Therapeutic Class Overview
Antiasthmatic Monoclonal Antibodies

Therapeutic Class Overview/Summary:
This review will focus on the antiasthmatic monoclonal antibodies. These agents are all used for the management of selective asthma diagnoses.[1-3] This class is subdivided into anti-immunoglobulin E (IgE) and anti-immunoglobulin G (interleukin-5 [IL-5]) monoclonal antibodies.[1-3] The IL-5 monoclonal antibodies include mepolizumab (Nucala®) and reslizumab (Cinqair®). Both are Food and Drug Administration (FDA)-approved for the add-on maintenance treatment of severe eosinophilic-phenotype asthma.[1,3] Omalizumab (Xolair®), is the only anti-IgE antibody currently available. It is FDA approved for the treatment of moderate to severe persistent asthma in patients with a positive skin test or in vitro reactivity to a perennial aeroallergen in addition to chronic idiopathic urticaria.[2] Both mepolizumab and omalizumab have been shown to be safe and effective for use in children 12 years of age and older.[1,2] There are currently no generic products available for these agents.

It is important to differentiate individuals with severe asthma based on their subgroups or phenotypes whenever possible because there is heterogeneity in this population. Some characteristics that can be used to distinguish these subtypes include, age, gender, age of asthma onset, atopic status, obesity, exacerbation frequency, aspirin exacerbated respiratory disease and glucocorticoid resistance. It should be noted, though, that there is substantial overlap that may exist between the subgroups.[4] An allergic form of asthma is found in approximately 90% of adult asthmatics.[5] Patients with allergic asthma with positive skin test reactions to a given aeroallergen tend to have exacerbations of asthma when exposed to that aeroallergen. IgE is believed to be pivotal in the pathogenesis of allergic asthma.[6] Omalizumab reduces the release of allergic response mediators by inhibiting the binding of IgE to its receptor on the surface of mast cells and basophils.[2] Although the mechanism by which treatment with omalizumab results in an improvement in the symptoms of chronic idiopathic urticaria is not fully understood, omalizumab binds to IgE and lowers free IgE levels, which down-regulates the IgE receptors on cells.[2] Another subgroup of severe asthmatics is eosinophilic asthma. Patients with severe asthma with an eosinophilic phenotype have both recurrent exacerbations and eosinophilic airway inflammation, which plays a significant part in airway remodeling, hyperresponsiveness and mucus accumulation.[4] There has been some level of tissue eosinophilia documented in 40 to 60% of patients with asthma and the intensity of eosinophilia has been correlated with asthma severity.[7] Mepolizumab and reslizumab both have high affinity and specificity for human IL-5, a key cytokine involved in the maturation, migration, activation, and survival of eosinophils. IL-5 has become a target in the inflammation pathways of asthma given that eosinophil levels have been linked to greater airway remodeling, increased asthma severity, and exacerbations. The resulting inhibition of IL-5 signaling reduces production and survival of eosinophils, as well as decreases overall eosinophil counts in patients with severe asthma. However, the exact mechanism of these agents action in asthma has not been definitively established.[1,3]

The safety and efficacy of the antiasthmatic monoclonal antibodies has been demonstrated in a number of clinical trials for their respective diagnoses.[8-29] It is important to note that these agents have been evaluated in combination with other asthma medications and are not utilized as monotherapy.[8-27] While there is a possibility that patients with severe asthma may meet criteria for treatment with both omalizumab (allergic asthma) and mepolizumab or reslizumab (eosinophilic asthma), there is currently no clinical trials evaluating combination therapy with two monoclonal antibodies..

Table 1. Current Medications Available in the Therapeutic Class[1-3]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Mepolizumab (Nucala®)	Severe eosinophilic-phenotype asthma in adults and children 12 years of age or older	Powder for Injection (vial): 100 mg	-
Omalizumab (Xolair®)	Chronic idiopathic urticaria and moderate-to-severe persistent allergic asthma in adults and children 12 years of age or older	Powder for Injection (vial): 150 mg	-
Reslizumab (Cinqair®)	Severe eosinophilic-phenotype asthma in adults	Solution for Injection: 100 mg/10 mL	-

Evidence-based Medicine

- The Food and Drug Administration (FDA)-approval of omalizumab for the treatment of allergic asthma was based on the results of three randomized, double-blind, placebo-controlled, multicenter trials conducted in patients at least 12 years of age with moderate to severe asthma for at least one year, and a positive skin test reaction to a perennial aeroallergen. All patients were required to have a baseline immunoglobulin E (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 four-week period. 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 and Solèr et al) and 16 weeks (Holgate et al) during which ICS dose reduction was attempted in a step-wise manner.[2]
  - In the first 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 to 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).[8]
  - In the second 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 (0.36 vs 0.75; P<0.001) phases.[10]
  - In the third 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 at least one asthma exacerbation were similar between omalizumab and placebo groups during both the stable steroid and steroid reduction phases (P value not reported).[12]
- The asthma development program for mepolizumab included three double-blind, randomized, placebo-controlled trials: one dose-ranging and exacerbation trial and two confirmatory trials. Mepolizumab was administered every four weeks in all trials as add-on to existing asthma treatment.[1]
  - The first trial, DREAM, was a 52-week phase IIb/III trial that evaluated different doses of the intravenous (IV) formulation of mepolizumab Treatment with IV mepolizumab 75 mg, 250 mg and 750 mg, as add-on therapy, resulted in significant reductions in the frequency of clinically significant asthma exacerbations compared with placebo (48%, 39%, and 52% respectively, with corresponding P values of <0.0001, 0.0005, and <0.0001).[21]
  - The second trial, MENSA, was the 32-week, phase III trial Treatment with mepolizumab 100 mg SQ and mepolizumab 75 mg IV as add-on therapy resulted in statistically significant reductions in the annualized frequency of clinically significant asthma exacerbations compared with placebo (53% and 47%, respectively; P <0.001).[22]
  - The third trial, SIRIUS, was a 24-week, phase III trial in 135 subjects with asthma and at least a six month history of maintenance treatment with OCS and blood eosinophil levels of ≥150 cells/µL at initiation of treatment or ≥300 cells/µL in the past 12 months. Unlike the DREAM

and MENSA trials, a history of exacerbations in the prior year was not required. Treatment with mepolizumab 100 mg SQ as add-on therapy, resulted in a significantly greater percent reduction from baseline in OCS dose during weeks 20 to 24 compared with placebo (odds ratio [OR], 2.39; P=0.008).[23]

- The safety and efficacy of reslizumab was evaluated in an asthma development program which consisted of four randomized, double-blind, placebo-controlled studies (Studies I to IV) of 16 to 52 week duration and involved a total of 981 patients 12 years of age and older. Of note, all patients continued their background asthma therapy throughout the duration of the studies.[25-27]
    - Studies I and II were duplicate, 52-week, multicentre, double-blind, parallel-group, randomized, placebo-controlled phase III trials. Patients were included in the study if their asthma was inadequately controlled by medium-to-high doses of ICS and who had blood eosinophils of greater than or equal to 400 cells/µL and one or more exacerbations in the previous year. A total of 953 patients were randomly assigned (1:1) to receive either intravenous (IV) reslizumab 3 mg/kg or placebo every four weeks. Results from both trials revealed that patients receiving reslizumab had a significant reduction in the frequency of asthma exacerbations (Study I: rate ratio [RR], 0.50; 95% confidence interval [CI], 0.37 to 0.67; Study II: RR, 0.41; 95% CI, 0.28 to 0.59; both P<0.0001) compared with those receiving placebo.[25]
    - Study III was a 16-week, double-blind, multicenter, placebo-controlled, parallel-group, phase III trial of 315 patients with asthma inadequately controlled by at least a medium-dose ICS and blood eosinophils greater than or equal to 400 cells/µL at screening (within three to four weeks of dosing). Of note, patients were not allowed to be on maintenance OCS during the trial. Patients were randomized to receive reslizumab 0.3 mg/kg IV, reslizumab 3 mg/kg IV, or placebo once every four weeks. Reslizumab improved FEV_1 compared to placebo for both reslizumab treatment arms (115 mL [95% CI, 16 to 215; P=0.0237] in the 0.3 mg/kg group and 160mL [95% CI 60 to 259; P=0.0018] in the 3 mg/kg group). However, it was noted that clinically meaningful increases in forced vital capacity (FVC) and forced expiratory flow at 25 to 75% of FVC ($FEF_{25-75\%}$) were only observed with the reslizumab 3 mg/kg group.[26]
    - Lastly, Study IV was a 16-week, double-blind, multicenter, placebo-controlled, phase III trial of 496 patients with asthma inadequately controlled by at least a medium-dose ICS at screening (fluticasone propionate ≥ 440 µg/day or equivalent). Of note, patients were not allowed to be on maintenance OCS during the trial and were not tested for blood eosinophil levels prior to enrollment. Patients were randomized 4:1 to reslizumab 3 mg/kg or placebo given IV once every four weeks. There was not a statistically significant mean change in FEV_1 from baseline to week 16 (255 mL for the reslizumab group and 187 mL for the placebo group giving a between-group difference of 68 mL: standard error [SE] 49.5; P=0.17).[27]
- The FDA-approval of omalizumab for the treatment of chronic idiopathic urticaria was based on two randomized, double-blind, placebo controlled, multi-center clinical trials, ASTERIA II and GLACIAL. Both studies included patients 12 to 75 years of age with moderate to severe chronic idiopathic urticaria who remained symptomatic despite $histamine_1$ antihistamine therapy.[28,29]
    - In the ASTERIA II trial, treatment with omalizumab in doses of 150 and 300 mg every four weeks for three doses resulted in a significant reduction in itch-severity scores compared to placebo. These reductions from baseline in mean weekly itch-severity score were dose-responsive with all three omalizumab doses (75, 150 and 300 mg) and were better than placebo at the time points evaluated prior to week 12. After 12 weeks, the mean weekly itch-severity scores for all omalizumab groups increased to reach values similar to those in the placebo group but did not return to baseline values for the duration of follow-up.[28]
    - In the GLACIAL trial, treatment with omalizumab 300 mg every four weeks for six doses resulted in a significantly greater improvement in the itch-severity score from baseline to week 12 compared to placebo. This difference was sustained at week 24. After week 24 and until week 40, the mean weekly itch-severity scores in the omalizumab group gradually increased to values similar to those in the placebo group but did not return to baseline values.[29]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - According to current clinical guidelines for the treatment of persistent asthma, inhaled corticosteroids (ICS) are the preferred treatment option for all severities. Generally, these guidelines recommend a step-wise approach to increasing doses or adding additional agents based on asthma control or severity.[30-33]
    - Severe asthma is generally defined by those requiring high intensity therapies for asthma control or where good control is not achieved despite high intensity therapy.
    - For severe asthma, guidelines recommend an ICS plus a second controller medication, usually an inhaled long-acting β-agonist (LABA), with or without the additional use of oral corticosteroids.
    - An alternative combination that may be considered is an ICS plus a leukotriene receptor antagonist.
    - The use of the anti-IgE monoclonal antibody, omalizumab, can be considered in addition to other therapies for patients with moderate-to-severe allergic asthma with elevated serum levels of IgE.
    - Treatment and control should be reevaluated frequently and adjustments to medication regimen should be made based on current severity or control.
    - Current clinical guidelines do not address the use of anti-IL-5 monoclonal antibodies at this time.
  - Clinical guidelines for the management of chronic urticaria follow a step-wise approach.[34-36]
    - monotherapy with a non-sedating antihistamine prescribed at a normal dose is recommended first line in most situations although a sedating antihistamine may be effective when given at night.
    - Generally treatment failure with normal dose antihistamine should be followed up by increasing the antihistamine dose to that above recommended (up to four times may be useful). If the patient continues to experience symptoms on a very high dose antihistamine guidelines recommend either adding a second antihistamine or adding a leukotriene antagonist.
    - Omalizumab is considered a second- or third-line option in patients who have failed antihistamine therapy.
- Other Key Facts:
  - Both omalizumab and reslizumab carry a black box warning due to the risk of anaphylaxis. Anaphylaxis was reported as early as the first or second dose for omalizumab and reslizumab, respectively, and may continue beyond the initial doses.[2,3]
  - Mepolizumab has a potential risk of hypersensitivity, but does not have a black box warning.[1]
  - Due to the associated risks and complicated administration, all three agents must be administered by a healthcare professional. Those healthcare professionals administering omalizumab and reslizumab should be prepared to observe patients for an appropriate amount of time and the ability to manage anaphylaxis.[1-3]
  - Mepolizumab and omalizumab are subcutaneous injections and reslizumab is an intravenous injection which is given over 20 to 50 minutes. All agents are administered every four weeks; although, omalizumab may be given every two to four weeks for a diagnosis of asthma.[1-3]
  - Antiasthmatic monoclonal antibodies have not been studied when used in combination with one another. The safety and efficacy of using omalizumab in combination with mepolizumab or reslizumab have not been established.

