

Anti-IgE Therapy in Asthma: Rationale and Therapeutic Potential

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Key Words

Asthma · Drug therapy · IgE · Anti-IgE antibody · Monoclonal antibody · Mast cell

Abstract

Airway inflammation is found in virtually all individuals with asthma symptoms. The factors contributing to asthma-related airway inflammation are multiple and involve a number of different inflammatory cells and mediators. Allergic responses at the level of the respiratory system are mostly mediated by IgE-dependent mechanisms. After sensitization of a susceptible individual and the synthesis and binding of allergen-specific IgE to target cells, atopic individuals respond immunologically to common, naturally occurring allergens by releasing mast cell-derived mediators. Subsequent allergen exposure in susceptible individuals produces a characteristic cascade of events orchestrated by immune effector cells, most prominently, mast cells, T lymphocytes and eosinophils. A new strategy, neutralizing IgE antibodies, inhibits expression of allergic symptoms by preventing the initial trigger of the allergic reaction, IgE binding to IgE-receptor bearing cells. rhuMab-E25 is a recombinant humanized monoclonal anti-IgE antibody currently under investigation that has been shown to reduce allergic responses in atopic individuals and to improve symptoms and reduce rescue medication and corticosteroid use in patients with allergic asthma. Thus, the clinical effectiveness of rhuMab-E25 supports the central role

of IgE in allergic reactions and the viability of anti-IgE therapy as a potentially effective treatment option for asthma.

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Introduction

Asthma is a common chronic inflammatory disease of the airways. A recent cross-sectional study of the UK general population reported a prevalence of asthma of 12% [1]. The prevalence of asthma is even higher in children; the prevalence rate of reported asthma was 23% in British children aged 6–7 years [2], and 21% in those aged 12–14 years [3].

Inflammation, reversible or partially reversible airway obstruction and airway hyperresponsiveness to various stimuli are the defining characteristics of asthma. Indeed, airway inflammation is found in virtually all individuals with asthma symptoms, an observation which has implications for the management of the disease. The factors contributing to asthma-related airway inflammation are multiple and involve a number of different inflammatory cells. In establishing the relationship between the pathological changes and clinical features of asthma, the involvement of resident cells (mast cells, epithelial cells, macrophages), inflammatory cells (eosinophils, lymphocytes, neutrophils), mediators, cytokines and adhesion molecules are key features of the inflammatory process of asthma (fig. 1) [4].

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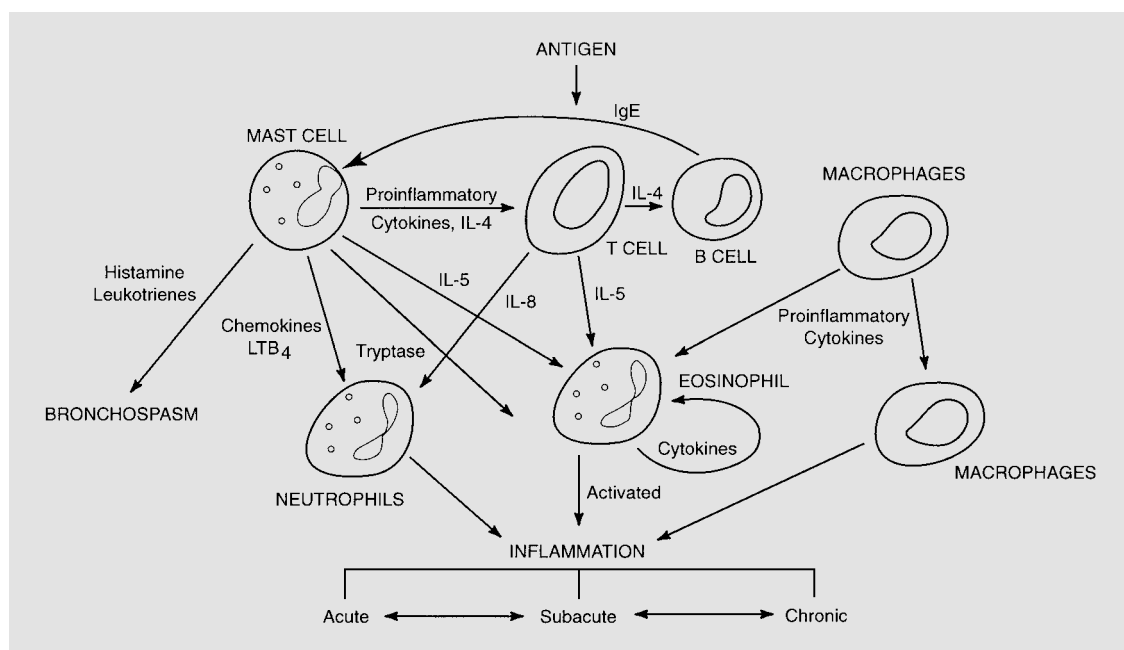


