dupilumab was found to be the most efficacious in terms of nasal polyp score (NPS), Sino-Nasal Outcome Test-22 (SNOT-22) score, University of Pennsylvania Smell Identification Test (UPSIT) score, and nasal congestion score (NCS) surface under the cumulative ranking curve (SUCRA) values of 0.900, 0.916, 1.000, and 0.807, respectively. Omalizumab ranked second in efficacy in SNOT-22, UPSIT, and NCS scores with SUCRA values of 0.606, 0.500, and 0.693, respectively. Mepolizumab had the highest risk of adverse events for SUCRA values of 0.746 (*Wu et al 2021*).

CLINICAL GUIDELINES

Asthma

- According to guidelines from the NHLBI/National Asthma Education and Prevention Program, pharmacologic therapy is based on a stepwise approach in which medications are increased until asthma is controlled and then decreased when possible to minimize side effects of treatments. The level of asthma control is based on (*NHLBI 2007*):
  - Reported symptoms over the past 2 to 4 weeks
  - Current level of lung function (FEV_1 and FEV_1/forced vital capacity [FVC] values)
  - Number of exacerbations requiring oral corticosteroids per year.
- The NHLBI guidelines state that omalizumab is used as adjunctive therapy in patients ≥ 12 years of age who have allergies and severe persistent asthma that is not adequately controlled with the combination of high-dose ICS and LABA therapy (*NHLBI 2007*).
  - A 2020 focused update of the 2007 NHLBI guidelines provided updated recommendations on limited topics for the clinical management of adolescents and adults with asthma, including intermittent ICSs, add-on therapy with long-acting muscarinic antagonists, fractional exhaled nitric oxide, indoor allergen mitigation and immunotherapy. Addition of the asthma biologics (eg, anti-IgE, anti-IL5, anti-IL5R, or anti-IL4/IL13) to therapy could be considered in steps 5 and 6 in the stepwise approach for management of asthma. However, the systematic reviews that informed the update did not include studies examining the role of asthma biologics, and therefore, the report did not contain specific recommendations for use of biologics in asthma.
- In 2021, the Global Initiative for Asthma (GINA) published updated guidelines for asthma management and prevention. In April 2021, GINA updated a guideline on diagnosis and management of difficult-to-treat and severe asthma. Criteria for establishing a diagnosis of severe asthma were included, which requires multiple interventions before a diagnosis can be made. For patients with a diagnosis of severe asthma, uncontrolled on Step 4 treatment (eg, medium dose ICS/formoterol with as needed low dose ICS/formoterol as the reliever therapy), phenotyping for Type 2 inflammation into categories such as severe allergic, aspirin-exacerbated, allergic bronchopulmonary aspergillosis, chronic rhinosinusitis, nasal polyposis, atopic dermatitis, or eosinophilic asthma is recommended. Treatment with a biologic agent should be considered in patients who are uncontrolled despite a high-dose ICS/LABA, and who have allergic or eosinophilic biomarkers or need maintenance oral corticosteroids. Anti-IgE treatment with omalizumab is recommended

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for patients ≥ 6 years of age with severe allergic asthma. Similarly, add-on anti-IL-5 therapy (ie, benralizumab, mepolizumab) is recommended for patients ≥ 12 years of age or reslizumab for patients ≥ 18 years of age with severe eosinophilic asthma. Anti-IL4 receptor therapy (ie, dupilumab) is recommended for patients ≥ 12 years of age with severe eosinophilic/Type 2 asthma or patients taking oral corticosteroids. Prior to initiation of these agents, several factors are recommended to consider including cost, insurance eligibility criteria, evaluation of predictors of response, delivery route, dosing frequency, and patient preference (*GINA 2021*).

  - The 2021 GINA report provides interim guidance on the management of asthma in the context of the coronavirus disease 2019 (COVID-19) pandemic. Patients with asthma should continue their prescribed asthma medications, including ICS with or without LABA and add-on therapies, during the pandemic. Use of nebulizers should be avoided when possible to prevent transmission of the virus to other patients or healthcare workers. Vaccination for COVID-19 is recommended for people with asthma (*GINA 2021*).