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Both omalizumab and reslizumab carry a black box warning due to the risk of anaphylaxis. Anaphylaxis was reported as early as the first or second dose for omalizumab and reslizumab, respectively, and may continue beyond the initial doses. Mepolizumab does not carry the same black box warning for anaphylaxis but warns about the potential risks of hypersensitivity. Mepolizumab and omalizumab are subcutaneous injections and reslizumab is an intravenous injection which is given over 20 to 50 minutes. All agents are administered every four weeks; although, omalizumab may be given every two to four weeks for a diagnosis of asthma. Due to the associated risks and complicated administration, all three agents must be administered by a healthcare professional. Those healthcare professionals administering omalizumab and reslizumab should be prepared to observe patients for an appropriate amount of time and the ability to manage anaphylaxis.[1-3]

The safety and efficacy of the antiasthmatic monoclonal antibodies has been demonstrated in a number of clinical trials for their respective diagnoses.[8-29] It is important to note that these agents have been evaluated in combination with other asthma medications and are not utilized as monotherapy.[8-27] While there is a possibility that patients with severe asthma may meet criteria for treatment with both

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According to current clinical guidelines for the treatment of persistent asthma, inhaled corticosteroids (ICS) are the preferred treatment option for all severities. Generally, these guidelines recommend a step-wise approach to increasing doses or adding additional agents based on asthma control or severity. Severe asthma is generally defined by those requiring high intensity therapies for asthma control or where good control is not achieved despite high intensity therapy. For severe asthma, guidelines recommend an ICS plus a second controller medication, usually an inhaled long-acting β-agonist (LABA), with or without the additional use of oral corticosteroids. An alternative combination that may be considered is an ICS plus a leukotriene receptor antagonist. The use of the anti-IgE monoclonal antibody, omalizumab, can be considered in addition to other therapies for patients with moderate-to-severe allergic asthma with elevated serum levels of IgE. Treatment and control should be reevaluated frequently and adjustments to medication regimen should be made based on current severity or control.[30-33] Current clinical guidelines do not address the use of anti-IL-5 monoclonal antibodies at this time.

Clinical guidelines for the management of chronic urticaria generally follow a similar step-wise approach Monotherapy with a non-sedating antihistamine prescribed at a normal dose is recommended first line in most situations although a sedating antihistamine may be effective when given at night. Generally treatment failure with normal dose antihistamine should be followed up by increasing the antihistamine dose to that above recommended (up to four times may be useful). If the patient continues to experience symptoms on a very high dose antihistamine guidelines recommend either adding a second antihistamine or adding a leukotriene antagonist. Omalizumab is considered a second- or third-line option in patients who have failed antihistamine therapy.[34-36]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Mepolizumab (Nucala®)	Anti-IL-5 antibody	-
Omalizumab (Xolair®)	Anti-IgE antibody	-
Reslizumab (Cinqair®)	Anti-IL-5 antibody	-

Indications

Table 2. Food and Drug Administration-Approved Indications[1-3]

Indication(s)	Mepolizumab	Omalizumab	Reslizumab
Asthma (allergic), moderate-to-severe persistent		a †	
Asthma, severe eosinophilic-phenotype	a *		a §
Idiopathic urticaria, chronic		a ‡	

*In adults and adolescents ≥12 years of age as an add-on maintenance treatment
†In adults and adolescents ≥12 years of age with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids
‡In adults and adolescents ≥12 years of age who remain symptomatic despite histamine$_1$ antihistamine treatment
§In adults as an add-on maintenance treatment

Pharmacokinetics

Table 3. Pharmacokinetics[1-3]

Generic Name	Bioavailability (%)	Metabolism	Excretion (%)	Active Metabolites	Serum Half-Life
Mepolizumab	80	Degraded by proteolytic enzymes distributed widely in the body	Not reported	None	16 to 22 days
Omalizumab	62	Degradation in the liver reticuloendothelial system	Bile (not	None	24 to 26 days

Generic Name	Bioavailability (%)	Metabolism	Excretion (%)	Active Metabolites	Serum Half-Life
		and endothelial cells	reported)		
Reslizumab	Not reported	Degraded by enzymatic proteolysis into small peptides and amino acids	Not reported	None	24 days

Clinical Trials

The Food and Drug Administration (FDA)-approval of omalizumab for the treatment of allergic asthma was based on the results of three randomized, double-blind, placebo-controlled, multicenter trials conducted in patients at least 12 years of age with moderate to severe asthma for at least one year, and a positive skin test reaction to a perennial aeroallergen. All patients were required to have a baseline immunoglobulin E (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 four-week period. 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 and Solèr et al) and 16 weeks (Holgate et al) during which ICS dose reduction was attempted in a step-wise manner.[2]

In the first 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 to 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).[8] In the second 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 (0.36 vs 0.75; P<0.001) phases.[10] In the third 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 at least one asthma exacerbation were similar between omalizumab and placebo groups during both the stable steroid and steroid reduction phases (P value not reported).[12]

The asthma development program for mepolizumab included three double-blind, randomized, placebo-controlled trials: one dose-ranging and exacerbation trial and two confirmatory trials. Mepolizumab was administered every four weeks in all trials as add-on to existing asthma treatment.[1]

The first trial, DREAM, was a 52-week phase IIb/III trial that evaluated different doses of the intravenous (IV) formulation of mepolizumab in 621 subjects with refractory asthma with a history of recurrent exacerbations requiring systemic corticosteroid and evidence of eosinophilic inflammation. Treatment with IV mepolizumab 75 mg, 250 mg and 750 mg, as add-on therapy, resulted in significant reductions in the frequency of clinically significant asthma exacerbations compared with placebo (48%, 39%, and 52% respectively, with corresponding P values of <0.0001, 0.0005, and <0.0001).[21] The second trial, MENSA, was the 32-week, phase III trial in 576 subjects with recurrent asthma exacerbations and blood eosinophil levels of ≥150 cells/µL at initiation of treatment or ≥300 cells/µL in the past 12 months. Treatment with mepolizumab 100 mg SQ and mepolizumab 75 mg IV as add-on therapy resulted in statistically significant reductions in the annualized frequency of clinically significant asthma exacerbations compared with placebo (53% and 47%, respectively; P <0.001). Treatment with mepolizumab 100 mg SQ and mepolizumab 75 mg IV demonstrated reductions in the rate of exacerbations requiring hospitalization or emergency department (ED) visits (61% and 32%; P=0.02 and P=0.3, respectively) and exacerbations requiring hospitalizations (69% and 39%; P=0.03 and P=0.33, respectively) compared to placebo.[22] The third trial, SIRIUS, was a 24-week, phase III trial in 135 subjects with asthma and at least a six month history of maintenance treatment with OCS and blood eosinophil levels of ≥150 cells/µL at initiation of treatment or ≥300 cells/µL in the past 12 months. Unlike the DREAM and MENSA trials, a history of exacerbations in the prior year was not required. Treatment with mepolizumab 100 mg SQ as add-on therapy, resulted in a significantly greater percent reduction from baseline in OCS dose during weeks 20

to 24 compared with placebo (odds ratio [OR], 2.39; P=0.008). Fifty-four percent of subjects treated with mepolizumab 100 mg SQ achieved at least a 50% reduction in the daily OCS dose compared with 33% of subjects treated with placebo (P=0.03). Mepolizumab demonstrated a 32% reduction in the annualized rate of clinically significant exacerbations compared to placebo at week 24 (1.44 vs 2.12 per year, respectively; P=0.04).[23]

The safety and efficacy of reslizumab was evaluated in an asthma development program which consisted of four randomized, double-blind, placebo-controlled studies (Studies I to IV) of 16 to 52 week duration and involved a total of 981 patients 12 years of age and older. Of note, all patients continued their background asthma therapy throughout the duration of the studies.[25-27]

Studies I and II were duplicate, 52-week, multicentre, double-blind, parallel-group, randomized, placebo-controlled phase III trials. Patients were included in the study if their asthma was inadequately controlled by medium-to-high doses of ICS and who had blood eosinophils of greater than or equal to 400 cells/µL and one or more exacerbations in the previous year. A total of 953 patients were randomly assigned (1:1) to receive either intravenous (IV) reslizumab 3 mg/kg or placebo every four weeks. Results from both trials revealed that patients receiving reslizumab had a significant reduction in the frequency of asthma exacerbations (Study I: rate ratio [RR], 0.50; 95% confidence interval [CI], 0.37 to 0.67; Study II: RR, 0.41; 95% CI, 0.28 to 0.59; both P<0.0001) compared with those receiving placebo.[25] Study III was a 16-week, double-blind, multicenter, placebo-controlled, parallel-group, phase III trial of 315 patients with asthma inadequately controlled by at least a medium-dose ICS and blood eosinophils greater than or equal to 400 cells/µL at screening (within three to four weeks of dosing). Of note, patients were not allowed to be on maintenance OCS during the trial. Patients were randomized to receive reslizumab 0.3 mg/kg IV, reslizumab 3 mg/kg IV, or placebo once every four weeks. The primary endpoint assessed was the change from baseline in pre-bronchodilator forced expiratory volume in one second (FEV_1) over 16 weeks. Reslizumab improved FEV_1 compared to placebo for both reslizumab treatment arms (115 mL [95% CI, 16 to 215; P=0.0237] in the 0.3 mg/kg group and 160mL [95% CI 60 to 259; P=0.0018] in the 3 mg/kg group). However, it was noted that clinically meaningful increases in forced vital capacity (FVC) and forced expiratory flow at 25 to 75% of FVC ($FEF_{25-75\%}$) were only observed with the reslizumab 3 mg/kg group.[26] Lastly, Study IV was a 16-week, double-blind, multicenter, placebo-controlled, phase III trial of 496 patients with asthma inadequately controlled by at least a medium-dose ICS at screening (fluticasone propionate $\geq$ 440 µg/day or equivalent). Of note, patients were not allowed to be on maintenance OCS during the trial and were not tested for blood eosinophil levels prior to enrollment. Patients were randomized 4:1 to reslizumab 3 mg/kg or placebo given IV once every four weeks. There was not a statistically significant mean change in FEV_1 from baseline to week 16 (255 mL for the reslizumab group and 187 mL for the placebo group giving a between-group difference of 68 mL: standard error [SE] 49.5; P=0.17).[27]

The FDA-approval of omalizumab for the treatment of chronic idiopathic urticaria was based on two randomized, double-blind, placebo controlled, multi-center clinical trials, ASTERIA II and GLACIAL. Both studies included patients 12 to 75 years of age with moderate to severe chronic idiopathic urticaria who remained symptomatic despite $histamine_1$ antihistamine therapy.[28,29] In the ASTERIA II trial, treatment with omalizumab in doses of 150 and 300 mg every four weeks for three doses resulted in a significant reduction in itch-severity scores compared to placebo. These reductions from baseline in mean weekly itch-severity score were dose-responsive with all three omalizumab doses (75, 150 and 300 mg) and were better than placebo at the time points evaluated prior to week 12. After 12 weeks, the mean weekly itch-severity scores for all omalizumab groups increased to reach values similar to those in the placebo group but did not return to baseline values for the duration of follow-up.[28] In the GLACIAL trial, treatment with omalizumab 300 mg every four weeks for six doses resulted in a significantly greater improvement in the itch-severity score from baseline to week 12 compared to placebo. This difference was sustained at week 24. After week 24 and until week 40, the mean weekly itch-severity scores in the omalizumab group gradually increased to values similar to those in the placebo group but did not return to baseline values. In terms of safety, the incidence and severity of adverse events and serious adverse events were similar between the omalizumab and placebo groups. Serious adverse events were reported by 7.1 and 6.0% of patients treated with omalizumab and placebo, respectively; however, no serious adverse events were suspected to have been caused by the study drug.[29]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Allergic asthma				
Busse et al[8] Omalizumab 150 or 300 mg SC every four weeks, or 225, 300 or 375 mg every two weeks [approximately 0.016 mg/kg/IgE (IU/mL) every four weeks] plus BDP 420 to 840 µg/day vs placebo plus BDP Allowed concomitant medications included albuterol, stable doses of immunotherapy, and other non-asthma medications. All other asthma medications were prohibited.	DB, MC, PC, PG, RCT Patients 12 to 75 years of age with allergic asthma symptomatic despite treatment with ICS, asthma duration ≥1 year, positive responses on skin prick testing to ≥1 allergen, total serum IgE ≥30 to ≤700 IU/mL, FEV_1 reversibility of ≥12% within 30 minutes after administration of albuterol, baseline FEV_1 ≥40 and ≤80% of predicted, treatment with 420 to 840 µg/day of BDP or its equivalent ICS for ≥3 months	N=525 28 weeks (16 weeks of steroid stable phase, followed by 12 weeks of steroid reduction phase)	Primary: Number of exacerbations during stable and steroid reduction phases Secondary: Number of patients with ≥1 exacerbation, daily asthma symptoms, rescue medication use, pulmonary function, treatment effectiveness, free and total serum IgE, safety	Primary: 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 to 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). Secondary: During the steroid stable phase, fewer patients in the omalizumab group had ≥1 exacerbation than the placebo group (14.6 vs 23.3%; P=0.009). Similarly, during the steroid reduction phase, the omalizumab treatment group had fewer subjects with exacerbations than placebo (21.3 vs 32.3%; P=0.0004). During the stable steroid phase, a smaller proportion of subjects in the omalizumab group than in the placebo group experienced exacerbations that were associated with a reduction in PEF to ≤50% of personal best value (0.4 vs 3.5%). During the steroid reduction phase, fewer omalizumab subjects than placebo subjects (0.8 vs 3.0%) had exacerbations associated with a decline in PEF of ≥50% (P value not reported). Omalizumab allowed for a greater median reduction in ICS use than seen in the placebo group (75 vs 50%; P<0.001). More omalizumab than control patients achieved >50% reduction in BDP dose (72.4 vs 54.9%; P<0.001). BDP was discontinued in 39.6% of omalizumab-treated patients compared to 19.1% of the placebo recipients (P<0.001). Omalizumab significantly improved daily asthma scores in comparison with placebo after week four, and rescue medication