Fig. 1. Cellular mechanisms involved with airway inflammation [4].

Atopy, the genetic predisposition for the development of an IgE-mediated response to common aeroallergens, is the strongest identifiable predisposing factor for developing asthma [4]. Immune mechanisms appear to be causally related to the development of asthma in 25–35% of all cases and to be contributory in perhaps another third [5]. Higher prevalences have been suggested, but it is difficult to know how to interpret the data because of confounding factors.

Role of IgE

IgE plays a central role in the pathogenesis of atopic diseases, including asthma [6, 7]. Allergen exposure is a common cause of asthma-related symptoms in both adults and children. The allergic response involves the following key elements (fig. 2):

- antigen-specific IgE antibody
- tissue mast cells and circulating basophils, which bind the IgE antibody through high affinity surface receptors (FcεRI)
- interaction of allergen with IgE-FcεRI complexes on mast cells and basophils that causes cross-linking of receptors triggering the release of a variety of pharmacological mediators, cytokines and chemokines
- the biologic effects that these mediators induce in various target organs [8, 9].

The onset of asthma occurs at all ages, but commonly begins in early life. Childhood asthma is frequently observed in association with atopy to common environmental allergens, such as dust mites, tree and grass pollens, and animal dander [10]. The formation of antigen-specific IgE antibody to aeroallergens does not usually occur until 2 or 3 years of age. Allergens continue to play an important role in the development of adult-onset asthma; however, IgE antibodies to allergens or a family history of asthma are not detected in some adults who develop asthma [4]. Such individuals on rare occasions have coexisting sinusitis, nasal polyps and sensitivity to aspirin or related non-steroidal anti-inflammatory drugs.

Asthma prevalence has been shown to be associated with increased levels of total IgE, even in subjects negative for specific IgE to common allergens (non-atopic individuals) [11, 12]. Total serum IgE levels during childhood track markedly with age: individuals aged less than 1 year with high serum IgE levels continued to have high IgE levels at ages 6 and 11 years [13]. Persistent wheezing and early sensitization were both associated with high serum IgE levels at all ages. In a survey of 875 young adults 20–44 years old, elevated serum IgE levels were associated with a 3-fold increase in bronchial hyperresponsiveness, independently of the presence of asthma symptoms or specific IgE [14]. Overall, these results suggest that asth-

