

PRACTICE

Immunoglobulin E-mediated airway inflammation is active in most patients with asthma

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Abstract

Purpose: To review the role of immunoglobulin E (IgE)-mediated inflammation in the pathogenesis of asthma, limitations of standard therapies, and IgE as a logical target for therapy with omalizumab aimed at attaining asthma symptom control.

Data sources: Review of worldwide scientific literature on the role of IgE-mediated inflammation in patients with asthma, supplemented with a clinical case study.

Conclusions: Clinical trials point to an important role for IgE blocker therapy as an add-on to current therapy to reduce exacerbations and corticosteroid use and to improve quality of life in patients with moderate-to-severe asthma. Omalizumab, a monoclonal antibody that binds IgE, has been shown to be an effective, well-tolerated treatment in these patients.

Implications for practice: A significant number of patients with moderate-to-severe asthma do not achieve asthma symptom control, despite adhering to current guidelines-based standards of therapy, including the use of inhaled corticosteroids, β -agonists, and leukotriene modifiers. None of these therapies directly addresses IgE-mediated inflammation. Therefore, patients with persistent symptoms of moderate-to-severe asthma should be evaluated and considered for therapy with the IgE blocker omalizumab.

Introduction

Asthma is a common and serious public health concern (American Lung Association Epidemiology & Statistics Unit, 2005; Mannino et al., 2002). The total economic cost of asthma, which affects about 20 million Americans, is estimated at \$16.1 billion annually in the United States, comprising direct asthma-related healthcare costs of \$11.5 billion and indirect costs related to lost productivity of \$4.6 billion (American Lung Association Epidemiology & Statistics Unit). Each year, asthma accounts for an estimated 12.8 million lost school days in children and 24.5 million lost workdays in adults, ranking it among the top 10 conditions causing limitations to daily activity (American Lung Association Epidemiology & Statistics Unit).

Treating asthma effectively relies at least partially on understanding its pathogenesis. Over the past 20 years,

a growing body of evidence has implicated immunoglobulin E (IgE)-mediated inflammation as an underlying pathologic feature of asthma in both children and adults (Allen-Ramey et al., 2005; Burrows, Martinez, Halonen, Barbee, & Cline, 1989; Pollart, Chapman, Fiocco, Rose, & Platts-Mills, 1989). In a prospective study of 145 children with a family history of asthma, onset of asthma by 3 years of age was positively associated with variables from the first year of life, including elevated total IgE (Klennert et al., 2001). Total serum IgE levels track with age: Children less than 1 year old with high serum IgE levels continued to have high IgE levels at ages 6 and 11 years (Klennert et al.). Persistent wheezing was associated with high serum IgE levels at all ages (Sherrill et al., 1999). Further, children between the ages of 6 and 12 years with severe asthma have higher mean IgE levels than those with moderate or mild asthma (Borish et al., 2005). Investigators have

shown that high total serum IgE levels and IgE-mediated sensitivity to house dust mite allergens are linked to asthma in adults (Freidhoff & Marsh, 1993). Total serum IgE has been linked to increased risk for acute asthma attacks in children and adults and, in turn, increased healthcare use secondary to hospital emergency room visits (Pollart et al., 1989; Sunyer et al., 1995). These findings suggest a link between elevated serum IgE levels and diminished pulmonary function in both children and adults.

While higher IgE levels are associated with worse asthma symptoms, low IgE levels do not exclude IgE-mediated disease. Defining the normal range of serum IgE has proven difficult because the levels vary widely among individuals (Klink, Cline, Halonen, & Burrows, 1990). Therefore, total IgE is not a useful diagnostic tool for asthma (Kerkhof, Dubois, Postma, Schouten, & de Monchy, 2003). Because a large and growing body of evidence suggests that IgE plays a central role in the development of asthma pathology, blocking the effects of IgE appears to be a rational approach to the management of asthma in many patients.

