Therapeutic Class Overview
Immunoglobulin E Monoclonal Antibodies

Therapeutic Class Overview/Summary:
Immunoglobulin E (IgE) monoclonal antibodies inhibit the binding of IgE to IgE receptors. The mechanism of action of IgE monoclonal antibodies may have utility in the treatment of various allergic conditions. Currently, there is one IgE monoclonal antibody approved by the Food and Drug Administration (FDA). Omalizumab (Xolair®) is a humanized monoclonal antibody that is FDA-approved for the treatment of adults and adolescents 12 years of age and older, with moderate to severe persistent asthma, who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids (ICS), as well as for the treatment of patients with chronic idiopathic urticaria refractory to histamine$_1$ antihistamine therapy.[1]

An allergic form of asthma is found in approximately 90% of adult asthmatics.[2] 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.[3] 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.[1] 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.[1]

Omalizumab is administered subcutaneously in a physician's office every two to four weeks in a dose that is determined by body weight and the levels of serum IgE for allergic asthma and 150 to 300 mg every four weeks for chronic idiopathic urticaria.[1,3] It carriers a black box warning due to the risk of anaphylaxis which may occur as early as after first dose, but also as long as beyond one year of treatment.[1]

The National Heart, Lung and Blood Institute and the National Asthma Education and Prevention Program recommend considering omalizumab as an adjunctive therapy in patients 12 years of age and older with allergies and severe persistent asthma that is inadequately controlled with the combination of high-dose ICS and long-acting β_2-agonist.[11] Similarly, Global Initiative for Asthma guidelines recommend omalizumab as an adjunctive therapy in patients with elevated serum levels of IgE who are not adequately controlled on controller medications.[12]

The National Institute for Health and Clinical Excellence guidelines recommend omalizumab add-on therapy for narrowly defined severely affected groups of asthma patients with unstable disease who have clinical confirmation of IgE mediation of asthma exacerbations and have had a trial of all standard asthma medications. In addition, omalizumab therapy may only be cost-effective for severely affected group of asthma patients at an elevated risk of asthma-related mortality, if therapy was discontinued in non-responders at 16 weeks and if vial wastage could be minimized to reduce costs.[13] Omalizumab is not recommended in children aged six to 11 because it does not provide enough benefit to justify its high cost.[14]

The European Academy of Allergology and Clinical Immunology/Global Allergy and Asthma European Network/European Dermatology Forum/World Allergy Organization consensus guidelines for the management of urticaria recommend omalizumab as a treatment option in patients who have failed treatment with two different histamine$_1$ antihistamines at four-times the labelled dose and combination therapy with a histamine$_1$ antihistamine in a leukotriene antagonist.[17] The British Association of Dermatologists Guidelines for the management of Urticaria in adults and children have not yet been updated to address the role of omalizumab in the treatment of urticaria.[18]

Although omalizumab is not FDA-approved for use in other allergic conditions, the evidence from several randomized controlled trials favors its efficacy in patients with allergic rhinitis.[1,19-22] Omalizumab is also being investigated in patients with peanut allergy, latex allergy, eosinophilic gastroenteritis, and other IgE mediated allergic conditions.[23]

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

Generic Name (Trade name)	Medication Class	Generic Availability
Omalizumab (Xolair®)	Anti-IgE Antibody	-

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 published, randomized, double-blind, placebo-controlled, multicenter trials. All studies enrolled patients 12 years of age and older with moderate to severe persistent asthma and a positive skin test to a perennial aeroallergen. Two studies showed significantly greater reductions in exacerbations with omalizumab vs placebo. In all three studies, the dose of inhaled corticosteroids was significantly reduced with omalizumab compared to placebo.[4-6]
- Multiple meta-analyses demonstrated the efficacy of omalizumab in decreasing steroid consumption and reducing asthma exacerbations when added to an ICS.[7-9] However, further assessment in pediatric populations and direct double dummy comparison with an ICS was recommended.[8] In addition, a five-year long observational study (EXCELS) is currently evaluating the safety of omalizumab in patients with moderate to severe asthma. In July 2009, the FDA announced that the interim data suggests a disproportionate increase in cardiovascular and cerebrovascular adverse events in patients treated with omalizumab compared to placebo; however, no changes to the prescribing information were recommended.[10]
- The FDA-approval of omalizumab for the treatment of chronic idiopathic urticaria was based on two published, randomized, double-blind, placebo-controlled, multicenter trials. 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. Both studies showed significant improvements in the itch-severity test compared to placebo.[15,16]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Omalizumab is recommended as adjunctive therapy in patients ≥12 years old with allergies and severe, persistent asthma with elevated immunoglobulin E (IgE) who are not adequately controlled on controller medications.[11,12]
  - The European Academy of Allergology and Clinical Immunology/Global Allergy and Asthma European Network/European Dermatology Forum/World Allergy Organization consensus guidelines for the management of urticaria recommend omalizumab as a treatment option in patients who have failed treatment with two different histamine$_1$ antihistamines at four-times the labelled dose and combination therapy with a histamine$_1$ antihistamine in a leukotriene antagonist.[17]
- Other Key Facts:
  - Currently, omalizumab is the only agent in this novel drug class that has been approved by the Food and Drug Administration and is commercially available in the United States.[1]
  - Omalizumab is administered subcutaneously by a health care provider in a health care setting. For the treatment of allergic asthma, omalizumab is given at a dose of 150 to 375 mg every two or four weeks according to IgE level and body weight. For the treatment of chronic urticaria, omalizumab is given at a dose of 150 or 300 mg every four weeks, regardless of IgE level or weight.[1]
  - Omalizumab is associated with a black box warning due to the risk of anaphylaxis that may occur as early as the first dose or as late as beyond one year after treatment initiation.[1]
  - The most common adverse side effects associated with omalizumab include injection site pain, nausea, arthralgia, headache and respiratory symptoms.

