

Asthma

Anti-Immunoglobulin E Therapy with Omalizumab for Asthma

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In 2002, the Centers for Disease Control and Prevention (CDC) found that an estimated 30.8 million people in the US had been diagnosed with asthma at some point in their lives. At that time, 20 million people had active asthma and 11.9 million had experienced an asthma episode/attack in the previous year. The CDC also determined that in 2002, asthma resulted in 13.9 million outpatient visits, 1.9 million emergency department (ED) visits, and 484 000 hospitalizations. In addition, it had caused 4269 deaths in 2001.¹ The total cost of asthma in the US in 2003, including direct and indirect costs, was \$16 billion.²

Our understanding of the pathophysiology of asthma has changed dramatically in the past decade. Immunoglobulin E (IgE)-dependent mechanisms have been found to play an important role in the development and maintenance of 3 major characteristics of asthma: airway inflammation, obstruction, and hyperresponsiveness. When these manifestations are triggered by exposure to an allergen, the patient can be classified as having allergic asthma.

The objectives of this article are to summarize unmet treatment needs, evaluate the role of anti-IgE antibodies in asthma therapy, and provide information about who may benefit from omalizumab.

Data Sources

Twenty-three articles on omalizumab clinical trials were reviewed, and 19 were used in the development of this pa-

OBJECTIVE: To evaluate data on anti-immunoglobulin E (anti-IgE) therapy for asthma.

DATA SOURCES: Information was selected from PubMed from 1989 to May 2007 using the search term *omalizumab* and included randomized, controlled trials. These studies evaluated asthma treatment with omalizumab and focused on its efficacy, tolerability, and cost-effectiveness in this population.

STUDY SELECTION AND DATA EXTRACTION: All randomized clinical trials were reviewed (23 were identified and 19 were included; 3 were not relevant and 1 contained duplicative data). Other articles using the search words anti-IgE therapy and cost-effectiveness were evaluated; relevant information was extracted.

DATA SYNTHESIS: IgE-dependent mechanisms play an important role in the development and maintenance of airway inflammation in asthma. Omalizumab is a subcutaneously administered monoclonal anti-IgE antibody that reduces unbound IgE concentrations and promotes down-regulation of IgE receptors. Results from clinical trials in adults, adolescents, and children with poorly controlled IgE-mediated asthma have shown that omalizumab improves symptom control and allows patients to be managed with lower doses of inhaled corticosteroids (ICS). It has been well tolerated in clinical trials lasting as long as 52 weeks, but injection-site reactions are common (45% in omalizumab group vs 43% in placebo group) and anaphylaxis has occurred in 0.2% of patients. A consensus expert panel has recommended that omalizumab should be considered for patients 12 years of age or older with allergic asthma who are inadequately controlled on guideline-based therapy and require maintenance therapy with systemic corticosteroids or high-dose ICSs, or who have poor adherence to ICS therapy.

CONCLUSIONS: Anti-IgE therapy provides an effective and generally safe approach to the treatment of patients with IgE-mediated asthma who are not adequately controlled by conventional guideline-based medications. However, the potential benefit must be weighed against the cost and inconvenience of this new therapy.

KEY WORDS: asthma, immunoglobulin E, monoclonal antibody.

Ann Pharmacother 2007;41:1397-410.

Published Online, 14 Aug 2007, www.theannals.com, DOI 10.1345/aph.1K005

per. Three were not relevant to the topic and 1 contained duplicative data. Other articles using the search terms *anti-IgE therapy* and *cost-effectiveness* were evaluated, and relevant information was included in this review.

Unmet Needs of Current Therapeutic Regimens

The therapeutic goals for asthma are to (1) ensure that the patient is symptom-free, living an unrestricted life with nor-

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mal physical activity, (2) maintain close-to-normal lung function with a minimum of medications, and (3) minimize exacerbations and prevent disease-associated mortality.^{3,4}

However, undertreatment is common,³ and guideline-based therapy often fails to meet therapeutic goals. For example, in TENOR (The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens), a study of patients managed by an allergist or pulmonologist, more than half of the patients with severe asthma had required oral corticosteroid bursts in the 3 months prior to entering the study; 40% with moderate and 50% with severe asthma had asthma-related unscheduled office visits (Figure 1).⁵ These findings highlight the lack of disease control in many individuals with asthma.

In another 1-year, randomized, stratified, double-blind, parallel-group study including 3421 patients with uncontrolled asthma who were treated with fluticasone propionate or salmeterol/fluticasone, treatment was increased until total control was achieved or until participants received a maximum inhaled corticosteroid (ICS) dose of 500 µg twice a day.⁶ Asthma became well controlled in 63% of patients treated with high-dose salmeterol/fluticasone and in 50% of those who received fluticasone alone; 68% and 76% of patients in these 2 groups were on the highest dose of their respective medications by the end of the treatment. While results from this study support that guideline-derived asthma control is achievable in many patients, the data show that 37% of patients did not achieve

control on combination therapy. These study findings have played a role in the update of the Global Initiative for Asthma (GINA) treatment guidelines⁷ and the proposed National Asthma Education and Prevention Program (NAEPP) guidelines,⁸ which added anti-IgE therapy to the recommendations.

Anti-IgE Therapy in Asthma

Omalizumab is a humanized, functional monoclonal antibody directed against IgE. Humanization of omalizumab overcomes 3 important nonhuman antibody limitations: stimulation of immune responses, relatively rapid clearance, and weak recruitment of effector functions.⁹ In vitro studies with omalizumab indicate that it down-regulates FcεRI expression and results in a slow dissociation of IgE antibodies from basophils over 3–4 weeks.¹⁰

Huang et al.¹¹ evaluated the effects of omalizumab on markers of inflammation in human bronchial epithelial cells maintained in vitro and stimulated with IL-1β, ragweed, dust mite, and epithelial growth factor. Study results indicated that omalizumab treatment inhibited the production of proinflammatory cytokines, growth factor, and nitric oxide. These results are consistent with findings in ragweed-allergic subjects, which showed that 2 treatments with omalizumab versus placebo resulted in significant decreases in free serum IgE levels as well as expression of FcεRI by basophils.¹² Other recent results have shown that omalizumab