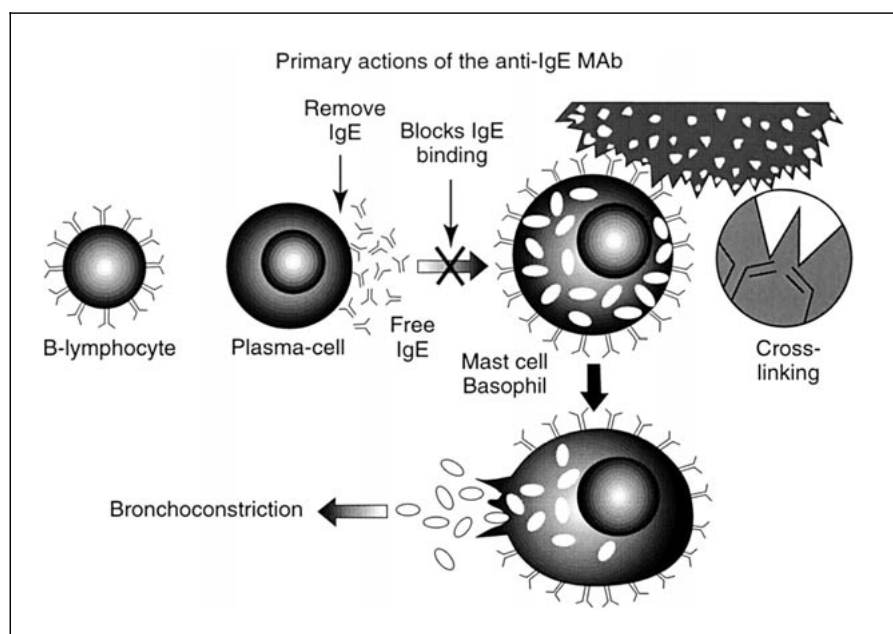


Fig. 2. Overview of the key elements involved in the allergic response [8].

ma is frequently associated with some type of IgE-related reaction and therefore has an allergic basis [11].

A minority of asthmatic patients have a late onset of asthma associated with negative skin tests to common allergens and a normal circulating IgE. These patients who have non-atopic, or 'intrinsic', asthma tend to have more severe disease. Recently, patients with 'intrinsic' asthma have been shown to produce IgE widely in the airways [15], suggesting that IgE also plays a role in these patients.

Allergic responses at the level of the respiratory system are mostly mediated by IgE-dependent mechanisms. Once IgE antibodies are produced, mast cells and possibly other airway cells, such as lymphocytes, are sensitized and become activated when specific antigens are encountered. During an allergic immune response, allergen-specific B cells are stimulated. IgE antibody production ensues following stimulation by IL-4/13 provided by T-helper type 2 (Th2) cells. IgE antibodies act by arming cells bearing either high-affinity (FcεRI) or low-affinity (FcεRII or CD23) receptors. The interaction of allergen with IgE-FcεRI complexes on mast cells and basophils causes cross-linking of receptors that trigger the release of a variety of pharmacological mediators, cytokines and chemokines (fig. 2).

Once sensitized, the airways respond to allergen with early- and late-phase bronchoconstriction [16]. The early phase response is believed to be mediated by IgE, and is

thought to represent a classic type I hypersensitivity reaction (e.g. allergen interacts with mast cell- or basophil-bound IgE to trigger cross-linking and aggregation of IgE receptors leading to cell degranulation and release of inflammatory mediators) [17]. These mediators are thought to produce the airway smooth muscle contraction, mucosal hypersecretion and mucosal edema representative of the immediate bronchoconstriction of the early asthmatic response.

The bronchoconstriction associated with the late-phase asthmatic response occurs two or more hours after allergen inhalation. This reaction is associated with increased airway reactivity to non-specific stimuli and inflammation in the bronchial lavage fluid. The late-phase reaction is associated with a bronchial inflammatory response and its reduction is more closely related to reduction in asthma symptoms than early-phase response [18]. The role of IgE and its high- and low-affinity receptors in the release of inflammatory mediators in the late asthmatic response to inhaled allergen is not well established. However, human lung mast cells can generate and release, via IgE-dependent signalling, a wide variety of cytokines [19, 20], suggesting that IgE has an important role in the ongoing airway inflammation associated with the late asthmatic response.

Overview of an Anti-IgE Antibody (rhuMAB-E25)

Available strategies to manage allergic disease consist of either attempts to desensitize the atopic individual to a given allergen or to diminish an ongoing allergic reaction. Because of the pivotal role of IgE in mediating the allergic response, inhibition of IgE responses with anti-IgE antibodies represents a novel and more direct approach in the treatment of atopic conditions.