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Overview/Summary

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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.[1]

Omalizumab is administered subcutaneously in a physician's office every two to four weeks in a dose that is determined by body weight and the levels of serum IgE for allergic asthma and 150 to 300 mg every four weeks for chronic idiopathic urticaria.[1,3] It carriers a black box warning due to the risk of anaphylaxis which may occur as early as after first dose, but also as long as beyond one year of treatment.[1]

The FDA approval of omalizumab for the treatment of allergic asthma was based on the results of three published, randomized, double-blind, placebo-controlled, multicenter trials. All studies enrolled patients 12 years of age and older with moderate to severe persistent asthma and a positive skin test to a perennial aeroallergen. Two studies showed significantly greater reductions in exacerbations with omalizumab vs placebo. In all three studies, the dose of ICS was significantly reduced with omalizumab compared to placebo.[4-6]

Multiple meta-analyses demonstrated the efficacy of omalizumab in decreasing steroid consumption and reducing asthma exacerbations when added to an ICS.[7-9] However, further assessment in pediatric populations and direct double dummy comparison with an ICS was recommended.[8] In addition, a five-year long observational study (EXCELS) is currently evaluating the safety of omalizumab in patients with moderate to severe asthma. In July 2009, the FDA announced that the interim data suggests a disproportionate increase in cardiovascular and cerebrovascular adverse events in patients treated with omalizumab compared to placebo; however, no changes to the prescribing information were recommended.[10]

The National Heart, Lung and Blood Institute and the National Asthma Education and Prevention Program recommend considering omalizumab as an adjunctive therapy in patients 12 years of age and older with allergies and severe persistent asthma that is inadequately controlled with the combination of high-dose ICS and long-acting β_2-agonist.[11] Similarly, Global Initiative for Asthma guidelines recommend omalizumab as an adjunctive therapy in patients with elevated serum levels of IgE who are not adequately controlled on controller medications.[12]

The National Institute for Health and Clinical Excellence guidelines recommend omalizumab add-on therapy for narrowly defined severely affected groups of asthma patients with unstable disease who have clinical confirmation of IgE mediation of asthma exacerbations and have had a trial of all standard asthma

medications. In addition, omalizumab therapy may only be cost-effective for severely affected group of asthma patients at an elevated risk of asthma-related mortality, if therapy was discontinued in non-responders at 16 weeks and if vial wastage could be minimized to reduce costs.[13] Omalizumab is not recommended in children aged six to 11 because it does not provide enough benefit to justify its high cost.[14]

The FDA-approval of omalizumab for the treatment of chronic idiopathic urticaria was based on two published, randomized, double-blind, placebo-controlled, multicenter trials. 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. Both studies showed significant improvements in the itch-severity test compared to placebo.[15,16]

The European Academy of Allergology and Clinical Immunology/Global Allergy and Asthma European Network/European Dermatology Forum/World Allergy Organization consensus guidelines for the management of urticaria recommend omalizumab as a treatment option in patients who have failed treatment with two different histamine$_1$ antihistamines at four-times the labelled dose and combination therapy with a histamine$_1$ antihistamine in a leukotriene antagonist.[17] The British Association of Dermatologists Guidelines for the management of Urticaria in adults and children have not yet been updated to address the role of omalizumab in the treatment of urticaria.[18]

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Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Omalizumab (Xolair®)	Anti-IgE antibody	-

Indications

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

Indication(s)	Omalizumab
Moderate to severe persistent asthma in patients with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids	✔
Chronic idiopathic urticaria in adults and adolescents ≥12 years of age who remain symptomatic despite histamine$_1$ antihistamine treatment	✔