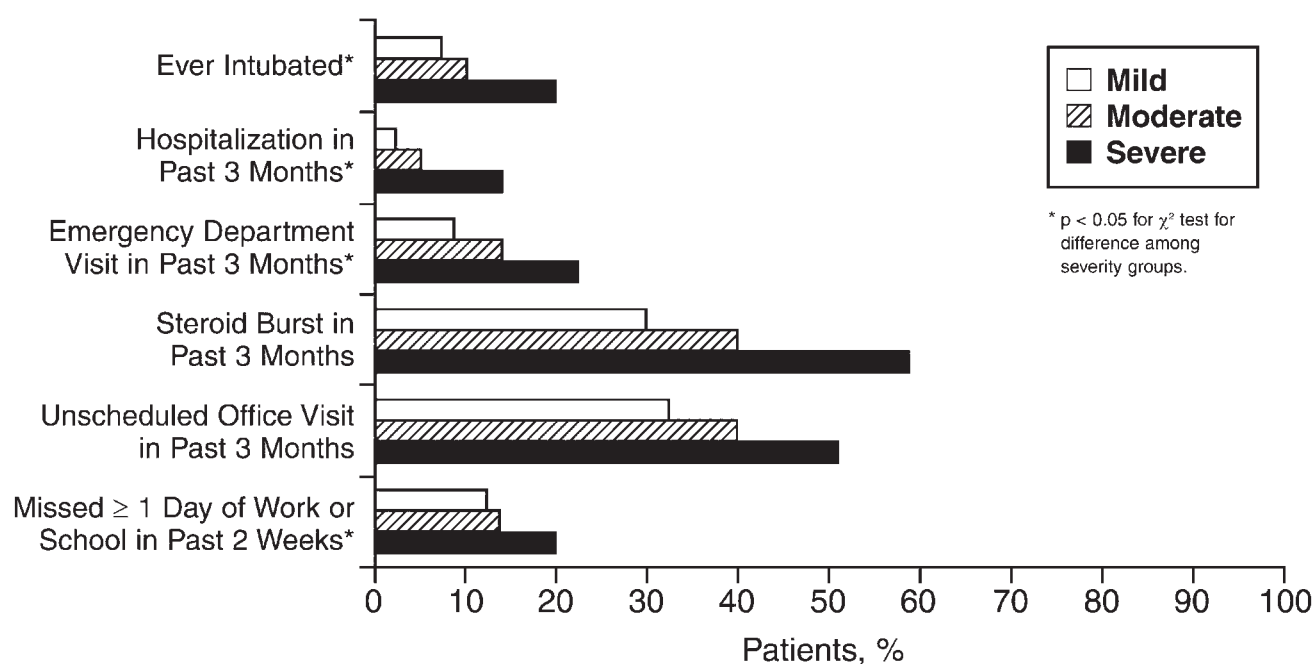


Figure 1. Healthcare resource utilization and missed work or school days by asthma severity. The TENOR study was a 3 year, multicenter, observational study of 4756 patients with severe or difficult-to-treat asthma enrolled by pulmonologists and allergists. Forty-eight percent of patients had severe asthma, 48% had moderate asthma, 3% had mild asthma, and 96% had difficult-to-treat asthma as determined by physician evaluation. Reproduced with permission.⁵

treatment of atopic subjects significantly decreased expression of FcεRI on mast cells, basophils, and dendritic cells, circulating IgE levels, eosinophil levels, and numbers of T cells expressing CD3, CD4, CD8, and CD20+ B cells¹³⁻¹⁵; and decreased airway responsiveness to adenosine, a robust marker of airway inflammation in individuals with allergic asthma.¹⁶ Noga et al.¹⁷ specifically studied the effects of omalizumab on eosinophils and found that the therapy caused an increase in eosinophil apoptosis, confirming that omalizumab treatment possesses antiinflammatory activity.

Pharmacokinetics of Omalizumab

After subcutaneous administration, omalizumab is well absorbed, with an average absolute bioavailability of 62%. Absorbed slowly, it reaches peak serum concentrations an average of 7–8 days after administration. The pharmacokinetics is linear at doses greater than 0.5 mg/kg and the area under the serum concentration–time curve increases after multiple doses. Omalizumab elimination involves immunoglobulin G (IgG) clearance processes, as well as clearance via a specific binding and complex formation with its target ligand, IgE. Hepatic elimination of IgG includes degradation in the liver reticuloendothelial system and endothelial cells. The serum elimination half-life for omalizumab averages 26 days^{18,19} and the drug remains detectable in serum for at least 4 months.¹⁹

Omalizumab treatment results in a rapid 84–99% reduction in unbound serum IgE levels within 1 hour of dosing, which is maintained with treatment every 4 weeks. The suppression of free IgE is slowly and completely reversible after omalizumab discontinuation without indication of rebound. This finding is consistent with clinical results indicating no rapid deterioration of symptoms or pulmonary function in patients with severe allergic asthma during a 3 month period after the cessation of omalizumab treatment.¹⁹

Efficacy of Anti-IgE Therapy in Asthma

PIVOTAL CLINICAL TRIALS IN ADULTS

Soler et al.²⁰ assessed omalizumab efficacy in a 28 week trial with a 16 week stable ICS phase and an 8 week phase during which the ICS dose was decreased to the lowest level that maintained symptom control, followed by a 4 week phase with the lowest ICS dose maintained (Table 1). The study enrolled patients with allergic asthma who remained symptomatic despite ICS. Subjects were randomized to receive subcutaneous injections of placebo or omalizumab every 2 or 4 weeks, with the dose based on body weight and total serum IgE. Doses ranged from 150 mg every 4 weeks to 375 mg every 2 weeks.

Patients receiving omalizumab had 58% fewer exacerbations compared with those receiving placebo during the

stable ICS phase ($p < 0.001$). When ICS doses were reduced to the lowest amount required for asthma control, 52% fewer exacerbations occurred in the omalizumab group versus the placebo group ($p < 0.001$), despite a significantly greater reduction in beclomethasone dose with omalizumab ($p < 0.001$).²⁰

The Busse et al.²¹ study followed a design similar to that used by Soler et al.²⁰ and provided comparable results (Table 1).²¹ This trial included participants with severe allergic asthma who required daily ICS for symptom control and who were randomized to 28 weeks' treatment with placebo or omalizumab as in the Soler et al. study. During the stable ICS phase, omalizumab treatment resulted in significantly fewer asthma exacerbations per subject (0.28 vs 0.54; $p = 0.006$) and fewer patients experienced an exacerbation (14.6%) compared with placebo (23.3%; $p = 0.009$). During the second phase, when the ICS dose was tapered to the lowest dose that did not result in an exacerbation, the number of exacerbations per subject was lower (0.39 vs 0.66, $p = 0.003$), as was the number of subjects with exacerbations (21.3% vs 32.3%; $p = 0.004$). As shown by Soler et al.,²⁰ there was a significantly greater reduction in ICS dose in subjects treated with omalizumab compared with placebo (75% vs 50%; $p < 0.001$).²¹ ICSs were discontinued in twice as many patients receiving omalizumab ($n = 106$, 39.6%) compared with placebo subjects ($n = 49$, 19.1%; $p < 0.001$).

LONG-TERM EXTENSIONS

Two 24 week extensions of the 2 protocols described above provided additional information about the long-term effectiveness of omalizumab (Table 1).^{22,23} Following each study's ICS-reduction phase, patients could enter a 24 week double-blind extension phase, continuing their study treatment at the lowest effective ICS dose. Investigators could change the beclomethasone dose and/or prescribe additional asthma medications as necessary. Results from both extension studies indicated that the use of omalizumab resulted in significantly lower numbers of exacerbations ($p = 0.02322$; $p < 0.00123$) despite lower ICS doses.