IgE and asthma: pathophysiology

IgE formation and immune response

IgE is fundamental to the allergic response to antigens (Platts-Mills, 2001), with IgE levels increasing notably in

patients with disorders such as asthma, allergic rhinitis, and atopic dermatitis (Oettgen & Geha, 1999). Patients with these disorders produce an overabundance of antigen-specific IgE antibody (Platts-Mills), which on exposure to the specific antigen (allergen), initiates early- and late-phase inflammatory reactions. In some patients, this leads to chronic airway inflammation (Oettgen & Geha). The inflammatory process begins when adjacent antigen-specific IgE antibody molecules bound to the surfaces of mast cells and basophils are cross-linked by an antigen molecule (Figure 1) (Lantz et al., 1997; Platts-Mills; Turner & Kinet, 1999). Resulting mast cell (and basophil) degranulation is accompanied by the release of preformed vasoactive mediators of inflammation (e.g., histamine and heparin) and the release of newly synthesized mediators of inflammation (e.g., cysteinyl leukotrienes, cytokines, and prostaglandins). Both groups of mediators contribute to the inflammatory cascade (Figure 1) (Lantz et al.; Platts-Mills; Turner & Kinet). These inflammatory mediators rapidly induce bronchial mucosal edema, mucus production, and smooth muscle contraction, causing allergic symptoms. IgE also mediates the upregulation of the high-affinity receptors on mast cells and other inflammatory cells, thus enhancing early-phase response and contributing toward late-phase response (Oettgen & Geha).

The late-phase reaction is characterized by the influx of neutrophils, lymphocytes, eosinophils, and macrophages, leading to heightened bronchovascular permeability and increased bronchial hyperresponsiveness to nonspecific

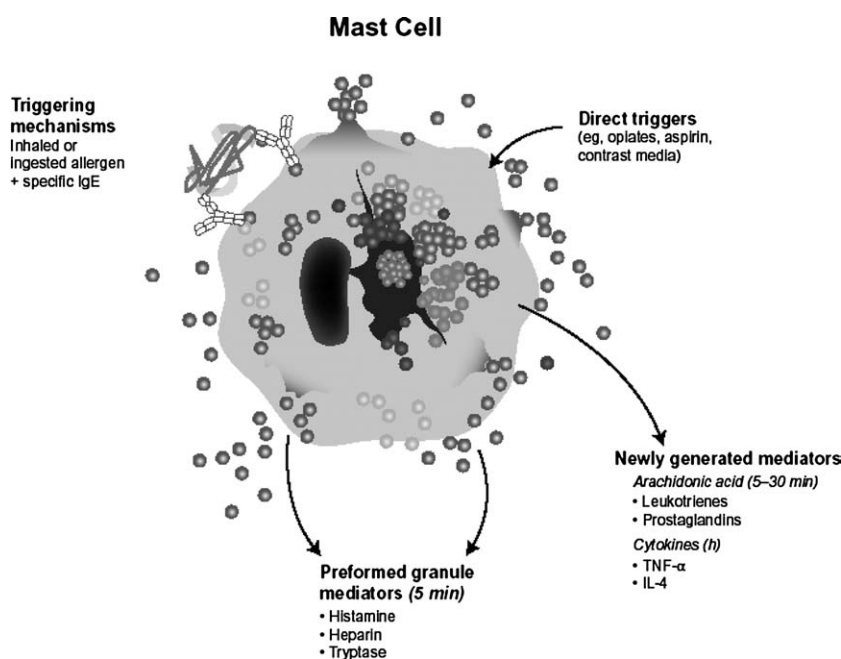


Figure 1 The release of preformed and newly generated mediators is triggered by cross-linking of IgE molecules on Fc ϵ R1.

stimuli (Baroody et al., 2000; Togias, 2004). In patients with asthma, the late-phase response manifests as a period of diminished airflow for 4–8 h after the initial allergic response and is caused in part by early-phase inflammatory mediator-stimulated eosinophil infiltration into the airways. This in turn leads to the release of additional proinflammatory mediators, a reduction in the airflow, and chronic airway inflammation, which continues to persist as long as antigen-specific IgE molecules remain in excess quantities (Lantz et al., 1997; Platts-Mills, 2001; Turner & Kinet, 1999).

IgE systemic effects

IgE-mediated inflammation is a systemic phenomenon. Local allergic reactions can induce secondary inflammatory events that intensify the original reaction or induce more distant inflammatory manifestations. Although unclear, the mechanisms that promote the development of systemic inflammation may include a complicated interplay between the mediators of acute allergic reactions, locally and systemically produced cytokines, the vascular epithelium, and adhesion molecules, and other systemic inflammatory responses, such as an increase in inflammatory cell production by the bone marrow (Togias, 2004).