Pharmacokinetics

Table 3. Pharmacokinetics[1]

Generic Name	Bioavailability (%)	Metabolism	Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Omalizumab	62	Degradation in the liver reticuloendothelial system and endothelial cells	Bile (not reported)	None	24 to 26 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.[1]

Each study was comprised of a run-in period to achieve a stable conversion to a common inhaled corticosteroid (ICS), followed by randomization to omalizumab or placebo. Patients received omalizumab for 16 weeks with an unchanged ICS dose unless an acute exacerbation necessitated an increase. Patients then entered an ICS reduction phase of 12 (Busse et al and Solèr et al) and 16 weeks (Holgate et al) during which ICS dose reduction was attempted in a step-wise manner.[1]

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).[4]

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.[5]

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).[6] The absence of an observed treatment effect may be related to differences in the patient population compared to the first two studies, study sample size, or other factors.[1]

A meta-analysis of three aforementioned trials (Busse et al, Solèr et al, Holgate et al) and their extension studies assessed the efficacy of omalizumab in a subgroup of 254 patients at high risk of serious asthma-related mortality and morbidity. Patients were defined as high-risk due to asthma histories that included the following: intubation history, emergency room visit within the last year, overnight hospitalization, or intensive care unit treatment. The primary outcome was an annualized rate of acute exacerbation episodes based on data from the initial 16-week stable steroid phase for high-risk patients. Two kinds of acute exacerbation episodes were considered as endpoints: significant acute exacerbation episodes and all acute exacerbation episodes (i.e., all episodes recorded by the investigator). Significant acute exacerbation episodes were defined as those requiring a doubling of baseline ICS dose (Busse et al and Solèr et al) or use of systemic steroids (all three studies). During the stable steroid phase, mean significant acute exacerbation episodes rates were 1.56 and 0.69/patient-year, respectively, a reduction of 56% with omalizumab (P=0.007). Similar reductions in exacerbations in favor of omalizumab were observed for the whole study period and for all acute exacerbation episodes. The authors concluded that 113 significant acute exacerbation episodes were prevented for every 100 patients treated with omalizumab for one year.[7]

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.[15,16]

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.[15]

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.[16]

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.[4] (2001) 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 use was