Pharmacology

A murine monoclonal antibody that binds circulating IgE at the same sight as the high-affinity receptor has been developed. An important aspect in the development of this compound was that the antibodies could not bind to FcεRI-bound IgE, since this would trigger release of histamine. Because of a number of fundamental problems with the clinical use of murine antibodies (e.g. stimulation of human immune response), humanization of this murine antibody was undertaken to avoid these problems [21]. The best of several humanized variants, version 25 (rhuMAB-E25), was selected because it possessed IgE-binding affinity and biologic activity comparable to the murine antibody [8]. In vitro assays showed that the recombinant humanized anti-IgE monoclonal antibody had the following characteristics that were similar to those of the murine monoclonal antibody:

- bound to free IgE but not to IgA or IgG
- did not bind to mast-cell- or basophil-bound IgE
- blocked the binding of IgE to FcεRI, its specific high-affinity receptor and
- inhibited mast cell degranulation following challenge with ragweed allergen [22].

These results confirmed that rhuMAB-E25 was effective at blocking mast cell degranulation and subsequent release of inflammatory mediators.

A number of preclinical studies were conducted in cynomolgus monkeys (which have naturally high levels of IgE) to characterize the formation of rhuMAB-E25:IgE complexes and to examine the disposition of the antibody in a relevant animal model. The rhuMAB-E25:IgE immune complexes were small and similar in size to those formed in vitro with human IgE [23], no complexes had a molecular weight of $>10^6$ and no precipitating immune complexes were detected [24]. These complexes cannot bind IgE receptors and thus lack the biological activity of IgE. Moreover, because these low-molecular weight complexes do not fix complement or accumulate in renal glo-

meruli, they do not pose a risk of immunopathogenicity [24].

The radiolabelled rhuMAB-E25 was mostly present in the blood and in the serum compartment, and no specific uptake into any tissue or organ was detected at either 1 or 96 h. The elimination half-life of rhuMAB-E25 ranged from 1 to 4 weeks after subcutaneous or intravenous administration [25]. Serum clearance decreased with increasing dose, and increased in animals with higher baseline concentrations of IgE. Urinary excretion was the primary route of elimination of radioactivity and $>90\%$ of the radioactivity found in the urine was not associated with protein [24].

In other pre-clinical studies in cynomolgus monkeys, free serum IgE concentrations decreased dose dependently at higher doses of rhuMAB-E25, and IgE levels effectively became undetectable following formation of rhuMAB-E25:IgE complexes [25]. rhuMAB-E25 reduced the skin reactivity to ragweed following weekly pre-sensitizing injections of this antigen, and skin test reactivity was abolished after a second injection of rhuMAB-E25 [22].

Clinical Studies

The pharmacodynamic and pharmacokinetic characteristics rhuMAB-E25 have been assessed in adults and children with a wide range of baseline serum IgE concentrations [26, 27]. Adults with or without allergic disease were randomized to receive rhuMAB-E25 0.005, 0.014, 0.05, and 0.14 mg/kg subcutaneously or rhuMAB-E25 0.05, 0.14, 0.5 and 1.0 mg/kg intravenously [25]. Total rhuMAB-E25 was cleared slowly from the circulation (elimination half-life ranged from 1 to 4 weeks) and free plasma IgE concentrations decreased dose dependently with increasing doses of rhuMAB-E25 [25].

A similar pharmacodynamic and pharmacokinetic profile was observed in a multiple-dose study in 34 children and adolescents aged 6–17 years with moderate to severe allergic asthma [27]. The serum profiles of rhuMAB-E25 and IgE across the groups and baseline IgE levels confirmed results from pre-clinical studies showing that rhuMAB-E25:IgE complexes are cleared more slowly from the circulation than free IgE, but are cleared more rapidly than uncomplexed rhuMAB-E25.

In a study in 12 atopic subjects, free IgE levels dropped rapidly after each biweekly dose of rhuMAB-E25 (0.015 and 0.03 mg/kg/IU/ml), averaging 1% of pre-treatment levels [28]. A marked downregulation of basophil FcεRI was also observed in 3 patients with very high baseline free IgE levels. The median pre-treatment density of