Atopic dermatitis, asthma, and allergic rhinitis commonly occur together and are considered IgE-mediated

reactions (Bousquet, Vignola, & Demoly, 2003). A close relationship is recognized between upper and lower respiratory disorders, that is, between allergic rhinitis and asthma. Allergic rhinitis, which is considered an independent risk factor for asthma (Bousquet et al.; Guerra, Sherrill, Martinez, & Barbee, 2002), has been reported in up to 80% of patients with asthma, and asthma is present in up to half of the patients with allergic rhinitis (Greisner, Settipane, & Settipane, 1998; Guerra et al.). Treatments that can improve the symptoms of allergic rhinitis, such as antihistamines and intranasal corticosteroids, can also improve the symptoms of asthma (Corren, Adinoff, Buchmeier, & Irvin, 1992; Corren, Manning, Thompson, Hennessy, & Strom, 2004; Corren et al., 1997; Durham, 1999; Foresi et al., 1996; Grant et al., 1995; Watson, Becker, & Simons, 1993). This co-occurrence suggests that they share pathogenic atopic mechanisms, such as IgE-mediated inflammation (Berger, Schenkel, & Mansfield, 2002; Watson et al., 1993).

Asthma severity versus control

Asthma severity describes the disease status based on pulmonary function, the level of daytime and nighttime symptoms, and the frequency of exacerbations. The National Asthma Education and Prevention Program (NAEPP, 2003) (Table 1) and the Global Initiative for

Table 1 NAEPP-defined levels of asthma severity: clinical features before treatment^a

Asthma level	Symptoms ^b	Symptoms at night	Lung function
Step 4: severe persistent	● Continual symptoms ● Limited physical activity ● Frequent exacerbations	Frequent	● FEV₁ or PEF $\leq$60% predicted ● PEF variability $>$30%
Step 3: moderate persistent	● Daily symptoms ● Daily use of inhaled SABA ● Exacerbations affect activity ● Exacerbations $\geq$2 times a week, may last for days	$>$ 1 time a week	● FEV₁ or PEF $>$60% to $<$80% predicted ● PEF variability $>$30%
Step 2: mild persistent	● Symptoms $>$2 times a week, but $<$1 time a day ● Exacerbations may affect activity	$>$ 2 times a month	● FEV₁ or PEF $\geq$80% predicted ● PEF variability 20%–30%
Step 1: mild intermittent	● Symptoms $\leq$2 times a week ● Asymptomatic and normal PEF between exacerbations ● Exacerbations brief (from a few hours to a few days), intensity may vary	$\leq$ 2 times a month	● FEV₁ or PEF $\geq$80% predicted ● PEF variability $<$20%

^aThe presence of one of the features of severity is sufficient to place a patient in that category. An individual should be assigned to the most severe grade in which any feature occurs. The characteristics noted in this table are general and may overlap because asthma is highly variable. Furthermore, an individual's classification may change over time.

^bPatients at any level of severity can have mild, moderate, or severe exacerbations. Some patients with intermittent asthma experience severe and life-threatening exacerbations separated by long periods of normal lung function and no symptoms.

PEF, peak expiratory flow.

From the National Asthma Education and Prevention Program. (1997). Clinical Practice Guidelines Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma (NIH Publication No. 97–4051). Bethesda, MD: National Heart, Lung, and Blood Institute.

Asthma (GINA) Management and Prevention (GINA, 2005) workshop updated in 2005 (Table 2) developed guidelines for the diagnosis and management of asthma. The NAEPP identifies four severity classes for asthma: severe persistent, moderate persistent, mild persistent, and mild intermittent (Bateman et al., 2004; NAEPP, 1997, 2003). The GINA guidelines also recognize four classes of severity for asthma: severe persistent, moderate persistent, mild persistent, and intermittent (the NAEPP classification is mild intermittent for the same level of severity).