EFFICACY WITH POORLY CONTROLLED MODERATE-TO-SEVERE ALLERGIC ASTHMA

Results from the INNOVATE (Investigation of Omalizumab in Severe Asthma Treatment) study showed that adding omalizumab to ongoing asthma therapy greatly reduced clinically significant exacerbations and ED visits for patients with severe asthma not controlled by the best currently available therapy (GINA 2002 Step 4 Therapy) (Table 1).²⁴ INNOVATE included results from 419 subjects with inadequately controlled asthma, despite therapy with high-dose ICS and a long-acting β_2 -agonist. Omalizumab addition to previous therapy significantly decreased the

Table 1. Summary of Omalizumab Clinical Trials

Reference	Design	Pts., N (age, y)	Treatment Duration ^a	Drug Regimens ^b	Primary Efficacy Endpoints ^c	Safety	Results
Milgrom (1999) ³⁶	R, DB, PC	317 (11–50) dropouts: C: 16 I: 18	run in: 4 wk SSP: 12 wk SRP: 8 wk follow-up: 10 wk total: 30 wk	C: triamcinolone, at least 200 µg bid or equivalent amounts of flunisolide or beclomethasone I: high dose 5.8 µg/kg/ng of IgE/mL or low dose 2.5 µg/kg/ng of IgE/mL 35 pts. also took oral corticosteroids (20 mg/day or 40 mg every other day)	daytime and nocturnal asthma scores exacerbations of asthma	no significant differences in incidence of AEs I: 6 dropped out due to AEs C: 5 dropped out due to AEs	SSP (12 wk) mean asthma score I: 4 to 2.8 in both high- and low-dose groups C: 4 to 3.1 p = 0.008 and 0.005 SRP I: 2.7 in high- and low-dose groups C: 2.9 p = 0.048 and p = 0.14 exacerbations I high dose: 32 (30%) I low dose: 30 (28%) C: 47 (45%) p = 0.03 and 0.01
Busse (2001) ²¹	R, DB, PC, parallel group	525 (12–75) dropouts: C: 34 I: 19	run in: 4–6 wk SSP: 16 wk SRP: 12 wk total: 7 mo	same as Soler rescue medication: albuterol 2 puffs prn (max: 8 puffs/day)	number of asthma exacerbations experienced per pt. during SSP and SRP	AEs identical in frequency no serious AEs	SSP: ≥1 exacerbations I: 39 (14.6%) C: 60 (23.3%) p = 0.009 SRP I: 57 (21.3%) C: 83 (32.3%) p = 0.004
Holgate (2001) ²⁷	meta-analysis ^{20,21,32}	1412 254 high-risk used in meta-analysis	16 wk	C: stable ICS therapy with BDP or fluticasone propionate with or without oral prednisolone I: ≥0.016 mg/kg/IgE (IU/mL) every 4 wk	annualized rate of sAEs during SSP	not analyzed	sAEE rate I: 0.69 per pt.-y C: 1.56 per pt.-y p = 0.007
Milgrom (2001) ²⁸	R, DB, PC	334 (6–12) dropouts: C: 12 I: 16	run in: 4–6 wk SSP: 16 wk SRP: 8 wk maintenance: 4 wk total: 28 wk	C: BDP 168–420 µg/day I: minimum dose of 0.016 mg/kg/IgE SRP: decreased BDP by 25% of baseline every 2 wk until elimination or worsening of symptoms rescue medication: albuterol as needed, up to 8 puffs daily	reduction in ICS dose exacerbations	study-related AEs: I: 14 (6.2%) C: 1 (0.9%) no serious AEs reported	mean reduction in BDP dose I: 100% C: 66.7% p = 0.001 BDP withdrawn completely I: 55% C: 39% p = 0.004 exacerbations SSP I: 35 (15.6%) C: 25 (22.9%) p = 0.095 exacerbations SRP I: 41 (18.2%) C: 42 (38.5%) p < 0.001

AE = adverse event; BDP = beclomethasone dipropionate; C = control group; DB = double-blind; I = intervention group (subjects receiving omalizumab); ICS = inhaled corticosteroid; IgE = immunoglobulin E; max = maximum; PC = placebo-controlled; R = randomized; sAEs = significant asthma exacerbation episodes; SRP = steroid reduction phase; SSP = steroid stable phase.

^aRun-in periods are not included in calculation of the total duration.

^bOmalizumab (intervention) given in addition to control (control) or best standard care (BSC).

^cAsthma exacerbation = worsening of symptoms requiring treatment with systemic steroids or doubling of baseline dose of BDP.

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Table 1. Summary of Omalizumab Clinical Trials (continued)

Reference	Design	Pts., N (age, y)	Treatment Duration ^a	Drug Regimens ^b	Primary Efficacy Endpoints ^c	Safety	Results
Soler (2001) ²⁰	R, DB, PC, parallel group	546 (12–76) dropouts: C: 40 I: 19	run in: 4–6 wk SSP: 16 wk SRP: 12 wk total: 7 mo	C: BDP 500–1200 µg/day I: ≥0.016 mg/kg ⁻¹ per IU total serum IgE mL ⁻¹ every 4 wk, 150–300 mg; given every 4 wk; 450–750 mg: half-dose given every 2 wk SRP: BDP reduced by 25% of baseline every 2 wk until elimination or until decrease in FEV ₁ ≥20% or asthma worsened; lowest dose for control was held for 4 wk rescue medication: albuterol was allowed throughout the study same as Soler ²⁰	number of asthma exacerbations experienced per pt. during SSP and SRP	AEs comparable between treatment groups (p = 0.504) no serious AEs	SSP, 1 or more exacerbations I: 35 (12.8%) C: 83 (30.5%) p < 0.001 SRP I: 43 (15.7%) C: 81 (29.8%) p < 0.001
Buhl (2002) ²²	extension of Soler ²⁰ study	483 of the initial 546 (12–76) dropouts: C: 26 I: 10	24 wk extension total: 1 y		asthma exacerbations FEV ₁ BDP use	no difference in incidence of AEs (p = 0.579) digestive system I: 32% C: 25%	exacerbations I: 61 (24%) C: 93 (40.6%) p < 0.001 BDP dose I: 253 µg/day C: 434 µg/day p < 0.001 FEV ₁ no statistically significant differences at any time point in extension mean BDP dose core study: 72 µg/day extension: 77 µg/day mean reduction in BDP dose core study: 74.3% extension: 72.5% no exacerbations extension: 72.5% FEV ₁ extension: remained stable core study: no difference between I and C
Berger (2003) ⁴⁰	OL, extension of Milgrom pediatric trial ²⁶	309 (6–12) 202 received I for 52 wk dropouts: not reported	24 wk extension total: 52 wk	only pts. receiving omalizumab were reported I: minimum dose of 0.016 mg/kg/IgE any asthma medications judged necessary were allowed rescue medication: same as in original trial	BDP use reduction in BDP dose exacerbations FEV ₁	AEs I: 15 (6.7%) urticaria: 5 severe AE: 1 case of urticaria	

AE = adverse event; BDP = beclomethasone dipropionate; C = control group; DB = double-blind; FEV₁ = forced expiratory volume in the first second; I = intervention group (subjects receiving omalizumab); OL = open label; PC = placebo-controlled; R = randomized; SRP = steroid reduction phase; SSP = steroid stable phase.