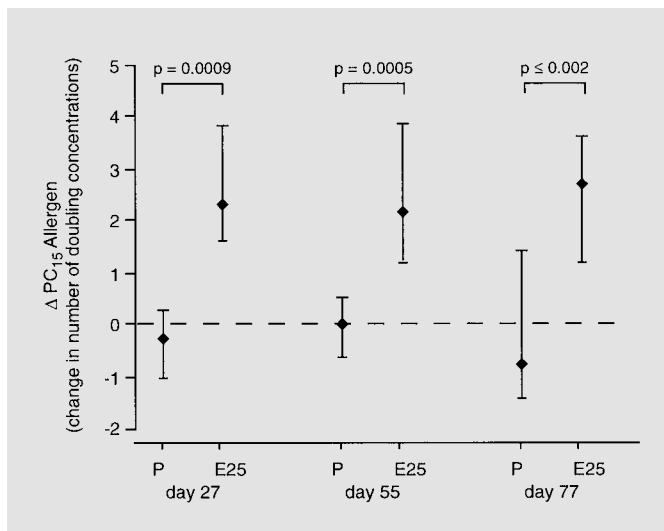


Fig. 3. Summary of the inhibitory effects of rhuMab-E25 on allergen-induced bronchospasm in 20 patients with asthma [29]. All values for rhuMab-E25 were significantly different from placebo ($p \leq 0.002$). PC_{15} represents the effect of treatment on the provocation concentration of allergen causing a 15% fall in FEV_1 .

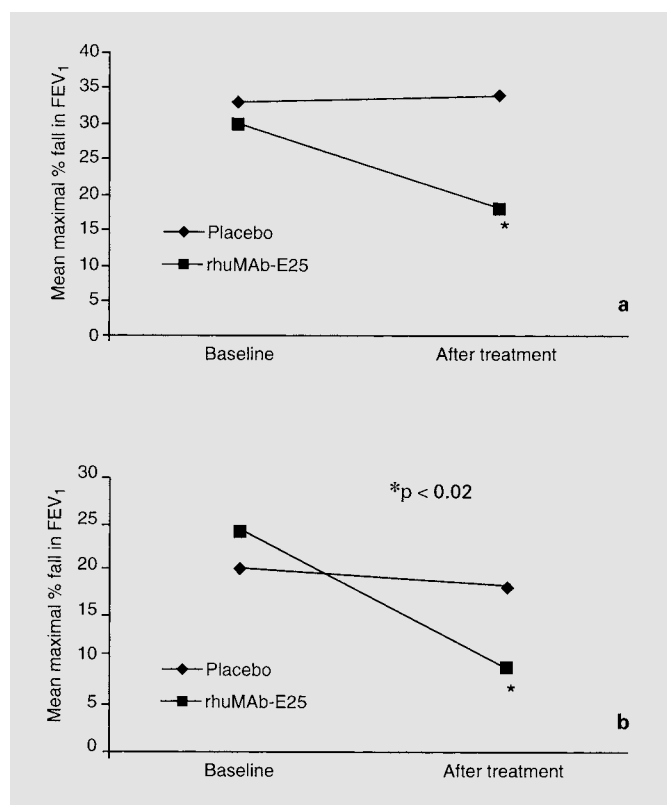


Fig. 4. Effects of treatment with rhuMab-E25 on the early (a) and late (b) phase responses to airway challenge in 19 patients with asthma. Responses were assessed by change in FEV_1 [30].

$Fc\epsilon RI$ receptors per basophil decreased from $\approx 220,000$ to $\approx 8,300$ receptors after 3 months of treatment with rhuMab-E25. Histamine release in response to dust mite antigen was reduced by about 90%, with about one-half the patients experiencing essentially no release. The decrease in both free IgE and $Fc\epsilon RI$ receptor density is important in that the functional consequences of the $>99\%$ reduction in plasma IgE levels might have been modest without a parallel decrease in $Fc\epsilon RI$ density [28]. Therefore, these changes support the potential for use of rhuMab-E25 in atopic patients.