There is an important difference between asthma severity assessment and asthma symptom control, a broader measure than encompasses patient-centered factors, among them quality of life (QOL) and daily functioning. Clinicians may underestimate asthma control of patients when they use a single endpoint such as lung function (forced expiratory volume in 1 s [FEV₁]). Wolfenden et al. (2003) reported that underestimated asthma control often results in poor control of asthma symptoms and a level of care that falls well short of guideline recommendations.

Table 2 GINA-defined levels of asthma severity

Level	Signs and symptoms
Severe persistent	● Symptoms daily ● Frequent exacerbations ● Frequent nocturnal asthma symptoms ● FEV₁ ≤60% predicted OR ● PEF ≤60% of personal best
Moderate persistent	● Symptoms daily ● Exacerbations may affect activity and sleep ● Nocturnal symptoms at least once a week ● 60% < FEV₁ < 80% predicted OR ● 60% < PEF < 80% of personal best
Mild persistent	● Symptoms more than once a week but less than once a day ● Nocturnal symptoms more than twice a month but less than once a week ● Normal lung function between episodes
Intermittent	● Symptoms less than once a week ● Brief exacerbations ● Nocturnal symptoms not more than twice a month ● Normal lung function between episodes

OR, odds ratio; PEF, peak expiratory flow.

From the Global Initiative for Asthma. (2004). Global Strategy for Asthma Management and Prevention (NIH Publication No. 02-3659). Issued January 1995 (updated 2002). Retrieved from www.ginasthma.org.

Measures of pulmonary function such as FEV₁ have been shown to correlate only weakly with patient's symptom-free days and QOL measures (Carranza Rosenzweig, Edwards, Lincourt, Dorinsky, & ZuWallack, 2004). In fact, only about 50% of patients with severe, persistent asthma considered their symptoms well controlled, despite treatment consistent with current guidelines (Rabe, Vermeire, Soriano, & Maier, 2000). In studies, criteria for asthma control used by clinicians may be quite variable and not consistent with established current treatment guidelines (Bateman et al., 2004).

In a retrospective analysis using data from three clinical trials, Juniper et al. (2004) explored the relationship between asthma symptoms and asthma-specific QOL. This analysis showed that the overall health status of patients with asthma encompasses four key factors: asthma-specific QOL, airway caliber, daytime symptoms and daytime β_2 -agonist use, and nighttime symptoms and nighttime β_2 -agonist use (Juniper et al.). Improvement in all four factors is needed to achieve beneficial symptom control. Although the majority of patients with asthma achieve adequate asthma symptom control, a large minority still have persistent symptoms, despite adhering to treatment guidelines (Bateman et al., 2004).

Current standard therapies

Asthma therapy includes both long- and short-term control medications. Long-term control medications, such as inhaled corticosteroids (ICS), long-acting β_2 -agonists (LABAs), and leukotriene receptor antagonists (LTRAs), are used to achieve and maintain control of asthma symptoms. Quick relief medications, such as short-acting β_2 -agonists (SABAs) and systemic corticosteroids, are used to treat symptoms and gain control of exacerbations. Current standard maintenance therapies include ICS, LABAs, and LTRAs and, on occasion, methylxanthines and cromones.

Despite using these therapies according to current guidelines, some patients will still have persistent symptoms. These symptoms result from comorbidities, such as upper airway disease (McGeehan & Busse, 2002), from noncompliance with the prescribed treatment regimen (Bender & Bender, 2005; Cochrane, Bala, Downs, Mauskopf, & Ben-Joseph, 2000), or from limitations of the asthma medications, such as steroid resistance or insensitivity, or the steroid plateau effect (Chan, Leung, Szeffler, & Spahn, 1998; Hojo & Kudo, 2004; Holt et al., 2001; Masoli, Weatherall, Holt, & Beasley, 2004).

Nonadherence, which is common, can be difficult to assess with ICS. Even if patients report taking their medication as prescribed, they may not be using the inhalation device properly, thus reducing the amount of drug delivered to the lung (Cochrane et al., 2000). The clinician can

assess the patient's ability to use the inhaler appropriately by asking him or her to demonstrate using the device, providing additional instruction, or ordering a more patient-friendly delivery device when needed. Patients and caretakers of children may also report medication use that is more frequent than indicated by the number of doses remaining in the metered dose inhaler. In a study of 163 patients with asthma aged 7–16 years Jonasson, Carlsen, Sodal, Jonasson, and Mowinckel (1999) examined adherence to low-dose ICS. Compliance was based on self-reported use recorded on diary cards compared to utilization indicated by the number of doses remaining in the ICS metered dose inhaler. Only 58% and 67% of patients obtained $\geq 75\%$ measured compliance for inhaler use in the morning and evening, respectively ($p = 0.007$; $p < 0.001$) (Jonasson et al., 1999).