^aRun-in periods are not included in calculation of the total duration.

^bOmalizumab (intervention) given in addition to control (control) or best standard care (BSC).

^cAsthma exacerbation = worsening of symptoms requiring treatment with systemic steroids or doubling of baseline dose of BDP.

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Table 1. Summary of Omalizumab Clinical Trials (continued)

Reference	Design	Pts., N (age, y)	Treatment Duration ^a	Drug Regimens ^b	Primary Efficacy Endpoints ^c	Safety	Results
Corren (2003) ²⁸	pooled analysis ^{20,21,26}	1405 (6–76)	28 wk	C: inhaled corticosteroid (see individual studies for dosing) I: omalizumab (see individual studies for dosing)	rate of serious exacerbations (unscheduled asthma-related outpatient visits, emergency department treatment, hospitalization)	not analyzed	outpatient visits (event rate per 100 pt.-y) I: 166/779.5 C: 187/526.7 p < 0.01 emergency department treatment (event rate per 100 pt.-y) I: 14/779.5 C: 20/526.7 p = 0.05 hospitalization (event rate per 100 pt.-y) I: 2/779.5 C: 18/526.7 p < 0.01
Lanier (2003) ²³	extension of Busse ²¹ trial	460 of the initial 525 (12–75) dropouts C: 8 I: 12	24 wk extension total: 1 y	same as Busse ²¹	asthma exacerbations, FEV ₁ , BDP use	similar AEs for I and C	exacerbations I: 78 (31.8%) C: 92 (42.8%) p = 0.015 BDP dose I: 227 µg/day C: 335 µg/day p < 0.001 FEV ₁ statistically significant in favor of I at wk 32, 36, 40, and 44 no significant difference at wk 48 and 52
Ayres (2004) ²⁵	R, OL, parallel group	312 (12–73) C: 106 I: 206 dropouts not reported	12 mo	C (BSC) adolescent: ≥400 µg/day and adult: ≥800 µg/day inhaled BDP or equivalent I: 0.016 mg/kg for every IU/mL of total IgE every 4 wk rescue medication: albuterol throughout study additional medications: 79% received LABA, 21% received systemic corticosteroids	annualized number of ADRI annualized number of clinically significant asthma exacerbations	all AEs: I: 85% C: 77.4% p = 0.116 10 I pts. withdrew because of nonserious AEs, most commonly skin and subcutaneous tissue disorders	ADRI/pt.-y I: 4.92 C: 9.76 p < 0.001 asthma exacerbations/pt.-y I: 1.12 C: 2.86 p < 0.001

ADRI = asthma deterioration-related incidents; AE = adverse event; BDP = beclomethasone dipropionate; C = control group; FEV₁ = forced expiratory volume in the first second; I = intervention group (subjects receiving omalizumab); LABA = long-acting β-agonist; OL = open label; R = randomized.

^aRun-in periods are not included in calculation of the total duration.

^bOmalizumab (intervention) given in addition to control (control) or best standard care (BSC).

^cAsthma exacerbation = worsening of symptoms requiring treatment with systemic steroids or doubling of baseline dose of BDP.

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Table 1. Summary of Omalizumab Clinical Trials (continued)

Reference	Design	Pts., N (age, y)	Treatment Duration ^a	Drug Regimens ^b	Primary Efficacy Endpoints ^c	Safety	Results
Holgate (2004) ³²	R, DB, PC	246 (12–75) dropouts: C: 11 (9.2%) I: 11 (8.6%)	run-in: 6–10 wk SSP: 16 wk SRP: 16 wk total: 32 wk	C: >1000 µg/d fluticasone I: omalizumab: ≥0.016 mg/kg/IgE (IU/mL) every 4 wk short-acting and LABA were allowed as needed	percent reduction in fluticasone dose exacerbation rate	AEs I: 96 (76.2%) C: 99 (82.5%) severe AEs I: 8 (6.3%) C: 22 (18.3%) urticaria I: 1 C: 3	reduction in fluticasone I: 57.2% C: 43.3% p = 0.003 exacerbation rate SSP I: 0.15 C: 0.23 p: NS SRP I: 0.19 C: 0.34 p value: NS
Vignola (2004) ³⁴	R, DB, PC, parallel group	405 (12–74) dropouts C: 15 I: 5	28 wk	C: budesonide ≥400 µg/day I: ≥0.016 mg/kg/IgE (IU/mL) every 4 wk pts. could take concomitant LABA and nasal corticosteroids rescue medication: nebulized and/or inhaled β ₂ -agonists, 3–10 days of systemic corticosteroids or doubling of budesonide dose	incidence of asthma exacerbations	AEs I: 35 (16.7%) C: 24 (12.2%) severe AEs I: 13 (6.2%) C: 18 (9.2%) serious AEs I: 3 (1.4%) C: 3 (1.5%)	exacerbations I: 43 (20.6%) C: 59 (30.1%) p = 0.02
Humbert (2005) ²⁴	R, DB, PC	482 (12–75) dropouts C: 22 I: 30 (11 subjects were unaccounted for)	run in: 8 wk, 28 wk	C: >800 µg/day BDP or ≥400 µg/day fluticasone propionate or equivalent and LABA therapy; additional asthma medications permitted (theophylline, oral β ₂ -agonists, antileukotrienes, oral corticosteroids) I: ≥0.016 mg•kg ⁻¹ per IU total serum IgE•mL ⁻¹ every 4 wk; 150–300 mg given every 4 wk; 450–750 mg half-dose given every 2 wk rescue medication: short-acting β ₂ -agonists allowed	rate of clinically significant asthma exacerbations (worsening of asthma symptoms requiring treatment with systemic corticosteroids)	similar overall incidence I: 72.7% C: 75.5% most common: injection site I: 5.3% C: 1.3% severe: pruritus, rash, and petechiae I: 1 C: 0	exacerbation rate I: 0.68 C: 0.91 p = 0.042 severe exacerbation rate I: 0.24 C: 0.48 p = 0.002

AE = adverse event; BDP = beclomethasone dipropionate; C = control group; DB = double-blind; I = intervention group (subjects receiving omalizumab); LABA = long-acting β-agonist; PC = placebo-controlled; R = randomized; SRP = steroid reduction phase; SSP = steroid stable phase.

^aRun-in periods are not included in calculation of the total duration.

^bOmalizumab (intervention) given in addition to control (control) or best standard care (BSC).

^cAsthma exacerbation = worsening of symptoms requiring treatment with systemic steroids or doubling of baseline dose of BDP.