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				use was significantly reduced in comparison with placebo for most weekly intervals (P value not reported). Increases in morning PEF were greater with omalizumab (from 320 to 335 L/minute) than with placebo, which remained at approximately 300 L/minute, from baseline to the end of the study (P value not reported). At week 16, the mean change from baseline in PEF was 18.5 L/minute with omalizumab and 6.9 L/minute with placebo. Mean FEV_1 increased from 68.20 to 72.53% of predicted in the omalizumab group and from 67.7 to 69.1% of predicted in the placebo group. Statistically significant improvements for FEV_1 in comparison with placebo were maintained for the entire study (P values<0.001 to .019). Across the omalizumab dosing regimens, median free IgE was reduced by between 89 and 98%. At weeks 16 to 24, free IgE concentrations ranged from 6 to 8 IU/mL for the omalizumab group; this compared to >62 IU/mL for the placebo group. Total IgE increased in the omalizumab-treated subjects and did not change appreciably in the placebo subjects (P value not reported). Overall, the frequency of adverse events in the omalizumab and placebo groups was similar (89.2 vs 89.1%). Adverse events reported more frequently in omalizumab-treated patients (≥1% more frequent) included upper respiratory tract infection (31.3 vs 29.6%), pharyngitis (14.6 vs 13.6%), arthralgia (9.7 vs 3.5%), rhinitis (8.2 vs 3.1%), sprains and strains (7.5 vs 5.4%), nausea (6.7 vs 6.2%), and pain (6.7 vs 5.4%). No serious adverse events were considered drug-related.
Lanier et al[9] (extension of a study by Busse et al[8]) (2003)	DB, MC, PC, PG, RCT Patients 12 to 75 years of age with allergic	N=460 24 weeks	Primary: Number of asthma exacerbations/patient, number of patients	Primary: Treatment with omalizumab resulted in fewer asthma exacerbations as compared to placebo (0.60 vs 0.83/patient; P=0.023). The number of patients experiencing at least one

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Omalizumab at least 0.016 mg/kg/IgE (IU/mL) SC every four weeks vs placebo Concomitant treatment with other asthma medication was allowed.	asthma who were symptomatic despite treatment with ICS		with ≥1 exacerbation Secondary: Changes in FEV_1, use of BDP and concomitant asthma medication, safety	exacerbation was also lower for omalizumab than placebo (31.8 and 42.8%; P=0.015). Secondary: Compared to placebo, treatment with omalizumab resulted in statistically significant differences in FEV_1 at weeks 32 (P=0.016), 36 (P=0.014), 40 (P=0.004), and 44 (P=0.037). Between-group differences in FEV_1 at weeks 48 and 52 were not statistically significant (P=0.28 and P=0.16, respectively). Cessation of BDP use was maintained by 27 and 10% of patients in the omalizumab and placebo groups, respectively. The mean BDP equivalent dose was lower in the omalizumab group than placebo (227 vs 335 µg/day). Treatment with omalizumab was well tolerated during the extension phase. The incidence and profile of adverse events were similar in the omalizumab and placebo groups during both the extension phase and the full 52 weeks of the trial.
Solèr et al[10] Omalizumab at least 0.016 mg/kg/IgE (IU/mL) SC (either 150 to 300 mg every four weeks, or 450 to 750 mg divided into two equal portions at two-week intervals) plus BDP 500 to 1,200 µg/day vs placebo plus BDP 500	DB, MC, PC, PG, RCT Patients 12 to 76 years of age with allergic asthma despite treatment with ICS, asthma duration ≥1 year, positive responses on skin prick testing to ≥1 allergen, total serum IgE ≥30 to ≤700 IU/mL, body weight ≤150 kg, FEV_1 reversibility of ≥12% within 30 minutes after administration of	N=546 28 weeks (16 weeks of steroid stable phase, followed by 12 weeks of steroid reduction phase)	Primary: The number of asthma exacerbations/patient during the stable steroid and steroid reduction phases Secondary: Number of patients with ≥1 asthma exacerbation during the stable steroid and steroid reduction phases, BDP	Primary: Asthma exacerbations/patient decreased in the omalizumab group compared to placebo during both the stable steroid (0.28 vs 0.66; P<0.001) and steroid reduction (0.36 vs 0.75; P<0.001) phases. Secondary: Fewer patients in the omalizumab group had ≥1 exacerbation compared to placebo for the stable steroid phase (35 vs 83; P<0.001) and steroid reduction phase (43 vs 81; P<0.001). The median daily BDP dose at the end of the steroid reduction phase was lower for patients on omalizumab (100 vs 300 µg; P<0.001). The proportion of patients able to reduce the BDP dose at the end of the steroid reduction phase was greater in the omalizumab group than the placebo (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
to 1,200 µg/day Allowed concomitant medications included salbutamol and BDP.	albuterol, baseline FEV_1 ≥40 and ≤80% of predicted, mean total daily symptom score ≥3 and ≤9, treatment with 500 to 1,200 µg/day of BDP or its equivalent ICS for ≥3 months		dose reduction, rescue medication use, asthma symptom scores, morning PEF and FEV_1, safety	The median number of puffs of rescue medication was lower in the omalizumab group than placebo (P<0.005). Statistically significant differences in favor of omalizumab were observed in the total symptom scores during the stable-steroid and steroid-reduction phases (P≤0.01). Mean morning peak PEF was greater in omalizumab group than placebo during the stable steroid and steroid reduction phase (P<0.01). Omalizumab resulted in greater improvements in FEV_1 than placebo between weeks four and 12 of the stable steroid phase (P<0.05) and between weeks 18 and 28 during the steroid reduction phase (P<0.05). There were no deaths in this study. Adverse events reported more frequently in omalizumab group than placebo included fatigue and paresthesia (1.1 vs 0.0%), and injection site reactions (11.8 vs 7.7%).
Buhl et al[11] (extension of a study by Solèr et al[10]) Omalizumab at least 0.016 mg/kg/IgE (IU/mL) SC (either 150 to 300 mg every four weeks, or 450 to 750 mg divided into two equal portions at two-week intervals vs placebo	DB, MC, PC, PG, RCT Patients 12 to 76 years of age with allergic asthma who were symptomatic despite treatment with ICS	N=483 24 weeks	Primary: The number of asthma exacerbations/patient, FEV_1, BDP use and concomitant asthma medication use, safety Secondary: Not reported	Primary: The mean number of asthma exacerbations/patient during the extension phase was lower in the omalizumab group compared to the placebo group (0.48 vs 1.14; P<0.001). The percentage of patients with ≥1 exacerbation was lower in patients treated with omalizumab than control (61 vs 93%; P<0.001). No statistically significant differences in FEV_1 were seen between the treatment groups at any time point during the extension phase (P value not reported). The mean BDP equivalent dose was lower in patients treated with omalizumab than placebo (253 vs 434 µg/day; P<0.001). The overall incidence of adverse events was similar between the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Concomitant treatment with other asthma medication was allowed.				treatment groups during the 24-week extension phase (P=0.548) and for the entire 52-week study period (P=0.579). Secondary: Not reported
Holgate et al[12] Omalizumab at least 0.016 mg/kg/IgE (IU/mL) SC (150 or 300 mg every four weeks, or 225, 300 or 375 mg given every two weeks) plus inhaled fluticasone 1,000 to 2,000 µg daily vs placebo plus inhaled fluticasone 1,000 to 2,000 µg daily Short-/long-acting β_2-agonists were allowed as needed.	DB, MC, PC, PG, RCT Patients 12 to 75 years old with severe allergic asthma who were symptomatic despite inhaled and/or oral corticosteroid use, positive responses on skin prick testing to ≥1 allergen, total serum IgE ≥30 to ≤700 IU/mL, treatment with at least 1,000 µg/day of inhaled fluticasone	N=246 32 weeks (16 weeks of steroid stable phase, followed by 16 weeks of steroid reduction phase)	Primary: Percentage reduction in fluticasone dose Secondary: Absolute reductions in fluticasone dose compared to baseline, reduction in asthma exacerbations, decrease in rescue medication use, PEF and post-bronchodilator spirometry, asthma symptom score, asthma related quality of life, safety	Primary: The percentage reduction in fluticasone dose was greater among patients treated with omalizumab than among patients treated with placebo (median, 60 vs 50%; P=0.003). Secondary: Omalizumab-treated patients achieved greater absolute reduction in fluticasone dose compared to baseline than placebo (median, 750 vs 500 µg/day; P=0.003). Patients treated with omalizumab had 35 to 45% lower exacerbation rates than placebo-treated patients and used less rescue medication from visit four onwards (P<0.01). Morning PEF remained overall unchanged including during the steroid-reduction phase. Omalizumab was associated with greater increases in FEV_1 than placebo which were statistically significant at weeks four, 20, 28 and 30 (P values were not reported). Treatment with omalizumab led to greater improvements in asthma symptoms over both the steroid-stable and the steroid-reduction phases as compared to placebo, yet P value was not significant for most time points. Overall, 58% of omalizumab patients compared to 39% of placebo patients had clinically detectable improvements in quality of life (P<0.01). The incidence of adverse events was similar between omalizumab and placebo groups (76.2 vs 82.5%, respectively).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Eisner et al[13] (Interim data from EXCELS) Omalizumab vs non-omalizumab Treatment was at the discretion of physicians and patients based on indication and treatment guidelines.	MC, OBS, PRO Patients ≥12 years of age with moderate to severe persistent asthma and a history of a positive response to allergy skin testing or in vitro reactivity to a perennial aeroallergen	N=7,858 2 years	Primary: Asthma control Secondary: Not reported	Primary: Among new omalizumab starts, the ACT score from baseline increased from 15.2 to 18.4 at month six and reached 19.4 by month 24. For established users, the mean ACT increased from 18.2 at baseline to 19.4 by month 24. Among non-omalizumab users, the mean ACT score increased from 18.4 at baseline to 20.0 by month 24. Over half (54%) of omalizumab new starts achieved a minimally important improvement in ACT (defined as ≥3 point change from baseline) by month six and this proportion increased to 62% at month 24. The proportion of patients achieving a minimally important improvement in the established users group increased from 29% at month six to 31% at month 24. The subgroup of new starts had a substantial increase in the proportion of patients considered to be well-controlled (ACT ≥20) from 26% at baseline to 50% at month six and 59% at month 24. The proportion of new starts with poorly-controlled asthma (ACT≤15) decreased from 51% at baseline to 24% at month six and 20% at month 24. In the well-established users subgroup, the proportion of patients with well-controlled asthma increased from 48% at baseline to 58% at month 24 and the proportion of patients with poorly-controlled asthma decreased from 29% at baseline to 21% at month 24. In the non-omalizumab group, the proportion of patients with well-controlled asthma increased from 48% at baseline to 65% at month 24 and the proportion of patients with poorly-controlled asthma decreased from 27% at baseline to 16% at month 24. Secondary: Not reported
Chen et al[14]	MC, OBS, PRO	N=7,858	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(Subanalysis of EXCELS[13]) Omalizumab vs non-omalizumab Treatment was at the discretion of physicians and patients based on indication and treatment guidelines.	Patients ≥12 years of age with moderate to severe persistent asthma and a history of a positive response to allergy skin testing or in vitro reactivity to a perennial aeroallergen	2 years	Percent change in dose of concomitant asthma medications, proportion of patients with any change in dose from baseline to month 12 and baseline to month 24 Secondary: Not reported	The mean total daily dose of ICS decreased in all groups from baseline to month 12 and month 24. The percent reduction was greatest for patients who were new starts (57.7% at month 24) compared to established users (44.7%) and non-omalizumab users (42.4%). Approximately 66% of omalizumab new starts achieved a decrease in total daily ICS use from baseline to month 24 compared to 57% of established users and 54% of non-omalizumab users. For short-acting beta agonist use, the number of puffs per day decreased in all groups from baseline to months 12 and 24, and the percent reduction was greatest in omalizumab new starts (73.7% at month 24), followed by established users (69.2%) and non-omalizumab users (64.3%). A dose reduction for short-acting beta agonist use was observed in a greater proportion of new starts (65%) than established users (55%) or non-omalizumab users (54%). At month 24, more than 50% of omalizumab new starts achieved reductions in leukotriene modifier dose compared to 44% of established users and 40% of non-omalizumab users. Secondary: Not reported
Busse et al[15] Omalizumab plus current asthma therapy vs placebo plus current asthma therapy	Pooled analysis (seven trials) Patients ≥12 years of age with moderate-to-severe IgE-mediated allergic asthma	N=4,308 Duration varied	Primary: Rescue use of systemic corticosteroid bursts (oral or IV), effectiveness of therapy Secondary: Not reported	Primary: Omalizumab-treated patients required significantly fewer systemic steroid bursts compared to the control group (RR, 0.57; 95% CI, 0.48 to 0.66; P<0.001). The mean number of systemic corticosteroid bursts was 0.4±0.87 in the omalizumab-treated group and 0.6±1.24 in the control group. Patients treated with omalizumab were more likely to be categorized as responders (complete control or marked improvement in control) than patients in the control group for both the physician and patient overall assessments. For the physician