- A European Respiratory Society/American Thoracic Society guideline on the management of severe asthma suggests the use of anti-IL-5 therapy as an add-on in adults with severe uncontrolled eosinophilic asthma or severe corticosteroid-dependent asthma. A blood eosinophil count of 150 cells/mcL or greater is suggested as a cut-point to guide initiation of anti-IL-5 therapy in adults with severe asthma and prior exacerbations. A blood eosinophil count of 260 cells/mcL or greater or an exhaled nitric oxide level of 19.5 parts per billion or greater may be used to identify adolescents and adults with severe allergic asthma who are likely to benefit from anti-IgE treatment. Dupilumab is suggested for adults with severe eosinophilic asthma, and for those with severe corticosteroid-dependent asthma regardless of eosinophil levels (*Holguin et al 2020*).

Chronic idiopathic urticaria (CIU)

- Guidelines developed by the American Academy of Allergy, Asthma & Immunology, the American College of Allergy, Asthma & Immunology, and the Joint Council of Allergy, Asthma & Immunology recommend a stepwise treatment approach for CIU. Treatment with omalizumab is recommended in patients inadequately controlled with antihistamines and a leukotriene receptor antagonist (*Bernstein et al 2014*).
- Joint guidelines by the European Academy of Allergy and Clinical Immunology, the Global Allergy and Asthma European Network, the European Dermatology Forum, and the World Allergy Organization recommend treatment with omalizumab in patients with symptoms despite treatment with a 4-fold dose of modern second-generation antihistamines. This is a change from previous guidelines in which use of either omalizumab or cyclosporine after failure of high-dose antihistamines was recommended. However, due to adverse effects and the lack of an approved indication, the new recommendation was that cyclosporine should only be considered if omalizumab does not provide an adequate response (*Zuberbier et al 2018*).
- Guidelines published by the British Society for Allergy and Clinical Immunology similarly recommend omalizumab as a potential second-line agent in patients inadequately controlled on a 4-fold dose of a non-sedating antihistamine (*Powell et al 2015*).

Eosinophilic granulomatosis with polyangiitis (EGPA)

- Both the EGPA (Churg-Strauss) Consensus Task Force recommendations and the American Society for Apheresis guideline recommend glucocorticoids alone for patients without life- and/or organ-threatening EGPA. For patients with life- and/or organ-threatening EGPA, both glucocorticoids and an immunosuppressant are recommended, as well as maintenance therapy with azathioprine or methotrexate. Guidelines from the American Society for Apheresis recognized mepolizumab as a future treatment option, and the EGPA Consensus Task Force recommendations noted that mepolizumab held promise for this condition based on the pilot studies available at the time of guideline development. IVIG can be considered for refractory EGPA or for treatment during pregnancy (*Groh et al 2015, Padmanabhan et al 2019*).

CRSwNP

- Treatment of CRSwNP is addressed in guidelines from the American Academy of Otolaryngology-Head and Neck Surgery; American Academy of Allergy, Asthma & Immunology, the American College of Allergy, Asthma & Immunology, and the Joint Council of Allergy, Asthma & Immunology; the International Forum of Allergy & Rhinology; and the European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA).
- Routine treatment recommendations include saline irrigation and/or intranasal glucocorticoids in patients with mild symptoms, and short-term systemic glucocorticoids and surgery in patients with severe or refractory symptoms (*Orlandi*

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et al 2016, Peters et al 2014, Rosenfeld et al 2015). While not approved at the time of writing, some guidelines acknowledged the demonstration of benefit with IL-5 antagonists (*Orlandi et al 2016, Peters et al 2014*).
- In 2019, EUFOREA published an expert consensus focused on the use of biologics for CRSwNP with or without asthma. Per EUFOREA, biologics are indicated in patients with bilateral nasal polyps and previous sinus surgery who also meet 3 of the following criteria: evidence of type 2 inflammation (biological biomarkers); the need for systemic corticosteroids in the past 2 years; significant quality-of-life impairment; significant loss of smell; and diagnosis of comorbid asthma. In patients who have never had surgery, 4 of the aforementioned criteria need to be met before a biologic is indicated. Patients with previous sinus surgery plus severe asthma may also qualify for treatment in consultation with their pulmonologist. Lastly, biologics should not be initiated in the following situations: CRSwNP and lack of signs of type 2 inflammation; cystic fibrosis; unilateral nasal polyps; mucoceles; general contraindications for biological treatments, such as immunodeficiencies; and patient-related factors such as noncompliance to therapy (*Fokkens et al 2019*).