ED visit rate compared with placebo (0.245 vs 0.43, $p = 0.038$) and significantly improved asthma-related quality of life (QOL; $p = 0.008$), increased morning peak expiratory flows (PEF; $p = 0.042$), and decreased asthma symptom scores ($p = 0.039$). In another study conducted in patients with poorly controlled (moderate-to-severe) allergic asthma, the addition of omalizumab to best standard care resulted in a reduction of clinically significant asthma exacerbations per patient-year (1.12 vs 2.86; $p < 0.001$).²⁵

PIVOTAL TRIALS OF OMALIZUMAB IN CHILDREN

Omalizumab has been evaluated in a 28 week trial that included children with moderate-to-severe allergic asthma (Table 1).²⁶ This study's design and dosing regimen followed those for the adult pivotal studies. One primary endpoint was the measurement of the ICS-sparing effects of omalizumab. Other significant benefits of omalizumab included a significantly lower rate of asthma exacerbations during the ICS reduction phase (18.2% vs 38.5%; $p < 0.001$), significantly fewer urgent, unscheduled outpatient physician visits (12.9% vs 30.3%; $p = 0.001$), fewer 2- or 3-consecutive-night awakenings requiring rescue medications (11.6% vs 21.1%; $p = 0.002$), and fewer school days missed (0.65 days vs 1.21 days; $p = 0.04$).

MORBIDITY AND HEALTHCARE RESOURCE UTILIZATION

Holgate et al.²⁷ carried out a meta-analysis of results from 3 of the core omalizumab allergic asthma trials (Table 1).^{20,21,27} Of the 1412 participants in these studies, data for the 254 high-risk patients were analyzed. The primary endpoint was the annualized rate of significant asthma exacerbation episodes requiring a doubling of baseline ICS dose (2 studies) or use of systemic corticosteroids (all 3) during the ICS-stable phase. The combined analysis indicated that the rate of episodes with omalizumab was 0.69 per patient-year versus 1.56 per patient-year for placebo ($p = 0.007$). Among 93 participants with a history of hospitalization during the previous year, 12% receiving placebo and 4.5% receiving omalizumab were rehospitalized during the study period. Omalizumab-treated subjects showed significantly greater improvements from baseline in PEF ($p = 0.026$), overall asthma-related QOL ($p = 0.042$), mean nocturnal symptoms ($p = 0.007$), and mean total ($p = 0.011$) asthma symptom scores compared with placebo.

A second pooled analysis of all participants, not just those at high risk, was conducted by Corren et al. (Table 1).²⁸ It included results from 2 randomized, double-blind, placebo-controlled omalizumab studies of adults and adolescents^{20,21} and 1 trial of children aged 6–12 years.²⁶ All participants required treatment with ICS for allergic asthma. Overall, 767 subjects received omalizumab and 638 received placebo. All measures of healthcare resource uti-

lization significantly favored omalizumab over placebo except the exacerbation rate in children during the ICS stable phase (Figure 2). The rate of unscheduled, asthma-related outpatient visits was lower for the omalizumab-treated group than for the placebo-treated group (21.3 vs 35.5 per 100 patient-years, $p < 0.01$), as were asthma-related ED visits (1.8 vs 3.8 per 100 patient-years; $p = 0.05$) and hospitalizations (0.26 vs 3.42 per 100 patient-years; $p < 0.01$).

Impact of Omalizumab on Quality-of-Life

META-ANALYSIS

Niebauer et al.²⁹ performed a systematic literature review and meta-analysis of asthma-related QOL data from 5 published clinical trials and unpublished clinical study reports that evaluated the effects of omalizumab on QOL in a total of 2056 adults, adolescents, and children with allergic asthma or asthma with allergic rhinitis. Five published trials and extensions^{20,21,26,30-34} and unpublished study reports from Genentech/Novartis Pharmaceutical Corporation were included in the analysis. The benefit of omalizumab in providing a clinically significant QOL score improvement was most apparent in each trial's ICS reduction phase. During this phase, the advantage of omalizumab over placebo was significant for each trial and in the combined analysis ($p < 0.05$). Combined analysis also demonstrated the benefit of omalizumab over placebo in the ICS stabilization and extension phases; however, statistical significance was not achieved for each study. Combined analysis also indicated significant superiority of omalizumab over placebo in providing 1.0 or more point improvements in Asthma Quality of Life Questionnaire scores during ICS stabilization and reduction studies phases ($p < 0.001$) and in providing 1.5 or more point improvements in all study phases ($p < 0.001$). (A 0.5 point improvement is accepted as clinically relevant.) Thus, the results of this meta-analysis demonstrate that omalizumab treatment provides significant improvements in QOL for participants with moderate-to-severe allergic asthma.

Safety of Anti-Immunoglobulin E Therapy

ADULTS

Safety results from all omalizumab clinical trials were summarized by Deniz and Gupta.³⁵ This analysis included information from 12 studies that enrolled 5328 subjects 5 years of age or older with moderate-to-severe allergic asthma. Overall, the safety profile of omalizumab was comparable to that of placebo, and there were no statistically significant differences. Injection site reactions were the most common adverse event (AE) in both treatment groups (45% with omalizumab, 43% with placebo). Results from this overall analysis are generally similar to those from individual trials (Table 1).^{20-23,32,36}

ANAPHYLAXIS

During clinical trials, there were 3 subjects (about 0.1% of those treated with active drug) who were reported to have experienced anaphylaxis. In February 2007, the US Food and Drug Administration issued an alert regarding serious and sometimes life-threatening allergic reactions in patients receiving omalizumab.³⁷ The frequency is estimated to be at least 0.2% based on an estimated exposure of about 57 300 patients between June 2003 and December 2006. This frequency is similar to that of anaphylaxis from oral penicillins, aspirin, or nonsteroidal antiinflammatory drugs.³⁸ Anaphylaxis and anaphylactoid reaction occurred after the first doses of omalizumab in 40% of these cases and after repeated administration in the remainder (up to 2 y of therapy).

While most cases of acute allergic reaction occurred within 2 hours of the injection, 30% occurred later—up to 24 hours after administration. Symptoms have included urticaria and throat and/or tongue edema treated with combinations of epinephrine, steroids, and antihistamines. There have been no reports of respiratory failure or deaths.

No incidences of serum sickness, serum sickness-like syndrome, or immune complex-mediated damage to the kidneys or other organs were observed in clinical studies following omalizumab administration.³⁵

MALIGNANCIES

Malignant neoplasms were observed in 20 of 4127 (0.5%) omalizumab-treated subjects compared with 5 of