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo alone				evaluation, 58.5% of omalizumab users were responders compared to 36.9% of patients in the control group. For the patient evaluation, 64.2% of omalizumab users were responders compared to 43.9% of the control group. Responders to omalizumab experienced a significantly greater improvement in quality of life compared to the placebo group. Although modest, a significantly greater improvement from baseline in FEV_1 was observed in patients treated with omalizumab compared to placebo (75.27 mL; 95% CI, 44.56 to 105.98; P<0.001). Secondary: Not reported.
Milgrom et al[16] Omalizumab at least 0.016 mg/kg/IgE (IU/mL) SC (150 or 300 mg every four weeks, or 225, 300 or 375 mg given every two weeks) and inhaled BDP 168 to 420 µg daily vs placebo and inhaled BDP 168 to 420 µg daily Short acting β_2-agonists were allowed	DB, MC, PC, PG, RCT Children ages 6 to 12 years of age with moderate to severe allergic asthma requiring daily ICS, asthma duration ≥1 year, positive responses on skin prick testing to ≥1 allergen, total serum IgE ≥30 to ≤1,300 IU/mL, body weight <90 kg, FEV_1 reversibility of ≥12% within 30 minutes after administration of albuterol, baseline FEV_1 ≥60% of predicted value, mean	N=334 28 weeks (16 weeks of steroid stable phase, followed by 8 weeks of steroid reduction phase, 4 weeks of steroid maintenance)	Primary: Median reduction in BDP or discontinuation, asthma exacerbations, adverse events, pulmonary function tests, global evaluation of treatment effectiveness Secondary: Not reported	Primary: More patients in the omalizumab group were able to decrease BDP dose from baseline (P=0.002), with a median reduction in BDP dose of 100% in the omalizumab group compared to 67% in the placebo group (P=0.001). Additionally, 55% of patients in the omalizumab group were able to discontinue BDP use compared to 39% of patients in the placebo group (P=0.004). Fewer patients treated with omalizumab required an urgent, unscheduled physician visit (13 vs 30%; P=0.001); experienced a decrease in morning PEF rate (7 vs 17%; P=0.002); and awakened on two or three successive nights requiring rescue medication (12 vs 21%; P=0.002). Both patients and investigators favored omalizumab over placebo in the GETE (P<0.001). Patients treated with omalizumab missed fewer school days than did those in the placebo group (0.7 vs 1.2 days; P=0.04). Fewer unscheduled medical contacts for asthma-related medication

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
as needed.	total daily symptom score ≥3 and ≤9, treatment with 168 to 420 µg/day of BDP or its equivalent ICS for ≥3 months, stable asthma			problems were needed for the omalizumab-treated group compared to placebo (0.2 vs 5.4; P=0.001). Adverse events reported more frequently in omalizumab-treated patients (≥1% more frequent) included headache, pharyngitis, viral infection, and fever. Secondary: Not reported
Schumann et al[17] XCLUSIVE study Omalizumab SC every two to four weeks (total dose calculated based on baseline serum IgE and body weight)	MC, OL, PM, PRO Patients with inadequately controlled severe asthma who were eligible for anti-IgE therapy	N=195 6 months	Primary: Disease-related changes, compliance and utilization of omalizumab Secondary: Not reported	Primary: The absolute and percent predicted values of FEV_1 were improved following a 16-week treatment period. The FEV_1 increased from 2.05 L±0.77 L to 2.31 L±0.84 L or 63.6±18.3% to 73.7±20.3%, representing a total difference of 270 mL or an increase of 10.1% predicted, respectively (P<0.05). The exacerbation rate at baseline decreased significantly from 3.99±6.49 to 1.0±18.87 (P<0.0001) after 16 weeks of treatment. A relative reduction in the exacerbation rate of 74.9% was achieved. In terms of absenteeism, missed work/school days could be significantly reduced from 6.21±8.08 to 0.49±1.34 (P<0.001) following 16 weeks of omalizumab treatment. During treatment with omalizumab, the ACQ score significantly decreased from 3.58±1.28 to 2.01±1.05 after 16 weeks (-43.7%) and to 1.92±1.13 after the six month treatment period (-46.3%) (P<0.0001 for both). Per the GETE, after 16 weeks of omalizumab therapy, the effectiveness was considered good of excellent in 119/151 cases (78.8%), as moderate in 19/151 cases (12.6%) and as poor/worsening in 13/151 cases (8.6%), respectively.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Asthma medications were adjusted in 103 (52.8%) of patients over the 16 week treatment period. Theophylline (47.7 vs 39%), oral corticosteroids (57.4 vs 32.8%) and leukotriene antagonists (54.4 vs 41.5%) could be reduced over the course of the study; however, high-dose ICS, long-acting beta agonists and fixed-dose combinations of both remained mostly unchanged. Improvements in symptoms of concomitant allergic disorders were observed, including allergic rhinitis (91.2%), atopic eczema (68.2%) and urticaria (66.7%) after six months. The mean monthly dose of omalizumab was 398.9 mg. Incorrect doses were received by 40% of patients when referenced to the dosing table in the package insert. Of these, 16.9% were under-dosed seven 3.6% were overdosed. Treatment was discontinued in 18.5% of patients, with 10.3% discontinuing at the control visit after 16 weeks and 8.2% discontinuing at the final visit after six months. Lack of efficacy was the most common reason for discontinuation. Of patients who discontinued, 33% were assigned to wrong schedules or were under-dosed. Secondary: Not reported
Niebauer et al[18] Omalizumab vs placebo	MA Patients with allergic asthma.	N=2,056 Duration varied	Primary: AQLQ Secondary: Not reported	Primary: Significant improvements in AQLQ scores favored omalizumab compared to placebo in the two largest trials included (008 and 009) in which mean score differences between treatment and placebo groups exceeded 0.20 to 0.30 point for AQLQ overall and subscale scores (with the exception of environmental stimuli in trial 009). No significant differences in AQLQ scores were observed between treatment groups in trials 010 and 011 for the steroid-stabilization phase. The largest effect size for the steroid-stabilization phase was

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				observed in trial 008, in which AQLQ overall, activities and symptoms scores had effect sizes of ≥1 for omalizumab. Effect sizes for AQLQ scores were higher among omalizumab patients compared to placebo. For the steroid-reduction phase, mean within-group changes in AQLQ scores were larger at the end of the phase compared to the previous phase. All mean score differences were significant and all differences favored omalizumab, with more than half of AQLQ score differences of ≥0.3. A greater proportion of patients treated with omalizumab achieved a ≥1.0 or ≥1.5 score change between baseline and the end of the steroid-reduction phase. With the exception of study 010, treatment with omalizumab resulted in greater improvements in AQLA overall scores at the end of the extension phase compared to placebo. Across all studies and all phases of the included trials, treatment with omalizumab is more effective than placebo at improving AQLQ overall scores by ≥0.5 (OR, 1.35; 95% CI, 1.11 to 1.64; P=0.003) and by ≥1.5 (OR, 1.80; 95% CI, 1.36 to 2.38; P<0.001).
Chipps et al[19] Omalizumab plus current asthma therapy vs current asthma therapy vs	Pooled analysis Patients with severe persistent allergic (IgE mediated) asthma	N=2,548 Duration varied	Primary: Change from baseline in AQLQ total score Secondary: Not reported	Primary: Significantly greater improvements in quality of life were observed in the omalizumab treatment group compared to placebo across all studies. The pooled change from baseline in total AQLQ score was 1.01 for the omalizumab group and 0.61 for the control group (P<0.001). Treatment with omalizumab resulted in a greater proportion of patients achieving a clinically meaningful (≥0.5-point) improvement in quality of life compared to control in each individual study. For the pooled population, significantly more patients in the omalizumab group achieved a clinically meaningful improvement in quality of life compared to the control group (66.3 and 52.4%;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo plus current asthma therapy				P<0.0001). In addition, patients receiving omalizumab were more likely to have moderate or large improvements (≥1.0 or 1.5 points) in AQLQ scores compared to control patients in each individual study and in the pooled analysis. Patients treated with omalizumab were also more likely to have clinically meaningful, moderate or large improvements in each of the individual domains of the AQLQ. Secondary: Not reported
Normansell et al[20] Omalizumab vs placebo	MA (25 RCT) Patients with allergic asthma	N=6,382 Duration varied	Primary: Asthma exacerbations, hospitalization, concomitant asthma medication use Secondary: Not reported	Primary: In patients with moderate to severe asthma receiving background ICS therapy, a significant advantage favored omalizumab with regard to experiencing an asthma exacerbation (OR, 0.55; 95% CI, 0.42 to 0.60; 10 studies, 3,261 patients). There was an absolute reduction from 26% for patients suffering an exacerbation on placebo to 16% on omalizumab therapy over 16 to 60 weeks. A significant benefit was observed for omalizumab vs placebo with regard to reducing hospitalizations (OR, 0.16; 95% CI, 0.06 to 0.42; four studies, 1,824 patients), representing an absolute risk reduction from 3% with placebo to 0.5% with omalizumab therapy over 28 to 60 weeks. Patients treated with omalizumab were significantly more likely to be able to withdraw with ICS completely compared to placebo (OR, 2.5; 95% CI, 2.00 to 3.13). A small but statistically significant reduction in daily inhaled steroid dose was reported for omalizumab-treated patients compared to placebo (weighted mean difference, -118 mcg BDP equivalent per day; 95% CI, -154 to -84). No difference was observed in the proportion of patients who were able to withdraw oral corticosteroid therapy. Patients treated with omalizumab as adjunct to corticosteroids required a small but significant reduction in rescue β_2 agonist therapy compared to placebo (mean difference, -0.39 puffs per

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				day; 95% CI, -0.55 to -0.24; nine studies, 3,524 patients). Significantly fewer serious adverse events were reported in patients receiving omalizumab compared to placebo (OR, 0.72; 95% CI, 0.57 to 0.91; 15 studies, 5,713 patients), but more injection site reactions were observed with omalizumab. Secondary: Not reported
Eosinophilic Asthma				
Pavord et al[21] DREAM Trial Mepolizumab 75 mg IV every four weeks vs mepolizumab 250 mg IV every four weeks vs mepolizumab 750 mg IV every four weeks vs placebo All subjects remained on existing maintenance asthma therapy throughout the trial.	DB, MC, PCT, RCT Patients 12 to 74 years of age with a history of two or more severe asthma exacerbations in the previous year despite regular use of high-dose ICS plus an additional controller(s) with or without OCS and signs of eosinophilic inflammation	N=621 52 weeks (treatment period)	Primary: Rate of clinically significant asthma exacerbations (requiring OCS, admission or a visit to an ED) Secondary: Annualized frequency of exacerbations requiring hospitalization or ED visits, annualized frequency of exacerbations requiring hospitalization, mean change from baseline in clinic pre-bronchodilator FEV_1 at week 52, mean change from baseline in scores on the ACQ at week 52, mean	Primary: At the end of the study, there were 776 exacerbations that were considered to be clinically significant. The rate of clinically significant exacerbations was 2.40 per patient year in the placebo group, 1.24 in the 75 mg mepolizumab group (48% reduction; 95% CI, 31 to 61%; P<0.0001), 1.46 in the 250 mg mepolizumab group (39% reduction; 95% CI, 19 to 54%; P=0.0005), and 1.15 in the 750 mg mepolizumab group (52% reduction; 95% CI, 36 to 64%; P<0.0001). Secondary: From the secondary endpoints that were evaluated, the ones that reached statistical significance included the mean change from baseline in blood eosinophil counts at week 52 compared to placebo (P<0.0001 for all mepolizumab groups) and the mean change from baseline in sputum eosinophil counts at week 52 compared to placebo (P=0.008, for the mepolizumab 750 mg group only). Compared with the placebo group, subjects in the groups treated with mepolizumab had lower rates of both exacerbations requiring hospitalization and exacerbations requiring hospitalization and/or ED visits. However, none reached statistical significance. Three deaths were reported during the study but none were