Hypereosinophilic syndrome (HES)
- The World Health Organization (WHO) guidance on eosinophilic disorders have stated that identification of rearranged *PDGFRA* or *PDGFRB* is important in the management of eosinophilic disorders as those variants respond to imatinib (*Shomali and Gotlib 2019*). For patients with idiopathic HES (without imatinib-sensitive variants), corticosteroids are first-line therapy; second-line options include hydroxyurea, interferon-alfa, other cytotoxic chemotherapy agents, and hematopoietic stem cell transplantation. The WHO listed use of mepolizumab or benralizumab as an area of active investigation. The WHO guidance was published prior to the FDA approval of mepolizumab for HES.

SAFETY SUMMARY

- All of the antiasthmatic monoclonal antibodies are contraindicated in patients with a history of hypersensitivity to the specific agent or excipients of the formulation.
- Abrupt discontinuation of systemic, topical or inhaled corticosteroids is not recommended when treatment with any of these agents are initiated. If appropriate, the corticosteroid dosage should be reduced gradually.

Cinqair
- Boxed warning: Anaphylaxis has been observed with Cinqair infusion in 0.3% of patients in placebo-controlled clinical studies. Anaphylaxis was reported as early as the second dose of Cinqair. Patients should be observed for an appropriate period of time after Cinqair administration by a healthcare professional prepared to manage anaphylaxis.
- Key warnings and precautions:
  - In placebo-controlled clinical studies, 6/1028 (0.6%) patients receiving 3 mg/kg Cinqair had ≥1 malignant neoplasm reported compared to 2/730 (0.3%) patients in the placebo group. The observed malignancies in Cinqair-treated patients were diverse in nature and without clustering of any particular tissue type.
  - Pre-existing helminth infections should be treated before therapy with Cinqair. If patients become infected while receiving Cinqair and do not respond to anti-helminth treatment, Cinqair should be discontinued until the parasitic infection resolves.
- The most common adverse reaction (≥ 2%) included oropharyngeal pain.

Dupixent
- Key warnings and precautions:
  - Hypersensitivity reactions (eg, anaphylaxis, erythema nodosum, erythema multiforme, serum sickness, urticaria, and rash) have occurred after administration of Dupixent. Dupixent should be discontinued in the event of a hypersensitivity reaction.
  - For patients with asthma, cases of eosinophilic pneumonia and vasculitis consistent with EGPA have been reported. Occurrence of vasculitic rash, worsening pulmonary symptoms, and/or neuropathy, especially upon reduction of oral corticosteroids should be monitored.
  - Pre-existing helminth infections should be treated before therapy with Dupixent. If a patient becomes infected while receiving Dupixent and does not respond to anti-helminth treatment, Dupixent should be discontinued until the parasitic infection resolves.

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- Adverse reactions:
  - Asthma: the most common adverse reactions included injection site reactions, oropharyngeal pain, and eosinophilia.
    - The safety profile in patients 6 to 11 of age was similar to the safety profile from studies in adults and adolescents with the addition of helminth infections. Adverse reactions of helminth infections were reported in pediatric patients (5 cases of enterobiasis and 1 case of ascariasis) who participated in clinical studies.
  - CRSwNP: the most common adverse reactions included injection site reactions, eosinophilia, insomnia, toothache, gastritis, arthralgia, and conjunctivitis.

Fasenra

- Key warnings and precautions:
  - Hypersensitivity reactions (eg, anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred after administration of Fasenra. Fasenra should be discontinued in the event of a hypersensitivity reaction.
  - Pre-existing helminth infections should be treated before therapy with Fasenra. If patients become infected while receiving Fasenra and do not respond to anti-helminth treatment, Fasenra should be discontinued until the parasitic infection resolves.
- The most common adverse reactions (≥ 5%) included headache and pharyngitis.

Nucala

- Key warnings and precautions:
  - Hypersensitivity reactions (eg, anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred after administration of Nucala.
  - Herpes zoster infections have occurred in patients receiving Nucala. Vaccination should be considered if clinically appropriate.
  - Pre-existing helminth infections should be treated before therapy with Nucala. If patients become infected while receiving Nucala and do not respond to anti-helminth treatment, Nucala should be discontinued until the parasitic infection resolves.
- The most common adverse reactions (≥ 5%) included headache, injection site reaction, back pain, and fatigue. Mouth/throat pain and joint pain have been reported in patients with CRSwNP.