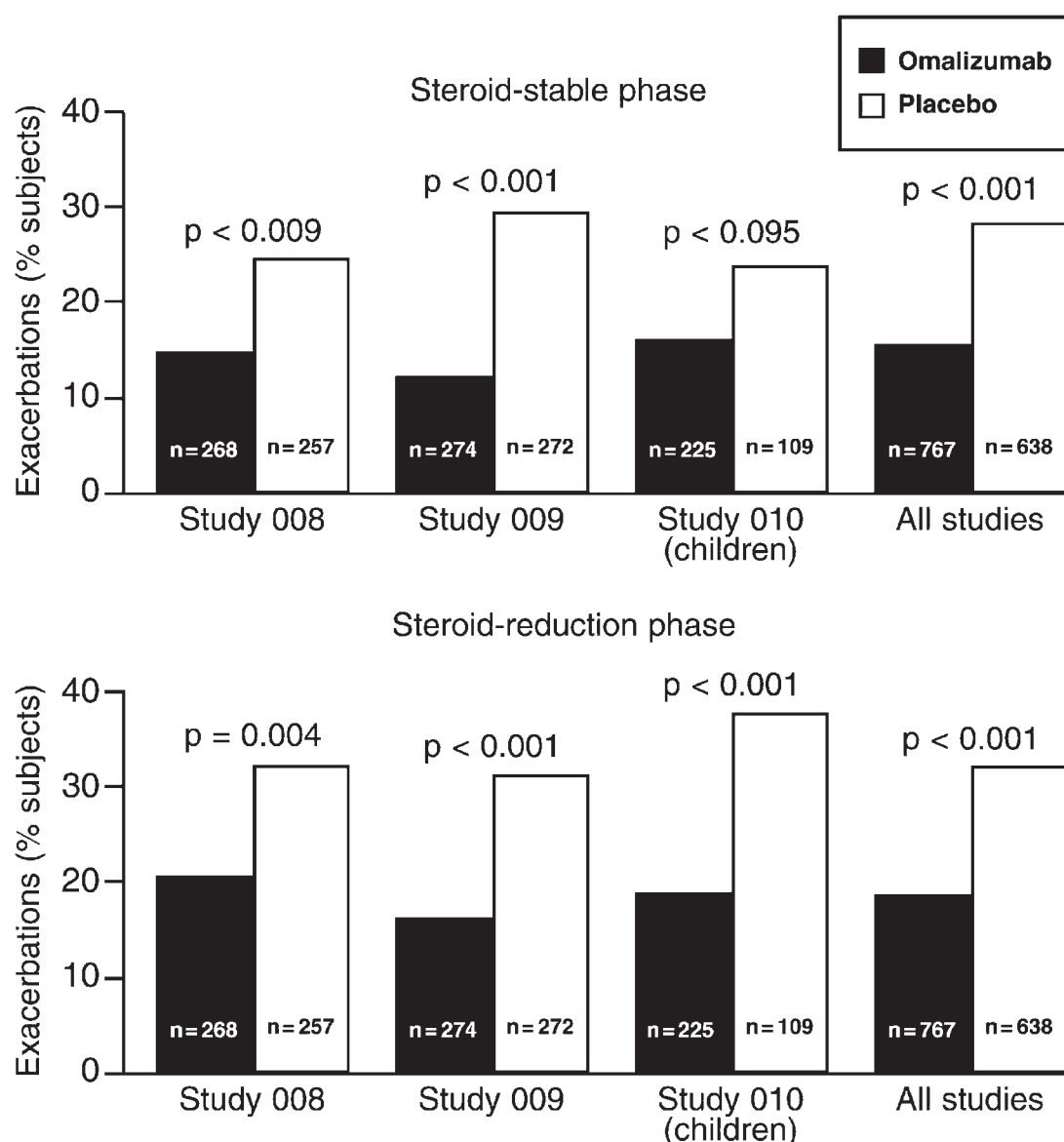


Figure 2. Proportion of patients experiencing asthma exacerbations during 28-week studies of omalizumab in adults, adolescents, and children. A pooled analysis of 3 multicenter, randomized, double-blind, placebo-controlled Phase 3 studies. Rates of serious exacerbations were calculated and compared between omalizumab- and placebo-treated subjects. Reproduced with permission.²⁸

2236 (0.2%) control subjects with asthma and other allergic disorders (difference not statistically significant). Comparison of results obtained in omalizumab-treated individuals vs expected cancer rates based on data compiled by the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute indicated no significant increase in cancer risk for subjects treated with omalizumab (12 observed independent primary cancers vs 9 expected; standardized incidence ratio 1.3; 95% CI 0.69 to 2.33).³⁹

PEDIATRICS

Omalizumab is well tolerated by children with allergic asthma. Berger et al.⁴⁰ provided a detailed safety analysis of the 28 week, double-blind trial of omalizumab in 334 children aged 6–12 years,²⁶ along with a combined analysis of results from this study and its 24-week extension including 309 of these children aged 6–12 years. Only 1 child withdrew from the study because of an AE, which was urticaria. Generally, AEs were similar in the omalizumab and placebo groups. No anaphylactic reactions or AEs suggestive of serum sickness or immune complex formation occurred, and no anti-omalizumab antibodies were detected in any child. Additionally, there was no evidence of clinically relevant changes in platelet counts.

PREGNANCY

The Xolair Pregnancy Registry: An Observational Study of the Use and Safety of Xolair (omalizumab) During Pregnancy (EXPECT), has been initiated to obtain data on pregnancy outcomes in women who are exposed to the drug.⁴¹ Females receiving at least 1 dose of omalizumab within 8 weeks prior to conception or at any time during their pregnancy will be followed to the completion of their pregnancy. Evaluation of the infants will be conducted at birth and at 6 month intervals until they reach 12 months of age.

Patient Considerations

ADHERENCE TO THERAPY

Therapy adherence is a significant problem in managing asthma. Results from one study indicate that nearly 85% of a sample of 573 individuals with asthma exhibited some degree of poor adherence to drug therapy.⁴² Results from another evaluation that included 171 pediatric patients with persistent asthma indicated prescription refill rates of 59% and 44%, respectively, for montelukast and fluticasone.⁴³ Patients with severe asthma may be at particularly high risk for poor adherence due to multiple medications to control their asthma, comorbid diseases, depression and anxiety, and the high cost of care.⁴⁴

Omalizumab is administered in the physician's office as a directly observed therapy. This has the potential to result in a high level of adherence⁴⁵ and may compensate clinically for poor adherence to inhaled steroids.⁴⁶ Omalizumab is not currently approved for self-administration at home and we recommend against this approach because of the risk of anaphylaxis. Since the onset of anaphylaxis may be delayed, many asthma specialists are now prescribing an epinephrine automatic injector (eg, EpiPen) and instructing patients as to when and how to use it (especially in the first 24 hours after receiving an omalizumab injection). At the University of Florida, patients also are required to remain in the clinic for observation for 1 hour after the first injection and for 30 minutes for subsequent injections. They are given a one page information sheet on the benefits and risks of this medication. They are asked to sign the sheet and a copy is placed in their chart.

DOSING

The monthly dose of omalizumab is 0.016 mg/kg per IgE unit administered subcutaneously. When the calculated dose exceeds 300 mg, the total monthly dose is divided in half, rounded to the nearest 75 mg, and given at 2 week intervals. The maximum dose at each injection site is 150 mg. Thus, a patient requiring the maximum dose of 750 mg would require 3 injections every 2 weeks. Omalizumab does not require any premedication or a gradual increase in dose. If therapy is discontinued or interrupted, it is resumed at the same dose.

ONSET OF CLINICAL EFFECTS

In 2 studies with 542 subjects,^{20,21} omalizumab decreased symptoms by week 4 of therapy, but in a third study where the above 2 studies were further analyzed, the maximum benefit was not achieved until 16 weeks of completed therapy.⁴⁷ Therefore, patients should be treated for a minimum of 16 weeks before deciding that omalizumab is not effective.