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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.[24] (extension of a study by Busse et al.[4]) (2003) Omalizumab at least 0.016 mg/kg/IgE	DB, MC, PC, PG, RCT Patients 12 to 75 years of age with allergic asthma who were symptomatic despite treatment with ICS	N=460 24 weeks	Primary: Number of asthma exacerbations/ patient, number of patients with ≥1	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 exacerbation was also lower for omalizumab than placebo (31.8 and 42.8%; P=0.015). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(IU/mL) SC every four weeks vs placebo Concomitant treatment with other asthma medication was allowed.			exacerbation Secondary: Changes in FEV_1, use of BDP and concomitant asthma medication, safety	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.[5] (2001) 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 to 1,200 µg/day Allowed concomitant	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 albuterol, baseline FEV_1 ≥40 and ≤80% of predicted, mean total daily symptom score ≥3	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	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). 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
medications included salbutamol and BDP.	and ≤9, treatment with 500 to 1,200 µg/day of BDP or its equivalent ICS for ≥3 months		phases, BDP dose reduction, rescue medication use, asthma symptom scores, morning PEF and FEV_1, safety	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.[25] (extension of a study by Solèr et al.[5]) (2002) 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 Concomitant treatment with other asthma medication was allowed.	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 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Eisner et al.[26] (Interim data from EXCELS) (2012) 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.[27] (Subanalysis of EXCELS)	MC, OBS, PRO Patients ≥12 years of	N=7,858 2 years	Primary: Percent change in dose	Primary: 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(2013) Omalizumab vs non-omalizumab Treatment was at the discretion of physicians and patients based on indication and treatment guidelines.	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		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	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.[28] (2007) Omalizumab plus current asthma therapy vs placebo plus current asthma therapy vs placebo alone	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 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.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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.
Holgate et al.[6] (2004) 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	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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			of life, safety	(P<0.01). The incidence of adverse events was similar between omalizumab and placebo groups (76.2 vs 82.5%, respectively).
Milgrom et al.[29] (2001) 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 as needed.	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 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	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 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Ädelroth et al.[19] (2000) Omalizumab 300 mg SC every four weeks (IgE≤150 IU/mL) or every three weeks (IgE>150 IU/mL) vs placebo Leukotriene receptor antagonist, 5-lipoxygenase inhibitor, or oral, nasal, or intramuscular corticosteroids use was prohibited.	DB, MC, PC, PG, RCT Patients 17 to 66 years of age with moderate to severe birch pollen-induced allergic rhinitis	N=251 8 weeks	Primary: Average daily nasal symptom severity score Secondary: Average daily ocular symptom severity score, average daily number of tablets of rescue antihistamines, proportion of days on which any seasonal allergic rhinitis medication was taken, quality of life scores, subjects' overall evaluation of treatment efficacy	Primary: The average daily nasal symptom severity score in the omalizumab group was similar in the beginning and the end of the eight-week treatment period, with mean values of 0.71±0.05 (±SE) and 0.70±0.04, respectively. In the placebo group it increased from 0.78±0.07 at baseline to 0.98±0.05 overall on treatment (difference in LSM, –0.23; P<0.001). Secondary: The average daily ocular symptom severity score was lower in the omalizumab group compared to placebo (difference in LSM, –0.09; P=0.031). The average number of tablets of rescue antihistamines taken/day was lower in the omalizumab group than in the placebo group (0.59 vs 1.37; difference in LSM, –0.78 tablets/day; P <0.001). The proportion of days on which any seasonal allergic rhinitis medication was taken was lower in the omalizumab group than placebo (28 vs 49%; difference in LSM, –0.21; P<0.001). Statistically significant differences in favor of omalizumab were observed in each of the seven domains of the RQLQ and in the total RQLQ score. Subjects' overall evaluation of treatment effectiveness favored omalizumab over placebo (P=0.001).
Schumann et al.[30] XCLUSIVE study (2012) Omalizumab SC every two to four weeks (total dose calculated based on baseline	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	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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
serum IgE and body weight)			Secondary: Not reported	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. 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,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				33% were assigned to wrong schedules or were under-dosed. Secondary: Not reported
Niebauer et al.[31] (2006) 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 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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Chipps et al.[32] (2006) Omalizumab plus current asthma therapy vs current asthma therapy vs placebo plus current asthma therapy	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%; 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.[33] (2013) 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.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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 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
Chronic idiopathic urticaria				
Maurer et al.[15] ASTERIA II (2013) Omalizumab 75 mg SC every four weeks for three doses vs omalizumab 150 mg SC every four weeks	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	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.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
for three doses vs omalizumab 300 mg SC every four weeks for three doses vs placebo			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 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	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 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.[16] GLACIAL (2013) Omalizumab 300 mg SC every four weeks	DB, MC, PC, RCT Patients 12 to 75 years of age with chronic idiopathic urticaria or chronic spontaneous	N=336 24 weeks	Primary: Safety, change from baseline in mean weekly itch-severity score at week	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.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
for six doses vs placebo	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		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	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). 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: DB=double-blind, MA=meta-analysis, MC=multicenter, OBS=observational, OL=open-label, PC=placebo-controlled, PG=parallel-group, PM=post-marketing, PRO=prospective, RCT=randomized controlled trial
Miscellaneous abbreviations: ACQ=asthma control questionnaire, ACT=asthma control test, AQLQ=Asthma Quality of Life Questionnaire, BDP=beclomethasone dipropionate, FEV_1=forced expiratory volume in 1 second, GETE=Global Evaluation of Treatment Effectiveness, ICS=inhaled corticosteroids, IgE=immunoglobulin E, IU=international units, LSM=least square mean, OR=odds ratio, PEF=peak expiratory flow, RQLQ=rhinoconjunctivitis-specific quality of life questionnaire, SE=standard error, UAS7=urticaria activity score during a 7-day period

Special Populations

Table 5. Special Populations[1]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
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.

Adverse Drug Events

Table 6. Adverse Drug Events[1]

Adverse Event	Omalizumab
Arm pain	2*
Arthralgia	8.0*, 2.9†
Cough	1.1 to 2.2†
Dermatitis	2*
Dizziness	3*
Earache	2*
Fatigue	3*
Fracture	2*
Headache	15.0*, 6.1 to 12.0†
Injection site reaction	45.0*, 0.6 to 2.7†
Leg pain	4*
Nasopharyngitis	6.6 to 9.1†
Nausea	1.1 to 2.7†
Pain	7*
Pharyngitis	11*
Pruritus	2*
Sinusitis	16.0*, 1.1 to 4.9†
Upper respiratory tract infection	20.0*, 1.1 to 3.4†
Viral infection	23*
Viral upper respiratory tract infection	0.5 to 2.3†

*Asthma.
† Chronic idiopathic urticaria.