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			change from baseline in scores on the AQLQ at week 52, mean change from baseline in blood and sputum eosinophil counts at week 52	deemed to be related to the treatments.
Ortega et al[22] MENSA Trial Mepolizumab 75 mg IV every four weeks vs mepolizumab 100 mg SQ every four weeks vs placebo All subjects remained on existing maintenance asthma therapy throughout the trial.	DB, DD, MC, PC, PG, RCT Patients ≥12 years of age and ≥45 kg with a documented requirement for regular treatment with high-dose ICS in the 12 months prior to Visit 1 with or without maintenance OCS, plus documented requirement of additional controller medication besides ICS in the past 12 months for at least three successive months, a prior documentation or high likelihood of eosinophilic asthma, persistent airflow obstruction <80% predicted at Visit 1 (subjects ≥18 years of age), a pre bronchodilator FEV_1	N=576 32 weeks (treatment period)	Primary: Annualized frequency of clinically significant asthma exacerbations Secondary: Annualized frequency of exacerbations requiring hospitalization or ED visits, annualized frequency of exacerbations requiring hospitalization, the mean change from baseline in clinic pre-bronchodilator FEV_1 at week 32, the mean change from baseline in SGRQ at week 32, the mean change from baseline in scores on the ACQ-5 at week 32	Primary: The estimated rates of clinically significant exacerbations per patient per year were 0.93 in the mepolizumab 75 mg group, 0.83 in the mepolizumab 100 mg group and 1.74 in the placebo group. As compared with placebo, the relative reduction in exacerbation rate was 47% (95% CI, 28 to 60; P<0.001) in the mepolizumab 75 mg group and 53% (95% CI, 36 to 65; P<0.001) in the mepolizumab 100 mg group. Secondary: Exacerbations necessitating an ED visit or hospitalization were reduced by 32% in the group receiving mepolizumab 75 mg (P=0.30) and by 61% in the group receiving mepolizumab100 mg (P=0.02) compared with those treated with placebo. At week 32, the mean increase from baseline in FEV_1 was 100 mL greater in patients receiving mepolizumab 75 mg than in those receiving placebo (P=0.02) and 98 mL greater in patients receiving mepolizumab 100 mg than in those receiving placebo (P=0.03). The improvement from baseline in the SGRQ score was 6.4 points and 7.0 points greater in the 75 mg and 100 mg mepolizumab groups, respectively, than in the placebo group (minimal clinically important change, 4 points), and the improvement in the ACQ-5 score was 0.42 points and 0.44 points greater in the two mepolizumab groups, respectively, than in the placebo group (minimal clinically important change, 0.5 points) (P<0.001 for all comparisons).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	<90% predicted or FEV_1/FVC ratio <0.8 at Visit 1 (subjects 12 to 17 years of age), a history of ≥two exacerbations requiring treatment with OCS in the 12 months prior to Visit 1 despite the use of high-dose ICS			The safety profile of mepolizumab was similar to that of placebo.
Bel et al[23] SIRIUS Trial Mepolizumab 100 mg SQ every four weeks vs placebo During the induction and OCS reduction phases, subjects remained on their optimized OCS dose along with their baseline asthma medications.	DB, MC, PC, PG,RCT Patients ≥ 12 years of age with severe asthma and peripheral blood eosinophilia (300 eosinophils/μL during the 12 months prior to study entry or 150 eosinophils/μL during the optimization phase) despite maintenance systemic glucocorticoid treatment (5 to 35 mg of prednisone or equivalent/day) and high-dose ICS in six months prior to Visit 1 and either proof of current treatment with an additional controller medication (LABA, LTRA or theophylline) for at least three months or failure of	N=135 24 weeks	Primary: The degree of reduction in the daily OCS dose during weeks 20 to 24 as compared with the dose determined during the optimization phase (90 to 100% reduction, 75 to less than 90% reduction, 50 to less than 75% reduction, more than 0 to less than 50% reduction and no decrease in OCS, a lack of asthma control during weeks 20 to 24 or withdrawal from treatment) Secondary: Proportions of patients who had a reduction ≥50% in the OCS	Primary: The likelihood of a reduction in the glucocorticoid-dose was 2.39 times greater in the mepolizumab group than in the placebo group (95% CI, 1.25 to 4.56; P=0.008). The median percentage reduction from baseline in the glucocorticoid dose was 50% in the mepolizumab group, as compared with no reduction in the placebo group (P=0.007). Secondary: Treatment with mepolizumab, as compared to placebo, resulted in significant improvements in all secondary outcomes of OCS reduction (P≤0.03), except for the outcome of a total cessation of daily oral glucocorticoids (P=0.41). Patients in the mepolizumab group, as compared with those in the placebo group, had a relative reduction of 32% in the annualized rate of exacerbations (1.44 vs 2.12; P=0.04) and a reduction of 0.52 points with respect to asthma symptoms (P=0.004), as measured on the ACQ-5 (the minimally clinically important difference is 0.5 points). Compared with placebo, mepolizumab significantly reduced blood eosinophil counts throughout the study (P<0.001). The safety profile of mepolizumab was similar to that of placebo.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	treatment with an additional controller medication for at least three months during the prior 12 months		dose compared with baseline dose, reduction in OCS dose to a value of ≤5 mg/day, total cessation in OCS use, median percentage reduction from baseline in the OCS dose, rate of asthma exacerbations, asthma control and safety	
NCT01842607[24] COSMOS Mepolizumab 100 mg SQ every four weeks All subjects remained on existing maintenance asthma therapy throughout the trial.	ES, MC, OL Patients ≥ 12 years of age who had completed the DB study drug treatment during MENSA or SIRIUS and whose asthma was being treated with a controller medication	N=651 52 weeks	Primary: Number of subjects with AEs, frequency of AEs, number of subject withdrawals due to AEs, number of subjects hospitalized due to AEs including asthma exacerbations Secondary: Frequency of positive anti-mepolizumab binding antibodies and neutralizing antibodies, annualized rate of exacerbations, ACQ score	Primary: By week 52, 311 subjects (48%) had experienced on-treatment exacerbations (exacerbation rate/year, 0.93; 95% CI, 0.83 to 1.04], P values not reported), 59 subjects (9%) experienced exacerbations requiring hospitalization or an ED visit, and 39 subjects (6%) experienced exacerbations requiring hospitalization. During OL treatment of all subjects with mepolizumab in COSMOS, the use of OCS remained low in the subjects who were previously treated with mepolizumab (2.5 mg/day for weeks 44 to 76). The use of OCS for the subjects who were previously treated with placebo in SIRIUS and switched to mepolizumab decreased over time during the COSMOS study (from 10 to 5 mg/day). The incidence of SAEs (14%; N=94) and the most frequent SAE (asthma, 6%; N=38) was similar to the placebo-controlled trials (MENSA and SIRIUS). Herpes zoster was reported by two subjects treated with mepolizumab compared with none in placebo; none of the herpes zoster occurrences were categorized as serious adverse events. Infections (all types) were the most frequently reported AEs of special interest (70%). Most of these infection events were common respiratory tract infections such as nasopharyngitis. No deaths were reported in the study.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Of the 646 subjects treated with mepolizumab and tested for anti-mepolizumab antibodies, 31 subjects (5%) were positive for anti-mepolizumab antibodies after at least 1 dose of mepolizumab in the COSMOS trial. Samples that were positive for anti-mepolizumab antibodies were then further tested for mepolizumab neutralizing activity; none of the subjects tested positive. There were no signals for serious acute hypersensitivity reactions or serum sickness-like reactions associated with positive anti-mepolizumab antibody status. While the ACQ-5 scores and blood eosinophil levels for subjects previously treated with mepolizumab remained unchanged from those observed in MENSA and SIRIUS trials, among those treated with placebo, the mean ACQ-5 scores decreased by 0.3 from baseline to week 52 and the geometric mean blood eosinophil counts decreased from 280 cells/µL from baseline to 50 to 60 cells/µL at week 52.
Castro et al[25] Reslizumab 3.0mg/kg IV once every four weeks vs placebo	DB, MC, PC, PG, RCT Patients from 12 to 75 years of age whose asthma was inadequately controlled by medium-to-high dose ICS and who had blood eosinophil counts of ≥ 400 cells/µL (within three to four weeks of dosing) and one or more asthma exacerbations requiring systemic corticosteroid use in the past 12	N=953 52 weeks	Primary: The annual frequency of clinical asthma exacerbations Secondary: Safety	Primary: In both studies, patients receiving reslizumab had a significant reduction in the frequency of asthma exacerbations (Study I: RR, 0.50; 95% CI, 0.37 to 0.67; Study II: RR, 0.41; 95% CI, 0.28 to 0.59; both P<0.0001) compared with those receiving placebo. Secondary: Common adverse events in both studies were worsening asthma symptoms (127 [52%] for placebo and 97 [40%] for reslizumab in Study I; 119 [51%] for placebo and 67 [29%] for reslizumab for Study II), upper respiratory tract infections (32 [13%] for placebo and 39 [16%] for reslizumab in Study I; 16 [7%] for placebo and eight [3%] for reslizumab for Study II), and nasopharyngitis (33 [14%] for placebo and 28 [11%] for reslizumab in Study I; 56 [24%] for placebo and 45 [19%] for reslizumab for Study II). There were two patients in the reslizumab groups who experienced

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	months			anaphylactic reactions, both of which responded to standard treatment and were withdrawn from the study.
Bjermer et al[26] Reslizumab 0.3 mg/kg IV once every four weeks vs reslizumab 3.0mg/kg IV once every four weeks vs placebo	DB, PC, PG, RCT Patients from 12 to 75 years of age with inadequately controlled asthma (ACQ-7 score ≥ 1.5), airway reversibility (≥ 12% to SABA), receiving treatment with at least a medium-dose ICS (fluticasone propionate ≥ 440 µg/day or equivalent) and at least one blood eosinophil count of ≥ 400 cells/µL	N=315 16 weeks	Primary: Change from baseline in pre-bronchodilator FEV_1 over 16 weeks Secondary: FVC, $FEF_{25\ to\ 75\%}$, patient-reported control of asthma symptoms, SABA use, blood eosinophils levels and safety	Primary: Reslizumab improved FEV_1 compared to placebo for both reslizumab treatment arms (115 mL; 95% CI, 16 to 215; P=0.0237 in the 0.3 mg/kg group and 160mL; 95% CI, 60 to 259; P=0.0018 in the 3 mg/kg group). FEV_1 improvements were seen as early as four weeks for the reslizumab 3 mg/kg group versus placebo (treatment difference: 153 mL) and was maintained for the duration of the study. Secondary: Clinically meaningful increases in FVC (130 mL) and $FEF_{25-75\%}$ (233 mL/second) were only observed with the reslizumab 3 mg/kg group. In addition, improvement in the ACQ and AQLQ as compared to placebo were only statistically significant with the reslizumab 3 mg/kg group (P<0.05). ASUI and SABA use were improved with both doses of reslizumab although the impact was greater in the 3 mg/kg group. Decreases in blood eosinophil levels were observed for both reslizumab groups but were greater for the 3.0 mg/kg group. Most commonly reported adverse events in this study were asthma worsening, headache and nasopharyngitis. There were no reported cases of anaphylaxis.
Corren et al[27] Reslizumab 3.0mg/kg IV once every four weeks vs placebo	DB, MC, PC, RCT Patients from 18 to 65 years of age with inadequately controlled asthma (ACQ-7 score ≥ 1.5), airway reversibility (≥ 12% to SABA), receiving treatment	N=496 16 weeks	Primary: Change in FEV_1 from baseline to week 16 Secondary: ACQ-7 score, rescue (SABA) use within the previous three days (assessed using	Primary: Results revealed that there was not a statistically significant mean change in FEV_1 from baseline to week 16 between the reslizumab and placebo group (255 mL for the reslizumab group and 187 mL for the placebo group giving a between-group difference of 68 mL: SE, 49.5; P=0.17). Secondary: The difference in change in FEV_1 from baseline to week 16