REQUIRED DURATION OF THERAPY

Clinical trials with omalizumab evaluated the effects of treatment for up to 1 year in 268 patients treated with omalizumab compared with 215 treated with placebo.²³ The effectiveness was maintained over this period. There is no evidence that omalizumab can be discontinued without a loss of clinical effect in allergic asthma. The drug must be administered continually to maintain its clinical benefit, consistent with the observation that serum IgE slowly increases to baseline levels over 4–8 weeks after discontinuation of omalizumab.^{48,49}

Pharmacoeconomic Analysis

Oba and Salzman⁵⁰ concluded that, from a pharmacoeconomic standpoint, omalizumab would be better used in patients with allergic asthma with poorly controlled symptoms despite maximal therapy. They noted further that omalizumab could be cost-saving if given to non-smoking individuals who were hospitalized 5 or more times per year or 20 or more days per year despite maximal asthma therapy. Miller and Reeves⁵¹ responded to that analysis by noting that the measures of cost-effectiveness used may not have been appropriate for a study of asthma. A second response to Oba and Salzman indicated that their use of clinical trial data is not representative of those in clinical practice.⁵² Therefore, scientifically rigorous studies are needed to determine the cost-effectiveness of omalizumab in different asthma phenotypes.

Disadvantages of Omalizumab

Treatment with omalizumab is inconvenient and costly. It requires 1–3 subcutaneous injections every 2–4 weeks in a clinician's office. Because of the boxed warning, many clinicians have instituted postinjection observation periods as well as issuance of epinephrine auto-injectors instructing the patients to keep on their person for the 24 hours following a dose. At the University of Florida, the acquisition cost is \$450 per 150 mg vial. Therefore, the annual cost for this drug is \$5400 to \$35 000 per year, depending on body weight and total IgE. No third-party payer, including Florida Medicaid, has refused to cover this treatment for appropriately selected patients at this institution. The cost of office visits for omalizumab to be administered is additional (approximately \$25/visit at our facility) and also is covered by payers.

Another disadvantage of omalizumab is that it is not recommended by the manufacturer for patients weighing more than 150 kg or for those with a total IgE greater than 700 IU.

Identifying Who Will Benefit from Anti-IgE Therapy

Bousquet et al.⁴⁷ performed a pooled analysis from 2 multicenter, double-blind, randomized, placebo-controlled studies of omalizumab^{20,21} with a total of 1071 adults with allergic asthma who were symptomatic despite moderate-to-high beclomethasone doses. Study endpoints included reductions in symptom scores and use of rescue medication, improved lung function, and improved QOL. The primary endpoints were a composite response definition consisting of at least 1 of the above measures and no asthma exacerbation during 16 weeks of treatment. For the composite definition, a history of emergency asthma treatment in the past year was the factor most predictive of the best response on active treatment ($p = 0.015$). Also, high-dose

ICS (≥ 800 $\mu\text{g/day}$ of beclomethasone or equivalent) and forced expiratory volume at 1 second of 65% or less were predictors of response to omalizumab (Figure 3). Adults with all 3 risk factors were 4 times more likely to respond to omalizumab than placebo.

A panel of experts convened by Genentech, Inc. and Novartis Pharmaceuticals Corporation has provided additional guidance on the use of anti-IgE therapy in patients with asthma. They recommended that omalizumab be used in patients 12 years of age or older with evidence of reversible disease and a documented allergic component, inadequately controlled asthma that requires rescue medication to maintain control, and a history of nonadherence to prescribed therapy.⁵³ Marshall and Sorkness⁵⁴ expanded these criteria to include patients with a history of high use of healthcare resources.

Additionally, the GINA guidelines include the addition of omalizumab for patients for whom control has not been achieved with combinations of the other controllers, including high doses of inhaled or oral glucocorticosteroids.⁷ It is anticipated that the new NAEPP guidelines will include omalizumab.⁸

Summary

Asthma is a common disease that imposes a significant burden on patients and society, including high treatment costs, lost productivity, work/school absences, and reduced QOL. Conventional therapies can control asthma in only about 70% of patients. Therefore, there is a clinical need for additional therapies for IgE-mediated asthma. Because of cost and inconvenience of therapy, omalizumab should be selected for patients who are most likely to benefit from this new therapy. It appears to be generally safe and well tolerated for at least a year.

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Dr. Hendeles has received honoraria for lectures sponsored by Genentech and a research grant from Novartis. Dr. Sorkness is the coinvestigator for a study partially funded by Novartis.

Advogent and Strategic Healthcare Alliance, medical communications companies, received financial support from Genentech to develop this article. The authors made all decisions regarding content and format. They also made revisions.

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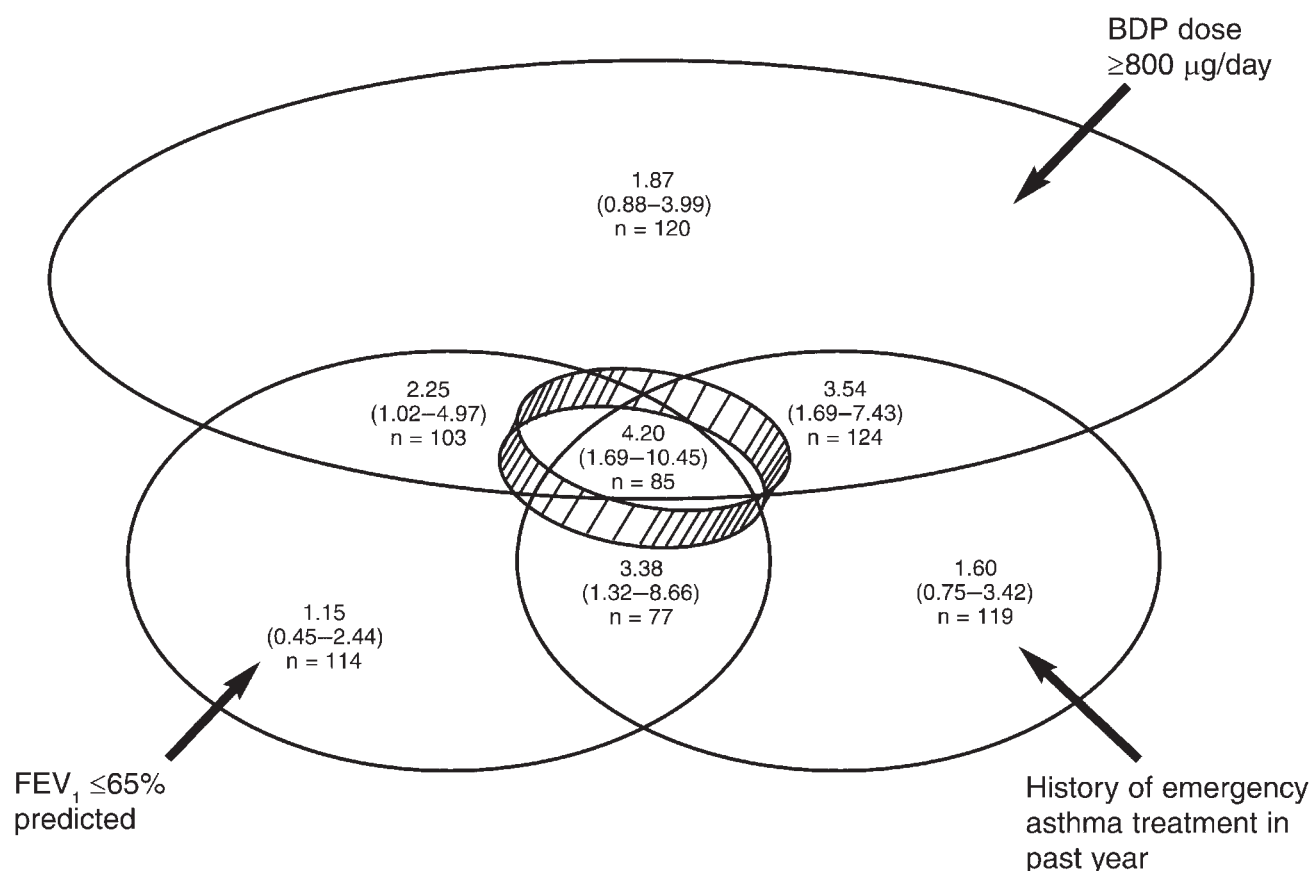