Contraindications/Precaution

Table 7. Contraindications[1]

Contraindication(s)	Omalizumab
Hypersensitivity	✔

Table 8. Warnings and Precautions[1]

Warning(s)/Precaution(s)	Omalizumab
Anaphylaxis has been reported after administration of omalizumab. Administer omalizumab in a health care setting by health care providers prepared manage life-threatening anaphylaxis.	✔
Avoid abrupt discontinuation of systemic or inhaled corticosteroids upon initiation of omalizumab therapy for allergic asthma. Corticosteroids should be decrease gradually under the direct supervision of a physician.	✔
Malignant neoplasms have been observed in omalizumab-treated patients. The impact of longer exposure or use in patients at increased risk for malignancy (e.g., elderly, current smokers) is not known.	✔
Patients at high risk of geohelminth infection should be monitored while on omalizumab therapy.	✔
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.	✔
Omalizumab is not intended for the treatment of acute asthma exacerbations. Do not use omalizumab to treat acute bronchospasm or status asthmaticus.	✔
Serum total immunoglobulin E levels increase following omalizumab 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.	✔
Symptoms including arthritis/arthralgia, rash, fever and lymphadenopathy have been reported one to five days after the first or subsequent injections of omalizumab. Symptoms recur with additional doses and are similar to symptoms observed in patients with serum sickness. If these symptoms develop, omalizumab should be discontinued.	✔

Black Box Warning for Xolair®

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.

Drug Interactions[1]

No formal drug interaction studies have been performed with omalizumab. The concomitant use of omalizumab and allergen immunotherapy has not been evaluated.

Dosage and Administration

Table 9. Dosing and Administration[1]

Generic Name	Adult Dose	Pediatric Dose	Availability
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.	Injection, single-use vial containing powder for reconstitution: 150 mg/5 mL

Table 8. Omalizumab Dosing for Asthma by Immunoglobulin E Level and Body Weight[1]

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
The National Heart, Lung, and Blood Institute/National Asthma Education and Prevention Program: **Guidelines for the Diagnosis and Management of Asthma (2007)**[11]	Diagnosis • 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 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,

Clinical Guidelines	Recommendations
	bronchoprovocation, chest x-ray, allergy testing and biomarkers of inflammation may be useful when considering alternative diagnoses. Treatment • 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. Long-term control medications • 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. • 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

<table>
<tr><th>Clinical Guidelines</th><th>Recommendations</th></tr>
<tr><td></td><td>

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.

<u>Assessment, treatment and monitoring</u>

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:

<table>
<tr><th>Inter-mittent Asthma</th><th colspan="5">Persistent Asthma: Daily Medication</th></tr>
<tr><th>Step 1</th><th>Step 2</th><th>Step 3</th><th>Step 4</th><th>Step 5</th><th>Step 6</th></tr>
<tr><td><u>Preferred</u>
SABA as needed</td><td><u>Preferred</u>
Low-dose ICS

<u>Alternative</u>
Cromolyn, leukotriene receptor antagonists, nedocromil, or theophylline</td><td><u>Preferred</u>
Low-dose ICS+LABA or medium-dose ICS

<u>Alternative</u>
Low-dose ICS+either a leukotriene receptor antagonists, theophylline, or zileuton</td><td><u>Preferred</u>
Medium-dose ICS+LABA

<u>Alternative</u>
Medium-dose ICS+either a leukotriene receptor antagonists, theophylline, or zileuton</td><td><u>Preferred</u>
High-dose ICS+ LABA and consider omalizu-mab for patients who have allergies</td><td><u>Preferred</u>
High-dose ICS+LABA+ oral steroid and consider omalizumab for patients who have allergies</td></tr>
</table>
<u>Management of exacerbations</u>

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

<u>Special populations</u>

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 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

</td></tr>
</table>

Clinical Guidelines	Recommendations
	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.
Global Initiative for Asthma: **Global Strategy for Asthma Management and Prevention (2011)**[12]	Treatment • 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. Controller medications • 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 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