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	with at least a medium-dose ICS (fluticasone propionate ≥ 440 µg/day or equivalent)		three-day recall at scheduled visits), FVC and blood eosinophil levels	between the reslizumab and placebo-treated patients in the subgroup with eosinophil levels of < 400 cells/µL was 33 mL (P=0.54) while the difference in change in FEV_1 in patients with eosinophils ≥ 400 cells/µL between groups was 270 mL (P=0.04). Improvements in other efficacy parameters (ACQ-7, ACQ-6, FVC and SABA use) relative to placebo in the overall population were modest and not statistically significant. A smaller proportion of reslizumab-treated patients experienced ≥ one adverse event as compared to placebo, 55% versus 74% respectively. The most common (≥3%) adverse events in the reslizumab group were asthma, upper respiratory tract infection and sinusitis. Two patients in the reslizumab group had anaphylaxis (one was due to ongoing allergen immunotherapy and one was associated with reslizumab).
Chronic idiopathic urticaria				
Maurer et al[28] ASTERIA II Omalizumab 75 mg SC every four weeks for three doses vs omalizumab 150 mg SC every four weeks for three doses vs omalizumab 300 mg SC every four weeks for three doses	DB, MC, RCT Patients 12 to 75 years of age with moderate to severe chronic idiopathic urticaria who remained symptomatic despite histamine$_1$ antihistamine therapy	N=323 28 weeks	Primary: Change from baseline in a weekly itch-severity score Secondary: Changes from baseline in the UAS7 and in the score for the weekly number of hives, time until reduction from baseline of ≥5 points in the weekly itch-severity score, proportions of patients with a UAS7 of ≤6, number of patients	Primary: At week 12, the mean change from baseline in the weekly itch-severity score was -5.1±5.6 in the placebo group, -5.9±6.5 in the 75 mg group (P=0.46), -8.1±6.4 in the 150 mg group (P=0.001) and -9.8±6.0 in the 300 mg group (P<0.001). The reductions from baseline in mean weekly itch-severity scores were dose-responsive with all three omalizumab doses and were better than placebo at the time points before week 12. After 12 weeks, the mean weekly itch-severity scores for all omalizumab groups increased to reach values similar to those in the placebo group but did not return to baseline values for the duration of follow-up. Secondary: There was a significant difference between the omalizumab 150 and 300 mg groups compared to placebo in terms of all prespecified secondary endpoints except for the difference in the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo			with a weekly minimally important difference response in itch-severity score, score for size of largest hive, overall score on the Dermatology Life Quality Index, proportion of angioedema-free days from week four to 12	number of angioedema-free days from week four to 12, which reached significance in the omalizumab 300 mg group, only. The weekly score for the number of hives decreased with all three doses of omalizumab to a greater extent than placebo, with the largest difference being with the 300 mg dose. After 12 weeks, the mean weekly score for the number of hives for all omalizumab groups increased to reach values similar to those in the placebo group and did not return to baseline values for the duration of follow-up.
Kaplan et al[29] GLACIAL Omalizumab 300 mg SC every four weeks for six doses vs placebo	DB, MC, PC, RCT Patients 12 to 75 years of age with chronic idiopathic urticaria or chronic spontaneous urticaria who remained symptomatic despite treatment with histamine$_1$ antihistamines at up to four-times the approved dose plus histamine$_2$ antihistamines, leukotriene receptor antagonists or both	N=336 24 weeks	Primary: Safety, change from baseline in mean weekly itch-severity score at week 12, changes from baseline in UAS7, weekly number of hives score, weekly size of largest hive score, health-related quality of life, proportion of patients with UAS7s of ≤6, proportion of patients with change from baseline in mean itch-severity score of ≥5, proportion of angioedema-free days from weeks 4 to 12, proportion of patients with UAS7=0 at week 12	Primary: The incidence and severity of adverse events and serious adverse events were similar between omalizumab and placebo groups. Serious adverse events were reported by 7.1 and 6.0% of patients treated with omalizumab and placebo, respectively; however, no serious adverse events were suspected to have been caused by the study drug. The mean change from baseline in weekly itch-severity score at week 12 was significantly improved in the omalizumab group compared to placebo (-8.6 vs -4.0; P<0.001). This difference was sustained at week 24 (-8.6 vs -4.0; LSM difference, -4.5; 95% CI, -6.1 to -3.0; P<0.001). After week 24 and until week 40, the mean weekly itch-severity scores in the omalizumab group gradually increased to values similar to those in the placebo group but did not return to baseline values. Significant improvements were observed for all additional efficacy endpoints with omalizumab compared to placebo. A significantly greater proportion of patients in the omalizumab group were completely itch- and hive-free (UAS7=0) at week 12 compared to placebo (34 vs 5%; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The significant improvements in the additional efficacy endpoints were maintained at week 24; however, after discontinuation of omalizumab, improvements decreased such that values were similar to placebo by week 40. Treatment with omalizumab was effective, regardless of the combination of protocol-approved concomitant urticaria medications.

Drug regimen abbreviations: IV=intravenous, SC=subcutaneous
Study abbreviations: CI=confidence interval, DB=double-blind, DD=double-dummy, ES=extension study, HR=hazard ratio, MA=meta-analysis, MC=multicenter, OBS=observational, OL=open-label, PC=placebo-controlled, PG=parallel-group, PM=post-marketing, OR=odds ratio, PRO=prospective, RCT=randomized controlled trial, RR=Rate Ratio, SE=standard error,
Miscellaneous abbreviations: ACQ=asthma control questionnaire, ACT=asthma control test, AE=adverse event, AQLQ=Asthma Quality of Life Questionnaire, ASUI=Asthma Symptom Utility Index, BDP=beclomethasone dipropionate, ED=emergency department, FEV_1=forced expiratory volume in 1 second, FEV1/FVC=ratio of forced expiratory volume in 1 second to forced vital capacity, FEF 25-75%= forced expiratory flow at 25 to 75% of FVC, FVC=forced vital capacity, GETE=Global Evaluation of Treatment Effectiveness, ICS=inhaled corticosteroids, IgE=immunoglobulin E, IU=international units, LABAs=long-acting β-agonists, LSM=least square mean, LTRA=leukotriene receptor antagonist, OCS=oral corticosteroids, PEF=peak expiratory flow, RQLQ=rhinoconjunctivitis-specific quality of life questionnaire, SABA=Short-acting β-agonist, SAE=serious adverse event, SGRQ=St George's Respiratory Questionnaire, UAS7=urticaria activity score during a 7-day period

Special Populations

Table 5. Special Populations[1-3]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Mepolizumab	Clinical trials did not include enough elderly patients to evaluate differences in safety or efficacy between elderly and younger adult patients. The safety and efficacy in pediatric patients younger than 12 years have not been established.*	Not studied in renal dysfunction.*	Not studied in hepatic dysfunction.*	Pregnancy exposure data is insufficient to inform on drug-associated risk.	Unknown; use with caution.
Omalizumab	Clinical trials did not include enough elderly patients to evaluate differences in safety or efficacy between elderly and younger adult patients. Safety and efficacy in children <12 years of age have not been established.* Risk-benefit assessment does not support the use in patients six to <12 years of age.*	Renal dosage adjustment not required. Not studied in renal dysfunction.*	Hepatic dosage adjustment not required. Not studied in hepatic dysfunction.*	B	Unknown; use with caution.
	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.*	Not studied in renal dysfunction.*	Not studied in hepatic dysfunction.*	Pregnancy exposure data is insufficient to inform on drug-associated risk.	Unknown; use with caution.

*No adequate or well-controlled trials.

Adverse Drug Events

Table 6. Adverse Drug Events [37]

Adverse Event (%)	Mepolizumab	Omalizumab	Reslizumab
Abdominal Pain (mild)	3	-	-
Alopecia (mild)	-	≥2	-
Antibody formation (moderate)	6	-	4.8 to 5.4
Anxiety (mild)	-	≥2	-
Arthralgia (mild)	-	2.9 to 8	-
Asthenia (mild)	≥3	-	-
Back Pain (mild)	5	-	-
Bone Fractures (severe)	-	2	-
Cough (mild)	-	1.1 to 2.2	-
Cystitis (moderate)	≥3	≥2	-
Dental pain (mild)	≥3	-	-
Dizziness (mild)	≥3	3	-
Dyspnea (moderate)	≥3	-	-
Fatigue (mild)	5	3	-
Fever (mild)	≥3	≥2	-
Headache (mild)	19	6.1 to 15	-
Infection (mild)	≥3	0.5 to 23	-
Injection site reaction (mild)	8	0.6 to 45	-
Migraine (moderate)	-	≥2	-
Muscle cramps (mild)	3	-	-
Musculoskeletal pain (mild)	≥3	≥2	2.2
Myalgia (mild)	-	≥2	-
Nasal congestion (mild)	≥3	-	-
Nausea (mild)	≥3	1.1 to 2.7	-
Otalgia (mild)	-	2	-
Peripheral edema (moderate)	-	≥2	-
Pharyngitis (mild)	≥3	6.6 to 11	2.6
Pruritus (mild)	3	2	-
Rash, unspecified (mild)	≥3	-	-
Rhinitis (mild)	≥3	-	-
Sinusitis (mild)	-	1.1 to 16	-
Urticaria (mild)	-	≥2	-
Vomiting (mild)	≥3	-	-

- Not reported or <2%

Contraindications/Precaution

Table 7. Contraindications[1-3]

Contraindication(s)	Mepolizumab	Omalizumab	Reslizumab
History of hypersensitivity to the active drug or any excipient	a	a	a

Table 8. Warnings and Precautions[1-3]

Warning(s)/Precaution(s)	Mepolizumab	Omalizumab	Reslizumab
Anaphylaxis has been reported after administration. Administer in a health care setting by health care providers prepared to manage life-threatening anaphylaxis.	a	a	a
Avoid abrupt discontinuation of systemic or inhaled corticosteroids upon initiation of therapy for allergic asthma. Corticosteroids should be decrease gradually under the direct supervision of a physician.	a	a	a
Malignant neoplasms have been observed in treated patients. The impact of longer exposure or use in patients at increased risk for malignancy (e.g., elderly, current smokers) is not known.		a	a
Patients at high risk of geohelminth infection should be monitored while on therapy.	a	a	a
Patients with asthma may present with serious systemic eosinophilia sometimes presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome. These events are usually associated with the reduction of oral corticosteroid therapy. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications and/or neuropathy presenting in their patients.		a	
Not intended for the treatment of acute asthma exacerbations. Do not use to treat acute bronchospasm or status asthmaticus.	a	a	a
Opportunistic Infections: Herpes Zoster has been reported in treated patients	a		
Serum total immunoglobulin E levels increase following administration and may persist for up to one year following discontinuation. Do not use serum total immunoglobulin E levels obtained <1 year following discontinuation to reassess the dosing regimen for patients with allergic asthma.		a	
Symptoms including arthritis/arthralgia, rash, fever and lymphadenopathy have been reported one to five days after the first or subsequent injections. Symptoms recur with additional doses. If these symptoms develop, discontinued use.		a	

Black Box Warning for omalizumab (Xolair®)[2]

WARNING
Anaphylaxis presenting as bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue, has been reported to occur after administration of Xolair®. Anaphylaxis has occurred as early as after the first dose of Xolair®, but also has occurred beyond one year after beginning regularly administered treatment. Because of the risk of anaphylaxis, observe patients closely for an appropriate period of time after Xolair® administration. Health care providers administering Xolair® should be prepared to manage anaphylaxis that can be life-threatening. Inform patients of the signs and symptoms of anaphylaxis and instruct them to seek immediate medical care should symptoms occur.

Black Box Warning for reslizumab (Cinqair®)[3]

WARNING
WARNING: ANAPHYLAXIS 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. Anaphylaxis can be life-threatening. Patients should be observed for an appropriate period of time after CINQAIR administration by a healthcare professional prepared to manage anaphylaxis. Discontinue CINQAIR immediately if the patient experiences signs or symptoms of anaphylaxis.

Drug Interactions

No formal drug interaction studies have been performed with mepolizumab, omalizumab and reslizumab.[1-3]

Dosage and Administration

Table 9. Dosing and Administration[1-3]

Generic Name	Adult Dose	Pediatric Dose	Availability
Mepolizumab	Severe eosinophilic-phenotype asthma in adults and adolescents ≥12 years of age as an add-on maintenance treatment: Injection: Inject 100 mg subcutaneously every 4 weeks into the upper arm, thigh, or abdomen.	Safety and efficacy in children <12 years of age have not been established.	Powder for Injection (vial): 100 mg Mepolizumab should be reconstituted and administered by a healthcare professional.
Omalizumab	Treatment of moderate to severe persistent asthma in patients ≥12 years old who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids: Injection: 150 to 375 mg subcutaneous every two or four weeks (see Table 9 below) Treatment of chronic idiopathic urticaria in patients ≥12 years old who remain symptomatic despite histamine$_1$ antihistamine treatment: Injection: 150 or 300 mg subcutaneous every four weeks	Safety and efficacy in children <12 years of age have not been established.	Powder for Injection (vial): 150 mg Omalizumab should be administered in a healthcare setting by a healthcare professional prepared to manage anaphylaxis.
Reslizumab	Severe eosinophilic-phenotype asthma in adults as an add-on maintenance treatment: Injection: 3 mg/kg via intravenous infusion over 20 to 50 minutes every 4 weeks.	Safety and efficacy in children have not been established.	Solution for Injection: 100 mg/10 mL Reslizumab should be administered in a healthcare setting by a healthcare professional prepared to manage anaphylaxis.