Xolair

- Boxed warning: Anaphylaxis, presenting as bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue, has been reported. Initiate Xolair in a healthcare setting and closely observe patients for an appropriate period of time after administration. Health care providers administering Xolair should be prepared to manage anaphylaxis that can be life-threatening. Selection of patients for self-administration of Xolair should be based on criteria to mitigate risk from anaphylaxis.
  - Patients with a prior history of anaphylactic reactions to other causes may be at an increased risk for anaphylaxis. The frequency of anaphylaxis is reported to be between 0.1 to 0.2% and may occur immediately or up to a year post-treatment. Approximately 60 to 70% of anaphylaxis cases have been reported to occur within the first 3 doses.
- Key warnings and precautions:
  - Malignant neoplasms were observed in a higher rate of Xolair-treated patients (0.5%) than control patients (0.2%) in clinical trials. A subsequent 5-year observational cohort study found similar rates of primary malignancies in Xolair- and non-Xolair-treated patients. However, study limitations preclude definitively ruling out a malignancy risk with Xolair (*Long et al 2014*).
  - Rarely, patients on therapy with Xolair may present with serious systemic eosinophilia, which may present with features of vasculitis consistent with Churg-Strauss syndrome. These events usually have been associated with the reduction of oral corticosteroid therapy.
  - Systemic or inhaled corticosteroids should not be abruptly discontinued upon initiation of Xolair therapy for asthma or nasal polyps.
  - Some patients have reported signs and symptoms similar to serum sickness, including arthritis/arthralgia, rash, fever, and lymphadenopathy.
- Adverse reactions:
  - Asthma: In patients ≥ 12 years of age, the most commonly observed adverse reactions in clinical studies (≥ 1% in Xolair-treated patients and more frequently than reported with placebo) were arthralgia, pain (general), leg pain,

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fatigue, dizziness, fracture, arm pain, pruritus, dermatitis, and earache. In clinical studies with pediatric patients 6 to < 12 years of age, the most common adverse reactions were nasopharyngitis, headache, pyrexia, upper abdominal pain, streptococcal pharyngitis, otitis media, viral gastroenteritis, arthropod bites, and epistaxis.
  - Cardiovascular and cerebrovascular events in asthma studies: In a 5-year observational cohort study, a higher incidence of overall cardiovascular and cerebrovascular serious adverse events was observed in Xolair-treated patients compared to non-Xolair-treated patients. To further evaluate the risk, a pooled analysis of 25 randomized, controlled, clinical trials was conducted. An increased risk of cardiovascular and cerebrovascular serious adverse events was not noted, but the low number of events, the young patient population, and the short duration of follow-up prevent a definite conclusion about the absence of a risk (*FDA 2014*).
- CIU: Adverse reactions from 3 placebo-controlled, multiple-dose CIU studies that occurred in ≥ 2% of patients receiving Xolair and more frequently than in those receiving placebo included arthralgia, cough, headache, nasopharyngitis, nausea, sinusitis, upper respiratory tract infection, and viral upper respiratory tract infection.
- Nasal polyps: The most common adverse reactions (≥ 3% of patients) in clinical studies included headache, injection site reaction, arthralgia, upper abdominal pain, and dizziness.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Cinqair (reslizumab)	Single-use vials	IV	Every 4 weeks	• Safety and effectiveness in pediatric patients ≤ 17 years of age have not been established. • Cinqair should be administered by a healthcare professional by IV infusion over 20 to 50 minutes.
Dupixent (dupilumab)	Single-dose pre-filled syringe, single-dose pre-filled pen	SC	Asthma: every other week In pediatric patients (6 to 11 years of age) weighing 15 kg to < 30 kg, dosing regimen for asthma can also include every 4 weeks. CRSwNP: every other week	• Safety and efficacy in patients < 6 years of age (asthma) and < 18 years of age (CRSwNP) have not been established. • Dupixent may be administered by a healthcare professional or self-administered via pre-filled syringe or pen.
Fasenra (benralizumab)	Single-dose pre-filled syringe, single-dose pre-filled pen (autoinjector)	SC	Every 4 weeks for first 3 doses, followed by every 8 weeks	• Safety and efficacy in pediatric patients < 12 years of age have not been established. • Fasenra may be administered by a healthcare professional or self-administered via an autoinjector.
Nucala (mepolizumab)	Single-dose vial for reconstitution, single-dose pre-filled pen (autoinjector), single-dose prefilled syringe	SC	Asthma: every 4 weeks EGPA: every 4 weeks HES: every 4 weeks CRSwNP: every 4 weeks	• Safety and efficacy in pediatric patients < 6 years (asthma), < 18 years (EGPA), < 12 years (HES) of age, and < 18 years of age (CRSwNP) have not been established. • Nucala may be administered by a healthcare professional or self-administered via an autoinjector or pre-filled syringe.