Corticosteroids may have limitations beyond nonadherence that may reduce their value in the management of asthma.

Limitations of corticosteroids

ICS still form the cornerstone of maintenance asthma therapy (GINA, 2005; NAEPP, 2003). Although patients who present with asthma exacerbations may often receive a short course of oral corticosteroids to gain prompt control of symptoms, ICS provide the most consistently effective symptom relief (NAEPP, 2003). ICS are generally well tolerated and safe when used at recommended dosages, and most patients with asthma respond to their anti-inflammatory properties. In contrast, there is considerable variation in the way individuals respond to corticosteroids, and a small proportion of patients with asthma fail to respond even to high doses (Adcock et al., 1995; Chan et al., 1998; Leung & Bloom, 2003; Loke, Sousa, Corrigan, & Lee, 2002; Matthews, Ito, Barnes, & Adcock, 2004; Szeffler et al., 2002; Tantisira et al., 2004). Although uncommon, these patients often present considerable management problems.

Steroid insensitivity and resistance

Some patients who do not benefit clinically from corticosteroid therapy are considered steroid insensitive (or steroid resistant), and a number of molecular abnormalities have been found in these patients (Adcock et al., 1995; Cho & Lee, 2003; Leung & Bloom, 2003; Loke et al., 2002; Matthews et al., 2004; Tantisira et al., 2004). The clinical definition of steroid insensitivity in patients with asthma is the failure to improve baseline morning airway obstruction (FEV_1) by at least 15% following a 2-week course of oral corticosteroid therapy (prednisolone 40 mg/day), despite evidence of clear reversibility ($>15\%$ improvement) with a β_2 -agonist (Loke et al.). This definition, how-

ever, may be too limited because certain aspects of airway inflammation may not respond to corticosteroid reversal. In addition, several conditions mimic corticosteroid-insensitive asthma, including fixed/irreversible airway disease, vocal cord dysfunction, obstructive sleep apnea, hyperventilation, cardiac disease, left ventricular dysfunction, and tracheomalacia/tracheal stenosis. Furthermore, poor compliance with medication may also be mistaken for corticosteroid-insensitive asthma. These morbidities and lack of adherence to treatment need to be ruled out in order to determine if a patient is truly corticosteroid insensitive (Loke et al.).

Dosing

ICS often display a characteristic "plateau effect," where increasing the dose above a certain point may increase the patient's risk for side effects without providing additional therapeutic benefits. Therefore, when guideline-recommended doses of ICS fail to adequately control symptoms, rather than increasing the dose of steroids, the preferred option in most patients is add-on therapy with another class of controller medication (GINA, 2005).

Safety issues

ICS are generally well tolerated and safe when used at recommended dosages. Local side effects may include oropharyngeal candidiasis, dysphonia, and occasional coughing from upper airway irritation. Generally, the risk for adverse effects depends on the dose and potency of the steroid, the level of hypothalamic-pituitary-adrenal axis suppression, and the age of the patient (GINA, 2005; NAEPP, 2003).

Limitations of other asthma medications

β -Agonists

Current treatment guidelines advocate adding an LABA when asthma symptoms are not well managed with ICS (GINA, 2005; NAEPP, 2003). LABAs provide bronchodilation for approximately 12 h after a single dose and are used for long-term control of asthma symptoms, especially at night, and to prevent exercise-induced bronchospasm (NAEPP, 1997, 2003), while SABAs are predominantly used as rescue medications.

Genetic variations among patients can affect their response to β_2 -agonist therapy and may be the basis for the higher rate of persistent asthma seen in certain populations, specifically African Americans (American Lung Association Epidemiology & Statistics Unit, 2005; Israel et al., 2000; Taylor et al., 2000; Weir et al., 1998).