In order to determine whether rhuMab-E25 would be useful therapy for asthma, two studies were conducted to assess the effect of rhuMab-E25 on bronchial challenge with allergen and on allergen-induced skin tests [29, 30]. The effect of rhuMab-E25 on the provocation concentration of allergen and methacholine causing a 15 and 20% fall (PC_{15} and PC_{20} , respectively) in forced expiratory volume in 1 s (FEV_1) during the allergen-induced early asthmatic response was assessed in 20 atopic patients with asthma [29]. rhuMab-E25 1 mg/kg produced significant inhibitory effects on allergen-induced bronchospasm relative to placebo, with an increase in allergen PC_{15} of 2.2–2.7 doubling doses compared with -0.8 to 0.1 for placebo (fig. 3) [29]. The methacholine PC_{20} improved slightly but significantly after rhuMab-E25 treatment while no change was observed with placebo. rhuMab-E25 treatment reduced mean serum free IgE levels by 89% (from 287.8 to 30 ng/ml at 77 days; $p < 0.001$) while no changes were observed with placebo. Free IgE levels fell to below the threshold for detection in 7 of 10 patients. Overall, these results showed that rhuMab-E25, administered at regular intervals over 10 weeks, effectively suppressed allergen-induced early asthmatic response in patients with asthma.

A further randomized double-blind study showed that rhuMab-E25 (0.5 mg/kg or placebo weekly for 9 weeks) suppressed both the early- and late-phase responses to inhaled allergen in 19 atopic patients with asthma [30]. Allergen reactivity was assessed by spirometry (allergen challenge until FEV_1 fell by $\geq 20\%$ or until the allergen concentration given was twice that given during baseline assessment); methacholine reactivity was assessed as described above (PC_{20}). rhuMab-E25 significantly reduced maximal bronchoconstriction to airway challenge during the early and late phase by 40% and 63% (both $p < 0.02$ from baseline and versus placebo), as evidenced by the reduction in magnitude of fall in FEV_1 (fig. 4) [30]. The PC_{20} improved slightly (by 1.6 doubling doses), but not significantly, in the rhuMab-E25 group relative to the

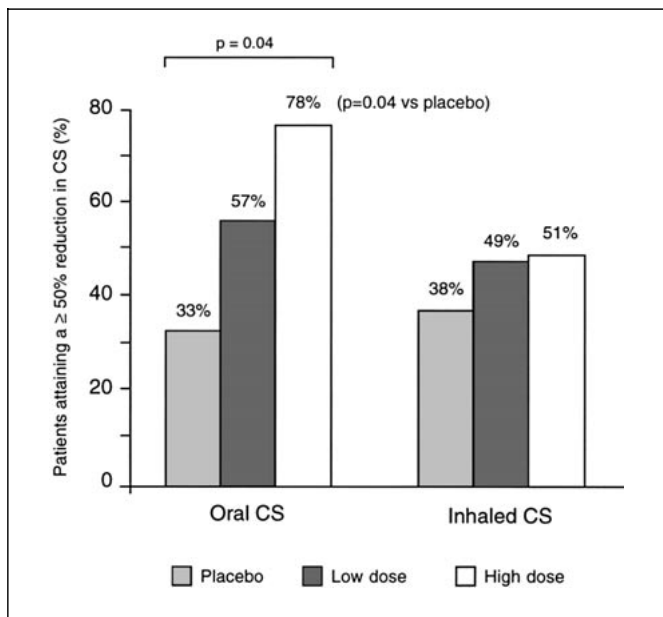


Fig. 5. Percentage of patients attaining a $\geq 50\%$ reduction in corticosteroid (CS) use following treatment with rhuMAb-E25 2.5 $\mu\text{g/kg}$ per nanogram of IgE per millilitre (low dose) or rhuMAb-E25 5.8 $\mu\text{g/kg}$ per nanogram of IgE per millilitre (high dose), or placebo in 317 patients with moderate to severe asthma [46].

placebo group. At 24 h after allergen challenge, eosinophilia in induced sputum was reduced 11-fold, while free serum IgE levels fell by about 90% in the rhuMAb-E25 group and were unchanged in the placebo group [30]. Treatment with rhuMAb-E25 also reduced the number of eosinophils in the sputum and decreased airway hyperresponsiveness [29, 30], suggesting that it has a long-term anti-inflammatory effect.