<table>
<tr><th>Clinical Guidelines</th><th>Recommendations</th></tr>
<tr><td></td><td>
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.
• 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="3">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</td><td colspan="2">Medium- or high-dose</td><td>Leukotriene</td><td>Anti-IgE</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Clinical Guidelines</th><th>Recommendations</th></tr>
<tr><td></td><td>
<table>
<tr><td></td><td>modifier</td><td>inhaled glucocorticosteroid</td><td>modifier</td><td>treatment</td></tr>
<tr><td></td><td>-</td><td>Low-dose inhaled glucocorticosteroids +leukotriene modifier</td><td>-</td><td>-</td></tr>
<tr><td></td><td>-</td><td>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>National Institute for Health and Clinical Excellence: Omalizumab for Severe Persistent Allergic Asthma (2010)[13]</td><td>• Omalizumab is recommended as an option for the treatment of severe persistent allergic asthma as add-on therapy to optimized standard therapy, only in adults and adolescents (12 years and older) who have been identified as having severe unstable disease.
• Optimized standard therapy includes high-dose ICS and LABA in addition to leukotriene modifiers, theophyllines, oral corticosteroids and β_2-agonists tablets and smoking cessation where clinically appropriate.
• Omalizumab add-on therapy should only be initiated if the patient fulfils the following criteria of severe unstable allergic asthma:
o Confirmation of IgE mediated allergy to a perennial allergen by clinical history and allergy skin testing.
o Unstable disease (either two or more severe exacerbations of asthma requiring hospital admission within the previous year, or three or more severe exacerbations of asthma within the previous year, at least one of which required admission to hospital, and a further two which required treatment or monitoring in excess of the patient's usual regimen, in an accident and emergency unit).
• Omalizumab add-on therapy should be initiated and monitored by a physician experienced in both allergy and respiratory medicine in a specialist center.
• Omalizumab add-on therapy should be discontinued at 16 weeks in patients who have not shown an adequate response to therapy. Response to treatment should be defined on the basis of a full clinical assessment comprising: degree of asthma control, quality of life, control of exacerbations, avoidance of unscheduled healthcare utilization; spirometry and peak expiratory flow measures and a global evaluation of treatment effectiveness, as assessed by the physician.
• Cost-effective treatment with omalizumab is possible for a narrowly defined severely affected group of asthma patients, at an elevated risk of asthma-related mortality, if therapy was discontinued in non-responders at 16 weeks and if vial wastage could be minimized to reduce costs.</td></tr>
<tr><td>National Institute for Health and Clinical Excellence: Omalizumab for Treatment of Severe Persistent Allergic Asthma in</td><td>• In the United Kingdom, omalizumab is approved as an add-on therapy to improve control of patients at six years and older with severe persistent allergic asthma despite daily high-dose ICS and LABA.
• Effectiveness of treatment should be assessed at 16 weeks after the start of therapy before administering further injections, and the decision to continue omalizumab should be based on whether a marked improvement in overall asthma control is seen.</td></tr>
</table>

Clinical Guidelines	Recommendations
Children Aged Six to 11 years (2010)[14]	• Omalizumab is not recommended for the treatment of severe persistent allergic asthma in children aged six to 11 years for the following reasons: o Omalizumab as an add-on to optimized standard care is more clinically effective than optimized standard care alone in terms of reducing clinically significant exacerbations for children aged six to 11 years with severe persistent allergic asthma only if they have experienced three or more clinically significant exacerbations in the previous year. o The incremental cost-effectiveness ratio is substantially higher with omalizumab than normally considered to be a cost-effective. • Children currently receiving omalizumab for the treatment of severe persistent allergic asthma should have the option to continue treatment until it is considered appropriate to stop. This decision should be made jointly by the clinician and the child and/or the child's parents or caregivers.
Allergic Rhinitis and its Impact on Asthma and the Global Allergy and Asthma European Network: **Guideline Revisions (2010)[35]**	<u>Diagnosis</u> • The diagnosis of allergic rhinitis is based upon the concordance between typical history of allergic symptoms and diagnostic response. • Typical symptoms of allergic rhinitis include rhinorrhea, sneezing, nasal obstruction and pruritus. • Diagnostic tests are based on the demonstration of allergen-specific IgE in the skin or blood. • Many asymptomatic patients can have positive skin tests or detectable serum levels of IgE. <u>Treatment</u> • The treatment of allergic rhinitis should consider the severity and duration of the disease, the patient's preference, as well as the efficacy, availability and cost of the medication. • A stepwise approach depending on the severity and duration of rhinitis is proposed. • Not all patients with moderate/severe allergic rhinitis are controlled despite optimal pharmacotherapy. • Intranasal glucocorticoids are recommended over oral H1-antihistamines for the treatment of allergic rhinitis in adults and children. They are the most effective drugs for treating allergic rhinitis. In many patients with strong preferences for the oral route, an alternative choice may be reasonable. • Second-generation oral or intranasal H1-antihistamines are recommended for the treatment of allergic rhinitis and conjunctivitis in adults and children. • First generation oral H1-antihistamines are not recommended when second-generation ones are available, due to safety concerns. • Intranasal H1-antihistamines are recommended for the treatment of adults and children with seasonal allergic rhinitis, but data regarding their relative safety and efficacy is limited. Therefore, their use in persistent allergic rhinitis is not recommended. • Intramuscular glucocorticoids and long-term use of oral glucocorticoids are not recommended due to safety concerns. • Topical cromones are recommended in the treatment of allergic rhinitis but they are only modestly effective. • Montelukast is recommended for adults and children with seasonal allergic rhinitis, and in pre-school children with persistent allergic rhinitis. Montelukast has limited efficacy in adults with persistent allergic rhinitis. • Intranasal ipratropium is recommended for the treatment of rhinorrhea