Table 8. Omalizumab Dosing for Asthma by Immunoglobulin E Level and Body Weight[2]

Pre-treatment Serum Immunoglobulin E (IU/mL)	Body Weight (kg)			
	30 to 60	>60 to 70	>70 to 90	>90 to 150
≥30 to 100	150 mg	150 mg	150 mg	300 mg
>100 to 200	300 mg	300 mg	300 mg	225 mg
>200 to 300	300 mg	225 mg	225 mg	300 mg
>300 to 400	225 mg	225 mg	300 mg	
>400 to 500	300 mg	300 mg	375 mg	
>500 to 600	300 mg	375 mg	**DO NOT DOSE**	
>600 to 700	375 mg			
Every 2 weeks dosing				
Every 4 weeks dosing				

Clinical Guidelines

Table 7. Clinical Guidelines

Clinical Guidelines	Recommendations
Global Initiative for Asthma (GINA): **Global Strategy for Asthma Management and Prevention Guidelines (2015)**[30]	· Emphasizes asthma management based on clinical control rather classification of the patient by severity. · Mild to moderate asthma is defined by those requiring low intensity therapies for asthma control (Steps 1 to 3). · Severe asthma is defined by those requiring high intensity therapies for asthma control (Steps 4 to 5) or where good control is not achieved despite high intensity therapy. · GINA guideline recommends a stepwise approach to pharmacologic therapy to maintain control. · Most treatment naïve patients with persistent asthma symptoms would initiate treatment at Step 2 (low-dose inhaled corticosteroids [ICS]) or Step 3 (low dose ICS plus other controller medication or medium-dose ICS) if symptoms at the initial consultation suggest that asthma is severely uncontrolled. · Patients with severe asthma are treated at Steps 4 or 5 (i.e., medium or high-dose ICS/ long-acting β-agonists [LABAs], high dose ICS plus leukotriene receptor antagonists (and/or theophylline), and anti-immunoglobulin E [IgE] treatment (no specific product recommended). Tiotropium is also recommended as a potential add-on therapy for Steps 4 and 5 in patients aged ≥ 18 years with a history of exacerbations for severe uncontrolled asthma. Treatment would then be stepped up or down depending on the level of asthma control achieved, with the goal of establishing the minimum necessary to maintain disease control.
European Respiratory Society (ERS)/American Thoracic Society (ATS) **Severe Asthma Guidelines (2014)**[31]	· Definition of severe asthma for patients aged ≥ 6 years is asthma requiring treatment with guidelines suggested medications for GINA Steps 4 to 5 (high-dose ICS and LABA or leukotriene modifier/theophylline) for the previous year or systemic corticosteroids (CS) for ≥ 50% of the previous year to prevent it from becoming uncontrolled or which remains uncontrolled despite this therapy. · Uncontrolled asthma is defined as at least one of the following: 1) poor symptom control: Asthma Control Questionnaire (ACQ) consistently > 1.5, Asthma Control Test (ACT) < 20 (or not well controlled by the National Asthma Education and Prevention Program [NAEPP] or GINA

Clinical Guidelines	Recommendations
	guidelines) 2) frequent severe exacerbations: two or more bursts of systemic corticosteroids (> 3 days each) in the previous year 3) serious exacerbations: at least one hospitalization, intensive care unit stay or mechanical ventilation in the previous year 4) airflow limitation: after appropriate bronchodilator withhold forced expiratory volume in one second (FEV_1) < 80% predicted (in the face of reduced ratio of forced expiratory volume in one second to forced vital capacity [FEV_1/FVC] defined as less than the lower limit of normal) 5) Controlled asthma that worsens on tapering of these high doses of ICS or systemic CS (or additional biologics) · Step-wise increases in the dose of ICS, in combination with a LABA, improve the control compared with ICS alone for some patients with severe asthma. · The use of tiotropium bromide aerosols for the relief of symptoms is common in moderate to severe asthma patients in an effort to reduce the daily use or overuse of β-agonists. · In patients with severe allergic asthma, the guidelines suggest a trial of omalizumab both in adults and in children ≥ 6 years of age (although it is a conditional recommendation with low quality evidence). · The guidelines recommend that both clinical criteria and sputum eosinophil counts should be considered when determining the appropriate treatment approach among adults while the therapy among children should be based on clinical criteria alone given low quality of evidence for use of sputum eosinophil counts in this population. · According to the guidelines, sputum eosinophil counts should be used only at centers with expertise in this technique. · No therapies are specifically recommended by the ERS/ATS guidelines for patients with severe asthma with an eosinophilic phenotype. · Alternative molecular-targeted therapies may be needed in severe asthma to modulate inflammation and improve corticosteroid insensitivity. Eosinophilic inflammation may persist in some severe asthma patients despite high-dose ICS and even systemic CS.
Global Initiative for Asthma: **Global Strategy for Asthma Management and Prevention (2011)**[32]	<u>Treatment</u> · Education should be an integral part of all interactions between health care professionals and patients, and is relevant to asthma patients of all ages. · Measures to prevent the development of asthma, asthma symptoms, and asthma exacerbations by avoiding or reducing exposure to risk factors should be implemented whenever possible. · Controller medications are administered daily on a long-term basis and include inhaled and systemic glucocorticosteroids, leukotriene modifiers, LABAs in combination with inhaled glucocorticosteroids, sustained-released theophylline, cromones, and anti-immunoglobulin E (IgE). · Reliever medications are administered on an as-needed basis to reverse bronchoconstriction and relieve symptoms and include rapid-acting inhaled β_2-agonists, inhaled anticholinergics, short-acting theophylline, and SABAs. <u>Controller medications</u> · Inhaled glucocorticosteroids are currently the most effective anti-inflammatory medications for the treatment of persistent asthma for patients of all ages. · Inhaled glucocorticosteroids differ in potency and bioavailability, but few

Clinical Guidelines	Recommendations
	studies have been able to confirm the clinical relevance of these differences. · To reach clinical control, add-on therapy with another class of controller is preferred over increasing the dose of inhaled glucocorticosteroids. · Leukotriene modifiers are generally less effective than inhaled glucocorticosteroids therefore may be used as an alternative treatment in patients with mild persistent asthma. · Some patients with aspirin-sensitive asthma respond well to leukotriene modifiers. · Leukotriene modifiers used as add-on therapy may reduce the dose of inhaled glucocorticosteroids required by patients with moderate to severe asthma, and may improve asthma control in adult patients whose asthma is not controlled with low or high doses of inhaled glucocorticosteroids. · Several studies have demonstrated that leukotriene modifiers are less effective than LABAs as add-on therapy. · LABAs should not be used as monotherapy in patients with asthma as these medications do not appear to influence asthma airway inflammation. · When a medium dose of an inhaled glucocorticosteroid fails to achieve control, the addition of a LABA is the preferred treatment. · Controlled studies have shown that delivering a LABA and an inhaled glucocorticosteroid in a combination inhaler is as effective as giving each drug separately. Fixed combination inhalers are more convenient, may increase compliance, and ensure that the LABA is always accompanied by a glucocorticosteroid. · Although the guideline indicates that combination inhalers containing formoterol and budesonide may be used for both rescue and maintenance, this use is not approved by the Food and Drug Administration (FDA). · Theophylline as add-on therapy is less effective than LABAs but may provide benefit in patients who do not achieve control on inhaled glucocorticosteroids alone. · Cromolyn and nedocromil are less effective than a low dose of an inhaled glucocorticosteroid. · Oral LABA therapy is used only on rare occasions when additional bronchodilation is needed. · Anti-IgE treatment with omalizumab is limited to patients with elevated serum levels of IgE. · Long-term oral glucocorticosteroid therapy may be required for severely uncontrolled asthma, but is limited by the risk of significant adverse effects. · Other anti-allergic compounds have limited effect in the management of asthma. <u>Reliever medications</u> · Rapid-acting inhaled β_2-agonists are the medications of choice for the relief of bronchospasm during acute exacerbations and for the pretreatment of exercise-induced bronchoconstriction, in patients of all ages. · Rapid-acting inhaled β_2-agonists should be used only on an as-needed basis at the lowest dose and frequency required. · Although the guidelines states that formoterol, a LABA, is approved for symptom relief because of its rapid onset of action, and that it should only be used for this purpose in patients on regular controller therapy with inhaled glucocorticosteroids, the use of this agent as a rescue inhaler is not approved by the FDA.

<table>
<tr><th>Clinical Guidelines</th><th>Recommendations</th></tr>
<tr><td></td><td>
· Ipratropium bromide, an inhaled anticholinergic, is a less effective reliever medication in asthma than rapid-acting inhaled β_2-agonists.
· Short-acting theophylline may be considered for relief of asthma symptoms.
· Short-acting oral β_2-agonists (tablets, solution, etc.) are appropriate for use in patients who are unable to use inhaled medication however they are associated with a higher prevalence of adverse effects.
· Systemic glucocorticosteroids are important in the treatment of severe acute exacerbations.

<u>Assessment, treatment, and monitoring</u>
· The goal of asthma treatment is to achieve and maintain clinical control.
· To aid in clinical management, a classification of asthma by level of control is recommended: controlled, partly controlled, or uncontrolled.
· Treatment should be adjusted in a continuous cycle driven by the patient's asthma control status and treatment should be stepped up until control is achieved. When control is maintained for at least three months, treatment can be stepped down.
· Increased use, especially daily use, of reliever medication is a warning of deterioration of asthma control and indicates the need to reassess treatment.
· The management approach based on control is outlined below:
<table>
<tr><th>Step 1</th><th>Step 2</th><th>Step 3</th><th>Step 4</th><th>Step 5</th></tr>
<tr><td colspan="5">Asthma education and environmental control</td></tr>
<tr><td colspan="5">As needed rapid-acting β_2-agonist</td></tr>
<tr><td rowspan="5">Controller options</td><td>Select one</td><td colspan="2">Select one</td><td>Add one or more</td><td>Add one or both</td></tr>
<tr><td>Low-dose inhaled gluco-corticosteroid</td><td colspan="2">Low-dose inhaled glucocorticosteroid +LABA</td><td>Medium- or high-dose inhaled glucocortico-steroid + LABA</td><td>Oral Gluco-corticosteroid</td></tr>
<tr><td>Leukotriene modifier</td><td colspan="2">Medium- or high-dose inhaled glucocorticosteroid</td><td>Leukotriene modifier</td><td>Anti-IgE treatment</td></tr>
<tr><td>-</td><td colspan="2">Low-dose inhaled glucocorticosteroids +leukotriene modifier</td><td>-</td><td>-</td></tr>
<tr><td>-</td><td colspan="2">Low-dose inhaled glucocorticosteroid +sustained-release theophylline</td><td>-</td><td>-</td></tr>
</table>

<u>Management of exacerbations</u>
· Repeated administration of rapid-acting inhaled β_2-agonists is the best method of achieving relief for mile to moderate exacerbations.
· Systemic glucocorticosteroids should be considered if the patient does not immediately respond to rapid-acting inhaled β_2-agonists or if the episode is severe.
</td></tr>
<tr><td>The National Heart, Lung, and Blood Institute/National Asthma Education and Prevention Program: Guidelines for the Diagnosis and Management of</td><td>
<u>Diagnosis</u>
· To establish a diagnosis of asthma, a clinician must determine the presence of episodic symptoms or airflow obstruction, partially reversible airflow obstruction and alternative diagnoses must be excluded.
· The recommended methods to establish a diagnosis are a detailed medical history, physical exam focusing on the upper respiratory tract, spirometry to demonstrate obstruction and assess reversibility and additional studies to exclude alternative diagnoses.
· A diagnosis of asthma should be considered if any of the following
</td></tr>
</table>