Patients who take β_2 -agonists regularly for their asthma may develop tolerance to the drugs' bronchodilator effects

and have inadequate disease control (Salpeter, Ormiston, & Salpeter, 2004). Cross-tolerance to different β -agonists can also develop with regular use, so that switching from one β -agonist to another may not be effective in improving symptoms (Lee, Jackson, Bates, & Lipworth, 2004).

Leukotriene receptor antagonists

Leukotrienes, which are secreted by mast cells, eosinophils, and basophils, are mediators that cause smooth muscles in the airway to contract, increasing vascular permeability and mucus secretions. LTRAs reduce airway hyper-responsiveness and improve pulmonary function (Busse & Kraft, 2005; NAEPP, 1997, 2003). In the current asthma guidelines, LTRAs are recommended as an alternative to ICS in mild persistent asthma and as an add-on therapy to ICS in moderate persistent asthma (NAEPP, 1997, 2003).

IgE blocker therapy for asthma

Despite advances in pharmacologic management of asthma over the past 20 years, patients with moderate-to-severe asthma often do not achieve adequate symptom control with standard-of-care therapy (Bateman et al., 2004). This 1-year, randomized, double-blind, stratified study of 3421 patients with uncontrolled moderate-to-severe asthma tested the efficacy of three step up dose escalations depending on ICS dose in the preceding 6 months. The maximum levels of salmeterol/fluticasone administered twice daily were 50/500 mcg or 500 mcg of fluticasone alone until asthma control was achieved. While 71% (1204 of 1709) patients on a high-dose treatment with a β -agonist and ICS had their asthma well controlled, the remaining 29% (505 of 1709) experienced uncontrolled asthma symptoms after 1 year. In the author's opinion, these results highlight the need for additional therapies.

Although the majority of patients with asthma have IgE-mediated inflammation (Burrows et al., 1989), most therapeutic approaches do not address IgE-mediated inflammation. Because of the role of IgE-mediated inflammation in asthma, IgE blockade presents a valid approach to treating asthma symptoms. To date, only one IgE blocker (omalizumab) has been approved by the Food and Drug Administration for the treatment of moderate-to-severe allergic asthma in adults and adolescents at least 12 years of age.

Omalizumab

Mechanism of action

Omalizumab (Xolair) is a humanized murine monoclonal antibody that binds to IgE at the site responsible for Fc ϵ RI receptor binding. When binding to the IgE molecule, omalizumab inhibits the binding of circulating IgE to mast cells and basophils, thereby preventing the

initiation of the inflammatory cascade. It does not displace already bound IgE (Figures 2a and 2b) (Presta et al., 1994; Rosenwasser & Nash, 2003). In a clinical study of 24 individuals with known allergies that were challenged intradermally with allergen, omalizumab significantly reduced both early-phase ($p = 0.0093$) and late-phase ($p = 0.012$) hypersensitivity responses, compared with placebo (Ong, Menzies-Gow, Matthews, & Kay, 2004). Rather than addressing the inflammatory process that is already underway, a characteristic of conventional therapies, omalizumab prevents IgE-mediated inflammation (Fox et al., 1996; Rosenwasser & Nash).

Omalizumab (Xolair) has been approved in the United States for the treatment of moderate-to-severe persistent asthma in adults and adolescents (12 years of age and above) who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with ICS. (Xolair[®] Omalizumab for subcutaneous use [package insert]). Omalizumab should be administered subcutaneously at doses of 150–375 mg every 2 or 4 weeks. Doses and dosing frequency are determined by body weight (kg) and serum total IgE level (IU/mL), measured before the start of treatment (Xolair[®] Omalizumab for subcutaneous use [package insert]). Due to the continued risk for anaphylaxis after *any* dose of omalizumab, the FDA has requested a Black Box warning be added to the full prescribing information (for full information, see <http://www.fda.gov/cder/drug/infopage/omalizumab/default.htm>).