Clinical Guidelines	Recommendations
	associated with allergic rhinitis. • Intranasal decongestants may be used for a short period (<5 days) for patients with severe nasal obstruction. Nasal decongestants should not be used in pre-school aged children. • Combination oral decongestants and oral H1-antihistamines may be used for the treatment of allergic rhinitis in adults, but should not be administered regularly due to adverse effects. • For patients experiencing ocular symptoms associated with allergic rhinitis intraocular antihistamines or chromones may be considered.
Institute for Clinical Systems Improvement: **Diagnosis and Treatment of Respiratory Illness in Children and Adults (2013)**[36]	<u>Diagnosis</u> • Patients can present with any of the following symptoms: congestion, rhinorrhea, pruritus, sneezing, posterior nasal discharge, and sinus pressure/pain. • A past medical history of facial trauma or surgery, asthma, rhinitis, atopic dermatitis, or thyroid disease may be suggestive of a rhinitis. In addition, a family history of atopy or other allergy associated conditions make allergic rhinitis more likely. • The most common physical findings suggestive of rhinitis tend to be swollen nasal turbinates, rhinorrhea and pruritus however allergic conjunctivitis may also be present. • Symptoms suggestive of allergic etiology include sneezing, itching of the nose, palate or eyes, and clear rhinorrhea. Nasal congestion is the most significant complaint in patients with perennial rhinitis. • Diagnostic testing should be considered if the results would change management. • Skin tests and radioallergosorbent tests identify the presence of IgE antibody to a specific allergen and are used to differentiate allergic from nonallergic rhinitis and to identify specific allergens causing allergic rhinitis. • A nasal smear for eosinophils is a good predictor of a patient's response to treatment topical nasal corticosteroids. • Peripheral blood eosinophil count, total serum IgE level, Rinkel method of skin titration and sublingual provocation testing are not recommended. <u>Treatment</u> • If a clinical diagnosis is obvious, symptomatic treatment, which consists of education on avoidance and medication therapy, should be initiated. • Avoidance of triggers is recommended. • Intranasal corticosteroids are the most effective single agents for controlling the spectrum of allergic rhinitis symptoms and should be considered first-line therapy in patients with moderate to severe symptoms. • Regular daily use of intranasal corticosteroids is required to achieve optimal results. • It may be best to start treatment one week prior to the start of the allergy season for prophylaxis. • Clinical response does not seem to vary significantly between the available intranasal corticosteroids. • Systemic corticosteroids should be reserved for refractory or severe cases of rhinitis. Injectable steroids are not generally recommended. • Antihistamines are effective at controlling all symptoms associated with allergic rhinitis except nasal congestion. • Antihistamines are somewhat less effective than intranasal corticosteroids but they can be used on a daily or as needed basis.

Clinical Guidelines	Recommendations
	• Second-generation antihistamines are recommended because they are less sedating and cause less central nervous system impairment. • Leukotriene inhibitors may be as effective as second-generation antihistamines for the treatment of allergic rhinitis and less effective than intranasal corticosteroids. • Oral decongestants are effective in reducing nasal congestion. Oral decongestants can be a useful addition to antihistamines. • Topical decongestants, which have the potential to induce rebound congestion after three days, are effective for the short-term relief of nasal congestion. • Cromolyn is less effective than intranasal corticosteroids and is most effective when used prior to the onset of allergic symptoms. • Cromolyn is a good alternative for patients who are not candidates for corticosteroids. • Intranasal anticholinergics are effective in relieving anterior rhinorrhea in allergic and nonallergic rhinitis. • Reserve immunotherapy for patients with significant allergic rhinitis in which avoidance activities and pharmacotherapy are insufficient to control symptoms. • If adequate relief is achieved appropriate follow-up should include further education on avoidance activities and medications. • If patients anticipate unavoidable exposure to known allergens they should begin the use of medications prior to exposure. • If adequate relief is not achieved within two to four weeks consider a trial of another medication, allergen skin testing by a qualified physician, a complete nasal examination, or a diagnosis of nonallergic rhinitis. • Treatment options for nonallergic rhinitis include azelastine nasal spray, intranasal corticosteroids, intranasal cromolyn, oral decongestants and antihistamines, topical antihistamines, and nasal strips.
American Academy of Family Physicians: **Treatment of Allergic Rhinitis (2010)**[37]	• Treatment should be based on the patient's age and severity of symptoms. • Intranasal corticosteroids are the most effective treatment and should be first-line therapy for mild to moderate disease. • Moderate to severe disease not responsive to intranasal corticosteroids should be treated with second-line therapies, including antihistamines, decongestants, cromolyn, leukotriene receptor antagonists, and nonpharmacologic therapies (e.g., nasal irrigation). • Immunotherapy should be considered in patients with inadequate response to usual treatments. • Omalizumab has been shown to be effective in reducing nasal symptoms and improving quality of life scores in patients with allergic rhinitis. However, its high cost (average wholesale price of $679 to $3,395/month) and lack of FDA approval for home administration are the main limitations to its use.
European Academy of Allergology and Clinical Immunology/Global Allergy and Asthma European Network/European Dermatology Forum/World Allergy Organization:	• Non-sedating histamine$_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