Clinical Guidelines	Recommendations
Asthma (2007)[33]	indicators are present: wheezing, history of cough, recurrent wheeze, difficulty breathing or chest tightness, symptoms that occur or worsen with exercise or viral infections and symptoms that occur or worsen at night. · Spirometry is needed to establish a diagnosis of asthma. · Additional studies such as additional pulmonary function tests, bronchoprovocation, chest x-ray, allergy testing and biomarkers of inflammation may be useful when considering alternative diagnoses. <u>Treatment</u> · Pharmacologic therapy is used to prevent and control asthma symptoms, improve quality of life, reduce the frequency and severity of asthma exacerbations and reverse airflow obstruction. · The initial treatment of asthma should correspond to the appropriate asthma severity category. · Long-term control medications such as inhaled corticosteroids (ICSs), long-acting bronchodilators, leukotriene modifiers, cromolyn, theophylline and immunomodulators should be taken daily on a long-term basis to achieve and maintain control of persistent asthma. · Quick-relief medications are used to provide prompt relief of bronchoconstriction and accompanying acute symptoms such as cough, chest tightness and wheezing. · Quick relief medications include short-acting β_2-adrenergic agonists (SABAs), anticholinergics and systemic corticosteroids. <u>Long-term control medications</u> · ICSs are the most potent and consistently effective long-term control medication for asthma in patients of all ages. · Short courses of oral systemic corticosteroids may be used to gain prompt control when initiating long-term therapy and chronic administration is only used for the most severe, difficult-to-control asthma. · When patients ≥12 years of age require more than low-dose ICSs, the addition of a long-acting β_2-adrenergic agonists (LABAs) is recommended. Alternative, but not preferred, adjunctive therapies include leukotriene receptor antagonists, theophylline, or in adults, zileuton. · Mast cell stabilizers (cromolyn and nedocromil) are used as alternatives for the treatment of mild persistent asthma. They can also be used as preventative treatment prior to exercise or unavoidable exposure to known allergens. · Omalizumab, an immunomodulator, is used as adjunctive therapy in patients 12 years and older who have allergies and severe persistent asthma that is not adequately controlled with the combination of high-dose ICS and LABA therapy. · Leukotriene receptor antagonists (montelukast and zafirlukast) are alternative therapies for the treatment of mild persistent asthma. · LABAs (formoterol and salmeterol) are not to be used as monotherapy for long-term control of persistent asthma. · LABAs should continue to be considered for adjunctive therapy in patients five years of age or older who have asthma that require more than low-dose ICSs. For patients inadequately controlled on low-dose ICSs, the option to increase the ICS should be given equal weight to the addition of a LABA. · Methylxanthines, such as sustained-release theophylline, may be used as an alternative treatment for mild persistent asthma.

Clinical Guidelines	Recommendations

- Tiotropium bromide is a long-acting inhaled anticholinergic indicated once-daily for chronic obstructive pulmonary disease and has not been studied in the long-term management of asthma.

Quick-relief medications

- SABAs are the therapy of choice for relief of acute symptoms and prevention of exercise induced bronchospasm.
- There is inconsistent data regarding the efficacy of levalbuterol compared to albuterol. Some studies suggest an improved efficacy while other studies fail to detect any advantage of levalbuterol.
- Anticholinergics may be used as an alternative bronchodilator for patients who do not tolerate SABAs and provide additive benefit to SABAs in moderate-to-severe asthma exacerbations.
- Systemic corticosteroids are used for moderate and severe exacerbations as adjunct to SABAs to speed recovery and prevent recurrence of exacerbations.
- The use of LABAs is not recommended to treat acute symptoms or exacerbations of asthma.

Assessment, treatment and monitoring

- A stepwise approach to managing asthma is recommended to gain and maintain control of asthma.
- Regularly scheduled, daily, chronic use of a SABA is not recommended. Increased SABA use or SABA use more than two days a week for symptom relief generally indicates inadequate asthma control.
- The stepwise approach for managing asthma is outlined below:

Inter-mittent Asthma	Persistent Asthma: Daily Medication				
Step 1	**Step 2**	**Step 3**	**Step 4**	**Step 5**	**Step 6**
Preferred SABA as needed	Preferred Low-dose ICS Alternative Cromolyn, leukotriene receptor antagonists, nedocromil, or theophylline	Preferred Low-dose ICS+LABA or medium-dose ICS Alternative Low-dose ICS+either a leukotriene receptor antagonists, theophylline, or zileuton	Preferred Medium-dose ICS+LABA Alternative Medium-dose ICS+either a leukotriene receptor antagonists, theophylline, or zileuton	Preferred High-dose ICS+ LABA and consider omalizu-mab for patients who have allergies	Preferred High-dose ICS+LABA+ oral steroid and consider omalizumab for patients who have allergies

Management of exacerbations

- Appropriate intensification of therapy by increasing inhaled SABAs and, in some cases, adding a short course of oral systemic corticosteroids is recommended.

Special populations

- For exercise induced bronchospasm, pretreatment before exercise with either a SABA or LABA is recommended. Leukotriene receptor antagonists may also attenuate exercise induced bronchospasm, and mast cell stabilizers can be taken shortly before exercise as an alternative treatment for prevention; however, they are not as effective as SABAs. The addition

Clinical Guidelines	Recommendations
	of cromolyn to a SABA is helpful in some individuals who have exercise induced bronchospasm. · Consideration of the risk for specific complications must be given to patients who have asthma who are undergoing surgery. · Albuterol is the preferred SABA in pregnant women because of an excellent safety profile. · ICSs are the preferred treatment for long-term control medication in pregnant women. Specifically, budesonide is the preferred ICS as more data is available on using budesonide in pregnant women than other ICSs.
British Society for Allergy and Clinical Immunology: **BSACI guideline for the management of chronic urticaria and angioedema (2015)**[34]	Treatment in Adults · Identify triggers and, if identified, the patient should be instructed on avoidance strategies (e.g., avoiding cold or pressure) o If the patient is taking a drug associated with chronic urticaria or angioedema, the patient must have a trial for at least several weeks without the treatment. o Treatment of underlying infections and malignancies may lead to amelioration or resolution of symptoms. o Alcohol can aggravate chronic urticaria by its effect of vasodilation. · Utilize a step-wise approach to treatment plan for chronic urticaria. · A short course of corticosteroids may be appropriate in severe episodes at any stage. · Step 1 o Standard dose non-sedating H_1 antihistamine is recommended first line for symptom control. o Once controlled, daily treatment is advised (three to six months for most patients, but treatment of up to six to 12 months is advised for urticaria with angioedema). o Avoid chronic use of first generation antihistamines due to sedation and interference with psychomotor performance. o Sedating antihistamines (e.g., hydroxyzine) may be useful at night, but may lead to day-time somnolence if the agent has a long half-life. o Limited head-to-head data limits stratification of efficacy. · Step 2 o Higher dose of H_1-antihistamine (up to four times the recommended dose) or add in a second antihistamine. o If higher than recommended doses of antihistamines are used, incremental up-dosing is advised. · For refractory cases that are resistant to high-dose antihistamines, there is no “recommended” second-line therapy, but there are several treatment options. · Step 3/4 o Leukotriene receptor antagonists may be useful in combination with antihistamines in a subgroup of patients, particularly those with adverse responses to aspirin, nonsteroidal antiinflammatory drugs (NSAIDs), and in those with delayed pressure urticaria. o If angioedema is present, use tranexamic acid. o Omalizumab is effective in patients with spontaneous and autoimmune chronic urticaria who have persistent symptoms despite high-dose antihistamines. § Highly effective (~80% of patients) with a rapid improvement § Treatment is recommended for six months § Relapses typically occur when treatment is discontinued. o Low-dose cyclosporine may be considered in patients with severe

Clinical Guidelines	Recommendations
	unremitting disease uncontrolled by antihistamines. o Data suggests that 1,000 mg twice daily of mycophenolate mofetil is useful; however, its speed of onset is slower than both omalizumab and cyclosporine. Treatment in Children · Avoidance of known provoking stimuli should be the primary strategy in any treatment. · Non-sedating antihistamines are the mainstay of treatment for children with chronic urticaria. o Up to four times the recommended dose may be required to adequately control symptoms. o A lack of response to high-dose antihistamine therapy should raise the possibility of an underlying diagnosis such as vasculitis o Treatment options § 1 year or older: cetirizine and desloratadine § 2 years or older: loratadine and levocetirizine § 12 years or older: fexofenadine § Most are available in syrup formulations · Children may become accustomed to the sedating effects of first-generation antihistamines; however, the risk of psychomotor impairment remains and this may impact on the child's safety and education. o Use diphenhydramine, hydroxyzine, or promethazine · Leukotriene receptor antagonists should be considered in addition to antihistamines in patients who had an inadequate response to antihistamines alone. o A one- to four-week trial is recommended. o It is not recommended to use a leukotriene receptor antagonist as monotherapy as clinical trial data is poor. · Oral corticosteroids are effective for short term use (three to five days) to gain control of symptoms. They are more effective in patients with delayed pressure urticaria and have limited efficacy in inducible urticaria unresponsive to first-line therapy. · Tranexamic acid can be effective in treatment of isolated angioedema. · Anti-IgE therapy with omalizumab evidence is increasing in children seven years of age or older resistant to first-line treatment. o Three to six injections administered monthly is recommended. o Omalizumab is well tolerated but should be restricted to specialist centers.
Academy of Allergy, Asthma & Immunology (AAAAI)/American College of Allergy, Asthma & Immunology (ACAAI)/Joint Council of Allergy, Asthma & Immunology: **The Diagnosis and Management of Acute and Chronic**	· Autoantibody-associated urticaria refers to the presence of autoantibodies (e.g., thyroid autoantibodies and IgE receptor autoantibodies) in conjunction with urticaria and can be considered a subset of chronic idiopathic urticaria (CIU) · Begin treatment at step appropriate for patient's level of severity and previous treatment history. · At each level of the step-approach, medication(s) should be assessed for patient tolerance and efficacy. · "Step-down" in treatment is appropriate at any step, once consistent control of urticaria/angioedema is achieved. · Step 1 o Monotherapy with second generation antihistamine o Avoidance of triggers (e.g., NSAIDs) and relevant physical factors if

Clinical Guidelines	Recommendations
Urticaria: 2014 update (2014)[35]	physical urticaria/angioedema syndrome is present · Step 2 o Dose advancement of second generation antihistamine used in Step o Add another second generation antihistamine o Add H_2-antagonist o Add leukotriene receptor antagonist o Add first generation antihistamine to be taken at bedtime · Step 3 o Dose advancement of potent antihistamines (e.g., hydroxyzine or doxepin) as tolerated · Step 4 o Add an alternative agent: § Omalizumab or cyclosporine § Other anti-inflammatory agents, immunosuppressants or biologics
European Academy of Allergology and Clinical Immunology/Global Allergy and Asthma European Network/European Dermatology Forum/World Allergy Organization: **Management of Urticaria (2009)[36]**	· Non-sedating histamine$_1$ antihistamines are recommended first-line. · If symptoms persist after two weeks of treatment with a histamine$_1$ antihistamine, increasing the dose up to four times is recommended. · If symptoms persist after one to four weeks of a high-dose histamine$_1$ antihistamine, the addition of a leukotriene antagonist or a change in histamine$_1$ antihistamine is recommended. For the treatment of an exacerbation, systemic steroids are recommended for three to seven days. · If symptoms persist after one to four weeks of histamine$_1$ antihistamine plus leukotriene or the alternative histamine$_1$ antihistamine, the addition of cyclosporine A, a histamine$_2$ antihistamine, dapsone or omalizumab is recommended. For the treatment of an exacerbation, systemic steroids are recommended for three to seven days.

Conclusions

The antiasthmatic monoclonal antibodies are subdivided into two subclasses, anti-IgE antibodies and anti-IL-5 antibodies.[1-3] The IL-5 monoclonal antibodies, mepolizumab (Nucala®) and reslizumab (Cinqair®), prevent the binding of IL-5 to receptors on the surface of eosinophils and are FDA-approved for the add-on maintenance treatment of severe eosinophilic asthma.[1,3] Omalizumab (Xolair®), is the only anti-IgE antibody currently available and it is FDA approved for the treatment of moderate to severe persistent asthma in patients with a positive skin test or in vitro reactivity to a perennial aeroallergen in addition to chronic idiopathic urticaria.[2] Both mepolizumab and omalizumab have been shown to be safe and effective for use in children 12 years of age and older.[1,2] There are currently no generic products available for these agents. Due to the associated risks of anaphylaxis and complicated administration, all three agents must be administered by a healthcare professional. Those healthcare professionals administering omalizumab and reslizumab should be prepared to observe patients for an appropriate amount of time and the ability to manage anaphylaxis.[1-3]

There are limited recommendations for the use of anti-IgE therapy in asthma. Generally, it is considered relatively safe while providing quick and efficient relief of symptoms. Guidelines generally recommend omalizumab as a 2nd or 3rd line option behind inhaled corticosteroids and another agent. Guidelines acknowledge omalizumab should be reserved for only the most severe cases due to the burdensome administration.[30-33] Current clinical guidelines do not address the use of anti-IL-5 monoclonal antibodies at this time. Omalizumab is considered a second- or third-line option in patients who have chronic idiopathic urticaria and have failed antihistamine therapy.[34-36]

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