Clinical studies

The clinical efficacy and safety of omalizumab in patients with moderate-to-severe asthma who remain symptomatic despite treatment with steroids have been evaluated in several large-scale, well-controlled studies (adults and adolescents) (Buhl, Soler et al., 2002; Busse, 2001; Finn et al., 2003; Holgate et al., 2004; Lanier, 2003; Soler et al., 2001). In a randomized, double-blind, placebo-controlled study, 546 patients with moderate-to-severe asthma were maintained on a steady dose of ICS for 16 weeks, followed by a steroid-reduction phase (12 weeks) (Soler et al.). Following these two phases, 483 of the initial 546 patients were maintained on randomized treatment for an additional 24 weeks (Buhl, Soler et al.). Omalizumab-treated patients experienced fewer exacerbations in all three phases of the study and attained better symptom control during the extension phase than those who received placebo (Buhl, Soler et al.; Soler et al.). Furthermore, patients treated with omalizumab demonstrated a statistically significant ($p < 0.001$) improvement in QOL

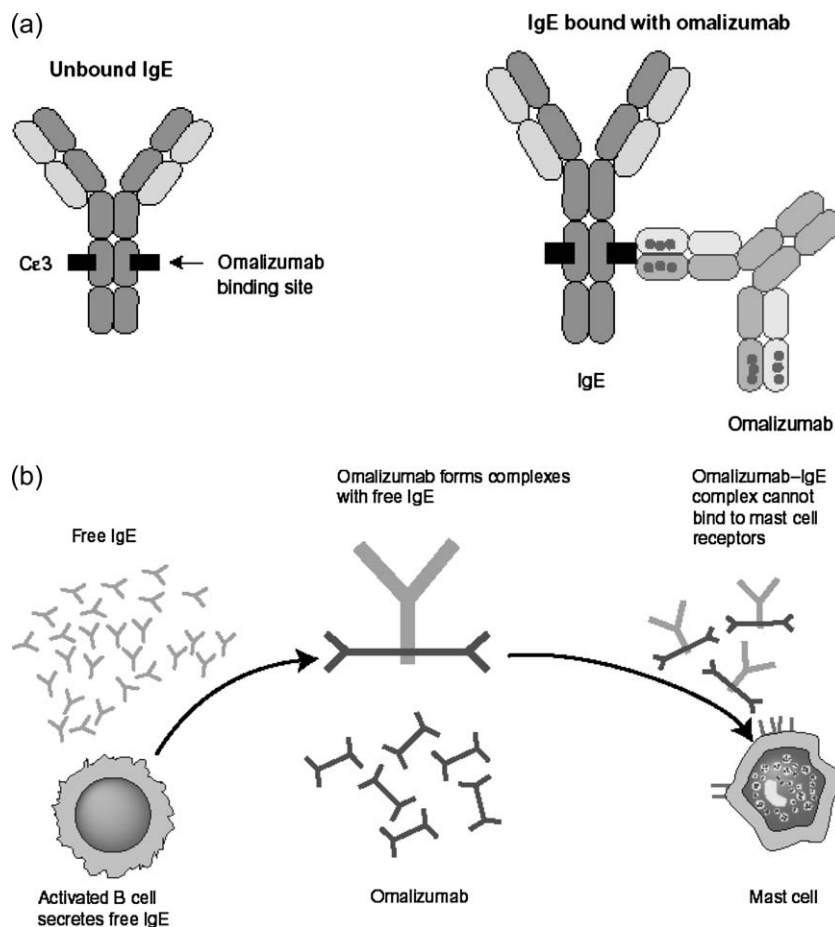


Figure 2 (a) Binding of omalizumab to IgE, (b) IgE–omalizumab complex prevents initiation of the allergic cascade.

over baseline. Treatment with omalizumab was rated as “excellent/good” by almost 70% of patients and investigators, compared with 40% for placebo, even though steroid reduction was greater in patients receiving omalizumab ($p < 0.001$) (Buhl, Hanf et al., 2002). These studies demonstrated that omalizumab improved control of asthma symptoms and QOL and reduced acute exacerbations while allowing the use of lower doses of ICS and rescue medications. Omalizumab was well tolerated in clinical studies with a low rate of adverse events that was similar to placebo (Deniz & Gupta, 2005; Xolair® Omalizumab for subcutaneous use [package insert]). Studies in children have similar positive results (Milgrom et al., 2001), but further studies are ongoing.