Clinical Guidelines	Recommendations
Management of Urticaria (2009)[38]	recommended. For the treatment of an exacerbation, systemic steroids are recommended for three to seven days.
British Association of Dermatologists: **Guidelines for Evaluation and Management of Urticaria in Adults and Children (2007)[39]**	• Non-specific aggravating factors such as overheating, stress, alcohol and drugs with the potential to worsen urticaria (e.g., aspirin, codeine) should be minimized. • All patients should be offered the choice of at least two non-sedating histamine$_1$ antihistamines because responses and tolerance vary between individuals. • The off-license addition of a histamine$_2$ antihistamine may sometimes give better control of urticaria than a histamine$_1$ antihistamine taken along; however, in practice, it may be more helpful for dyspepsia that may accompany severe urticaria. • Anti-leukotrienes may be taken in addition to a histamine$_1$ antihistamine for poorly controlled urticaria but there is little evidence that they are useful as monotherapy. • Oral corticosteroids may shorten the duration of acute urticaria (e.g., prednisolone 50 mg daily for three days in adults); however, lower doses are often effective. • Parenteral hydrocortisone is often given as adjunct for severe laryngeal edema and anaphylaxis, although its action is delayed. • Short tapering courses of oral steroids over three to four weeks may be necessary for urticarial vasculitis and severe delayed pressure urticaria, but long-term oral corticosteroids should not been used in chronic urticaria except in select cases under specialist supervision. • Intramuscular epinephrine can be life-saving in anaphylaxis and in severe laryngeal angioedema but should be used with caution in hypertension and ischemic heart disease. • Cyclosporine is effective in approximately 66% of patients with severe autoimmune urticaria unresponsive to antihistamines; however, only approximately 25% of responders remained clear or much improved four to five months after initiation.

Conclusions

Immunoglobulin E (IgE) monoclonal antibodies inhibit the binding of IgE to IgE receptors. The mechanism of action of IgE monoclonal antibodies may have utility in the treatment of various allergic conditions. Omalizumab (Xolair®) is FDA-approved for the treatment of adults and adolescents 12 years of age and older, with moderate to severe persistent asthma, who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids (ICS), as well as for the treatment of patients with chronic idiopathic urticaria refractory to histamine$_1$ antihistamine therapy.[1]

The drug carries a black box warning due to the risk of anaphylaxis. Omalizumab is administered subcutaneously in a physician's office every two to four weeks in a dose that is determined by body weight and the levels of serum IgE for allergic asthma and 150 to 300 mg every four weeks for chronic idiopathic urticaria.[1]

Current clinical evidence suggests that treatment with omalizumab is effective in reducing asthma exacerbations and increasing the number of patients who are able to reduce or withdraw their ICS.[4-6] In addition, treatment with omalizumab has been shown to improve itch severity in patients with chronic idiopathic urticaria.[15,16]

Although omalizumab therapy is generally safe, an interim analysis of a five-year long epidemiological study (EXCELS) showed an increased number of cardiovascular and cerebrovascular adverse events in patients receiving omalizumab for the treatment of allergic asthma compared to placebo.[10] In clinical trials omalizumab was also associated with higher frequency of injection site reactions than placebo.[8]

Asthma guidelines recommend omalizumab therapy in patients with severe allergic asthma that is inadequately controlled with a combination of high-dose ICS and long-acting β_2-agonist.[11,12] National Institute for Health and Clinical Excellence guidelines do not recommend omalizumab therapy in children aged six to 11 as it does not provide enough benefit to justify its high cost.[14]

Although not all consensus guidelines have been updated to address the place in therapy for omalizumab in the treatment of chronic idiopathic urticaria, the European Academy of Allergology and Clinical Immunology/Global Allergy and Asthma European Network/European Dermatology Forum/World Allergy Organization consensus guidelines recommend omalizumab as a treatment option in patients who have failed treatment with two different histamine$_1$ antihistamines at four-times the labelled dose and combination therapy with a histamine$_1$ antihistamine in a leukotriene antagonist.[38,39]

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