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Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Xolair (omalizumab)	Single-dose vial for reconstitution, single-dose prefilled syringe	SC	Allergic asthma: Every 2 or 4 weeks CIU: Every 4 weeks Nasal polyps: Every 2 or 4 weeks	• Safety and efficacy in pediatric patients < 6 years of age (asthma), < 12 years of age (CIU), < 18 years of age (nasal polyps) have not been established. • Xolair should be initiated in a healthcare setting: once therapy has been safely established, Xolair may be administered by a healthcare professional or self-administered via a pre-filled syringe. • For allergic asthma and nasal polyps, dose and frequency are determined by serum total IgE level (measured before the start of treatment) and body weight. • Dosing in CIU is not dependent on serum IgE level or body weight.

See the current prescribing information for full details.

CONCLUSION

- Xolair is a humanized monoclonal antibody that is FDA-approved for patients ≥ 6 years of age with moderate to severe persistent asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with an ICS. Xolair has been shown to decrease the incidence of asthma exacerbations in these patients.
  - Although clinical trial results have been mixed and several trials had an open-label design, there is some evidence to indicate that Xolair may decrease asthma-related emergency visits and hospitalizations, as well as decreasing the dose of ICS and rescue medication and increasing symptom-free days (*Buhl et al 2002, Busse et al 2011, Holgate et al 2004, Lanier et al 2003, Solèr et al 2011*).
  - Xolair carries a boxed warning due to the risk of anaphylaxis, and thus must be initiated in a healthcare setting. Once therapy has been safely established, select patients may be able to self-administer Xolair using a pre-filled syringe.
  - Although Xolair therapy is generally safe, analysis of a 5-year, observational cohort, epidemiological study (EXCELS) showed an increased number of cardiovascular and cerebrovascular adverse events in patients receiving Xolair compared to placebo (*Iribarren et al 2017*). However, a pooled analysis of 25 randomized, double-blind, placebo-controlled clinical trials did not find notable imbalances in the rates of cardiovascular and cerebrovascular serious adverse events (*FDA 2014*).
  - Asthma guidelines generally recommend Xolair therapy in patients with severe allergic asthma that is inadequately controlled with a combination of high-dose ICS and LABA (*Cloutier et al 2020, GINA 2021, NHLBI 2007*). Based on a limited place in therapy, Xolair is appropriate for a small percentage of patients with asthma.
- Xolair received FDA approval for the treatment of adults and adolescents (≥ 12 years of age) with CIU who remain symptomatic despite H_1-antihistamine treatment. Two randomized, placebo-controlled trials demonstrated its efficacy in reducing weekly itch severity scores and weekly hive count scores significantly greater than placebo at week 12. Xolair was well-tolerated, with a safety profile similar to that observed in asthma patients.
  - In patients with CIU, Xolair is administered at 150 or 300 mg SC every 4 weeks.
  - Guidelines for the treatment of CIU recommend treatment with Xolair in patients who are inadequately controlled with a 4-fold dose of modern second-generation antihistamines. Although previous guidelines suggested the use of omalizumab after a leukotriene receptor antagonist, the most recent guideline from the European Academy of Allergy and Clinical Immunology, the Global Allergy and Asthma European Network, the European Dermatology Forum, and the World Allergy Organization state that a recommendation regarding use of a leukotriene receptor antagonist cannot be made due to a low level of evidence. Additionally, use of Xolair is recommended before treatment with cyclosporine (*Bernstein et al 2014, Zuberbier et al 2018, Powell et al 2015*).