Overall, these studies show that omalizumab provides benefits for patients whose asthma symptoms have not been adequately controlled, reduces the need for ICS, and improves the overall QOL in patients. This evidence of efficacy and tolerability in the management of patients with moderate-to-severe asthma has led a consensus panel to support the use of an IgE blocker as an additional

therapeutic approach in patients whose symptoms are inadequately controlled with standard therapies, including medium-dose ICS and LABAs or LTRAs (Rosenwasser & Nash, 2003). Duration of treatment with omalizumab is unknown. IgE is not monitored as conventional testing will not discriminate between bound and unbound IgE. Thus, the total IgE measured may actually increase when little is present in the unbound and potentially active form (Corren, Diaz-Sanchez et al., 2004). This was observed in a clinical study in which treatment with omalizumab in 19 patients reduced the concentration of serum-free IgE in a dose-dependent manner by 97%–99%. In contrast, total IgE increased by approximately three- to fourfold from baseline levels (Corren, Diaz-Sanchez et al.). Further, at this time, administration is recommended under the supervision of a healthcare provider, with emergency treatment available.

Case study

Karen, a 40-year-old nonsmoker with a history of asthma since childhood, presented to her primary care provider's

office with moderate persistent asthma that was limiting her activities, especially her ability to sleep and exercise regularly. Her medical history indicated that her asthma symptoms were often aggravated by upper respiratory infections and by recurrent seasonal rhinitis. Karen lives with two household pets, a dog and a cat, and has in the past experienced an anaphylactic reaction in response to a bee sting.

On presentation, Karen, who weighs 55 kg, was taking inhaled fluticasone/salmeterol (ADVAIR®) 250/50 mcg twice a day and oral montelukast (SINGULAIR®) 10 mg every day. During the past year, she required albuterol rescue approximately three or four times weekly and short-course oral corticosteroid therapy three to five times over the past year.

Clinical findings revealed decreased lung functions, with FEV₁ and forced expiratory vital capacity (FVC) levels at 54% and 68% of predicted levels, respectively, before bronchodilation. After bronchodilation, the FEV₁ and FVC levels were 68% and 74%, respectively. Skin tests were positive for dust mite, grass mix, multiple trees, and weeds. A chest x-ray revealed inflation with coarse bilateral markings without infiltrates. Karen had a total serum IgE of 380 IU/mL (maximal levels of IgE often do not exceed 120 IU/mL in healthy, nonallergic adults) (Wittig, Belloit, De Fillippi, & Royal, 1980). Evidence of osteopenia was noted on a bone dual energy x-ray absorptiometry scan. These findings raised issues regarding the appropriate choice of therapy. ICS are the first choice to attain symptom control. However, with osteopenia already present, the long-term use of moderate- to high-dose ICS is not ideal. Once Karen's symptoms were stabilized with a short burst of oral steroids and a higher dose of ICS for 2 weeks, an attempt was made to reduce the dose of ICS needed by adding an IgE blocker. Follow-up visits with assessment of asthma control and spirometry were scheduled every 3 months.

After 9 months of treatment with omalizumab 225 mg (subcutaneous injection) every 2 weeks in her asthma specialist's office, Karen's FEV₁ increased from 54% to 80% of predicted. More importantly, during therapy, she was able to reduce her use of ICS and did not require any oral corticosteroids. Karen reported significant improvement in her QOL with the start of omalizumab therapy; she experienced an increase in her ability to exercise and noted no seasonal exacerbations of asthma or allergy symptoms.

Conclusions

Guidelines-recommended therapy for moderate-to-severe asthma is typically well tolerated. For many patients with asthma, however, treatment falls short of achieving the best possible management of symptoms. Symptoms may persist for a variety of reasons, including the failure of

patients to adhere to prescribed treatment regimens. New treatments that help alleviate symptoms and improve the QOL in patients with asthma have been developed. Understanding the pathogenesis of asthma can help nurse practitioners understand why particular therapies may not be effective in specific patients with persistent asthma symptoms and help them to select the most appropriate therapy for these patients. Currently, none of the treatment options advocated by treatment guidelines directly addresses IgE-mediated inflammation, the underlying pathologic feature of asthma in both children and adults. IgE blockers such as omalizumab have demonstrated clear and well-tolerated benefits in the management of moderate-to-severe asthma, reducing acute exacerbations and the need for ICS, as well as improving measurements of QOL.

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