Figure 3. Venn diagram of odds ratio (95% CI) for response to omalizumab relative to placebo. Reproduced with permission.⁴⁷

BDP = beclomethasone dipropionate; FEV₁ = forced expiratory volume in the first second.

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Terapia de Anti-Inmunoglobulina E con Omalizumab para Asma

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Ann Pharmacother 2007;41:1397-410.

EXTRACTO

OBJETIVO: Evaluar la información de la terapia con anti-inmunoglobulina E (anti-IgE) para asma.

FUENTES DE INFORMACIÓN: Se realizó una búsqueda de literatura a través de PubMed publicada de 1989 a Mayo 2007 utilizando el término omalizumab e incluyendo los términos estudios clínicos randomizados. Estos estudios evaluaron el uso de omalizumab en el tratamiento de asma y se enfocaron en su eficacia, tolerabilidad, y costo-efectividad en la población asmática.

SELECCIÓN DE ESTUDIOS Y EXTRACCIÓN DE INFORMACIÓN: Se revisaron todos los estudios clínicos randomizados, se identificaron 23 y se incluyeron 19 (3 no eran de relevancia y 1 contenía información repetida). Se revisaron otros artículos que se identificaron utilizando los términos terapia anti-IgE y costo-efectividad y se extrajo la información relevante.

SÍNTESIS: Los mecanismos dependientes de IgE juegan un papel importante en el desarrollo y mantenimiento de la inflamación de las vías respiratorias en la condición de asma. Omalizumab es un anticuerpo monoclonal de IgE, administrado por vía subcutánea que reduce las concentraciones de IgE no enlazado y promueve la baja-regulación de receptores IgE. Los estudios clínicos en adultos, adolescentes, y niños con pobre control de asma mediada por IgE han demostrado que omalizumab mejora el control de los síntomas y permite que los

pacientes sean manejados con dosis más bajas de corticosteroides inhalados. Omalizumab ha sido bien tolerado en los estudios clínicos que han durado hasta 52 semanas. Sin embargo, las reacciones en el sitio de inyección son frecuentes (45% en el grupo de omalizumab vs 43% en el grupo placebo) y ha ocurrido anafilaxis en 0.2% de los pacientes. Un consenso de un panel de expertos ha recomendado que se considere el uso de omalizumab en pacientes de 12 años o más con asma alérgica con un control inadecuado a la terapia recomendada por las guías y que requieren el uso de corticosteroides sistémicos como terapia de mantenimiento o de altas dosis de corticosteroides inhalados o que tienen pobre adherencia a los corticosteroides inhalados.

CONCLUSIONES: La terapia con anti-IgE provee una alternativa efectiva y generalmente segura en el tratamiento de pacientes con asma mediada por IgE que no obtienen un control adecuado con los medicamentos convencionales recomendados en las guías de manejo. Sin embargo, se debe sopesar el beneficio potencial con el costo e inconveniencia de esta nueva terapia.

Traducido por Annette Pérez

Le Traitement de l'Asthme avec des Antiimmunoglobulines E et l'Omalizumab

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Ann Pharmacother 2007;41:1397-410.

RÉSUMÉ

OBJECTIF: Évaluer les données sur le traitement de l'asthme avec des antiimmunoglobulines E (anti-IgE).

SOURCES DE DONNÉES: L'information a été obtenue à partir d'une recherche dans PubMed de 1989 à mai 2007 en utilisant les mots-clés omalizumab et randomized controlled trials. Ces essais cliniques évaluaient le traitement de l'asthme avec l'omalizumab avec un intérêt sur son efficacité, innocuité et coût-efficacité dans les populations étudiées.

SÉLECTION DES ÉTUDES ET EXTRACTION DES DONNÉES: Tous les essais cliniques ont été revus (23 ont été identifiés, 19 inclus; 3 ont été jugés non pertinents et un seul contenait de l'information en double). D'autres publications identifiées avec les mots-clés anti-IgE therapy et cost-effectiveness ont été évaluées, et l'information pertinente a été extraite.

SYNTHÈSE DES DONNÉES: Les mécanismes reliés aux IgE jouent un rôle important dans le développement et le maintien de l'inflammation des voies respiratoires dans l'asthme. L'omalizumab (Genentech, Inc. et Novartis) est un anticorps monoclonal anti-IgE administré par voie sous-cutanée qui réduit la concentration d'IgE libres et qui favorise la diminution du nombre de récepteurs des IgE. Les résultats d'essais cliniques chez des adultes, adolescents, et enfants avec un asthme mal contrôlé et relié aux IgE ont démontré que l'omalizumab améliore le contrôle des symptômes et permet une diminution des doses de corticostéroïdes en inhalation (CSI). Le produit a été bien toléré dans les essais cliniques d'une durée jusqu'à 52 semaines mais les réactions au site d'injection sont communes (45% des patients traités avec l'omalizumab et 43% des patients sous placebo). Des réactions anaphylactiques ont été notées chez 0.2% des patients. Un groupe d'experts a recommandé que l'omalizumab soit considéré pour les patients âgés de 12 ans et plus souffrant d'asthme allergique et qui ne sont pas adéquatement contrôlés suivant les lignes directrices et qui nécessitent une dose de maintien avec des stéroïdes par voie systémique ou avec des doses élevées de CSI, ou qui présentent une faible observance au traitement avec les CSI.

CONCLUSIONS: Le traitement avec les anti-IgE constitue une approche efficace et généralement sécuritaire dans le traitement de l'asthme relié aux IgE qui n'est pas traité efficacement selon les lignes directrices en vigueur. Cependant, les bienfaits potentiels doivent être mis en perspective avec les coûts et les inconvénients de cette nouvelle thérapie.

Traduit par Nicolas Paquette-Lamontagne