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- Xolair was approved as add-on maintenance treatment for nasal polyps in adult patients with an inadequate response to nasal corticosteroids, based on results from 2 identical, randomized, multicenter, double-blind, placebo-controlled, Phase 3 studies [POLYP 1 and POLYP 2] (*Gevaert et al 2020*). Results from both studies revealed that Xolair was associated with a significantly greater improvement from baseline at week 24 in NPS and weekly average NCS as compared to placebo. Adverse events were similar between groups.
- Cinqair, Fasenra, and Nucala are IL-5 antagonists approved as add-on treatment options for patients with severe eosinophilic asthma, and have demonstrated effectiveness in reducing asthma exacerbations (*Bel et al 2014, Bjermer et al 2016, Castro et al 2015, Corren et al 2016, Pavord et al 2012, Ortega et al 2014, Bleecker et al 2016, Fitzgerald et al 2016*).
  - The mechanism of action of Fasenra is slightly different, in that it binds to the IL-5 receptor on immune effector cells, whereas Cinqair and Nucala bind to the IL-5 cytokine. All of these agents provide a more targeted treatment option for patients with severe asthma and should be considered in patients who are uncontrolled despite a high-dose ICS/LABA, and who have allergic or eosinophilic biomarkers or need maintenance oral corticosteroids (*GINA 2021*).
- Dupixent is an IL-4/IL-13 antagonist approved for the treatment of patients ≥ 6 years of age with moderate-to-severe asthma of the eosinophilic type or dependent on oral corticosteroids, and as an add-on treatment in adults with inadequately controlled CRSwNP.
  - According to GINA guidelines, the use of Dupixent for severe asthma with an eosinophilic phenotype can be considered for patients with severe eosinophilic/Type 2 asthma or patients taking oral corticosteroids.
- Dupixent was approved for CRSwNP after the publication of several guidelines, although some acknowledged the potential role for biologic therapies (*Orlandi et al 2016, Peters et al 2014).*
  - In a 2019 EUFOREA expert consensus publication focused on the use of biologics for CRSwNP with or without asthma, biologics were indicated in patients with bilateral nasal polyps and previous sinus surgery who also meet 3 of the following criteria: evidence of type 2 inflammation (biological biomarkers); need for systemic corticosteroids in the past 2 years; significant quality-of-life impairment; significant loss of smell; and diagnosis of comorbid asthma. In patients who have never had surgery, 4 of the aforementioned criteria need to be met before a biologic is indicated. Patients with previous sinus surgery plus severe asthma may also qualify for treatment in consultation with their pulmonologist. Lastly, biologics should not be initiated in the following situations: CRSwNP and lack of signs of type 2 inflammation; cystic fibrosis; unilateral nasal polyps; mucoceles; general contraindications for biological treatments, such as immunodeficiencies; and patient-related factors such as noncompliance to therapy (*Fokkens et al 2019*).
- Nucala is the only antiasthmatic monoclonal antibody approved for the treatment of adult patients with EGPA and patients ≥ 12 years of age with HES. Nucala is also approved as an add-on treatment in adults with inadequately controlled CRSwNP.
- There are no head-to-head trials comparing Cinqair, Fasenra, Dupixent and Nucala.
  - A systematic review of the IL-5 antagonists conducted in patients with asthma poorly controlled by ICS revealed that all of the IL-5 antagonists reduced asthma exacerbations by approximately 50% and improved FEV_1 by 0.08 L to 0.11 L. Overall, there was not an increase in serious adverse events with any IL-5 antagonist; however, more patients discontinued benralizumab (36/1599) than placebo (9/998) due to adverse events (*Farne et al 2017*).
  - One network meta-analysis of IL-4, IL-5 and IL-13 antagonists demonstrated that all agents reduced FEV_1 and improved ACQ and AQLQ scores, except for the investigational agent, tralokinumab; other analyses found that dupilumab, mepolizumab, reslizumab, and benralizumab significantly reduced the risk of exacerbations compared with placebo (*Iftikhar et al 2018, Edris et al 2019, Ando et al 2020, Ramonell et al 2020*).
  - Treatment rankings in a 2020 network meta-analysis estimate that dupilumab is most effective at reducing the risk of asthma exacerbation, followed by mepolizumab, reslizumab, and benralizumab (*Ramonell et al 2020*).
- Compared to Nucala and Fasenra, Cinqair has various limitations, including an indication for patients ≥ 18 years of age (vs ≥ 6 and 12 years of age with Nucala and Fasenra, respectively), IV administration (SC for Nucala and Fasenra), and a boxed warning for anaphylaxis. Dupixent is indicated for treatment of patients ≥ 6 years of age with moderate-to-severe asthma.
- Subcutaneous autoinjector formulations are available for Dupixent, Fasenra, and Nucala.

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