The clinical efficacy and safety of rhuMAb-E25 has recently been assessed in a multicentre, randomized, double-blind, placebo-controlled study in 317 patients with moderate to severe allergic asthma requiring inhaled and/or oral corticosteroids [31]. Following a 4-week run-in period, patients received either placebo, rhuMAb-E25 2.5 $\mu\text{g/kg}$ per nanogram of IgE per millilitre (low dose) or rhuMAb-E25 5.8 $\mu\text{g/kg}$ per nanogram of IgE per millilitre (high dose) intravenously on days 0 (half a dose), 4 (half a dose), and 7 (full dose) and then at biweekly intervals for 20 weeks. During the last 8 weeks of treatment, the dosages of corticosteroids were tapered in an attempt to discontinue this therapy.

Both high- and low-dose rhuMAb-E25 produced a greater than 95% mean decrease in serum IgE levels [31]. The proportion of patients in the high-dose and low-dose

rhuMAb-E25 groups experiencing a $\geq 50\%$ reduction in asthma symptom scores (the primary outcome measure) was significantly higher than that in the placebo group (49 and 47% vs. 24%; both $p < 0.001$). A significantly higher proportion of patients in the high-dose group than in the low-dose and placebo groups was able to achieve a $\geq 50\%$ reduction in oral corticosteroids (fig. 5). For high-dose, low-dose and placebo groups, respectively, oral corticosteroids were discontinued in 33, 43 and 17% of patients (both NS vs. placebo), and inhaled corticosteroids were discontinued in 18% ($p = 0.27$), 23% ($p = 0.048$) and 12% of patients.

Compared with placebo, the improvement in mean morning peak expiratory flow (PEF) from baseline to week 12 was significantly greater in the high-dose group (+30.7 litres/min; $p = 0.007$), but not in the low-dose group (+18.6 litres/min; $p = 0.10$) [31]. At 20 weeks, the differences in PEF improvement between the high-dose (+29.9 litres/min; $p = 0.02$) and low-dose (+20.8 litres/min; $p = 0.046$) rhuMAb-E25 groups and placebo reached statistical significance. After 12 weeks of treatment, rescue beta-agonist use was reduced by 1.8 puffs/day ($p = 0.02$) in the high-dose group, 1.2 puffs/day ($p = 0.24$) in the low-dose group and 0.8 puffs/day in the placebo group. The proportions of patients experiencing asthma exacerbation during the 20-week treatment period were 30% ($p = 0.03$) in the high-dose, 28% ($p = 0.01$) in the low-dose as compared with 45% in the placebo group [31]. There were no significant differences in adverse events between the active-treatment and placebo groups, and no serious drug-related adverse events were reported. This suggests that rhuMAb-E25 may be a useful steroid-sparing therapy in patients with severe asthma [32].

Subcutaneous rhuMAb-E25 300 mg, administered every 3 or 4 weeks depending on baseline IgE levels, has also been shown to produce improvements in daily nasal symptoms (sneezing, itchy nose, runny nose and stuffy nose), concomitant antihistamine rescue medication use and rhinitis-specific quality of life in patients with seasonal allergic rhinitis [33, 34]. Improvement in seasonal allergic rhinitis symptom severity and rescue medication use was directly related to reduction in free IgE levels [33–35].

Conclusions

Despite an improved understanding of the relationship of inflammation to the disease process and better pharmacological treatments, asthma morbidity and mortality

continue to rise in the US and worldwide [36–38]. Asthma is a multifactorial and complex disease in which interaction between allergic factors and non-allergic triggers result in bronchial obstruction and inflammation. Most patients with asthma have atopy, with specific IgE antibodies to antigens in inhaled indoor and outdoor allergens (e.g. house dust mites allergen, cockroach allergen, pollen, and mold) which drive the inflammatory process in the airways. A small proportion of individuals with asthma have no evidence of atopy as assessed by total and specific IgE levels in plasma or by skin-prick tests to common allergens. These patients with non-atopic or ‘intrinsic’ asthma tend to have more severe disease. Despite the absence of atopy, IgE may be produced locally in the airways, suggesting that IgE-mediated mechanisms may be involved in intrinsic asthma [39].

Although allergen avoidance is always recommended in the management of allergic asthma, it is rarely completely effective. There are a number of pharmacological treatment strategies available that attempt to reduce the ongoing allergic inflammation; however, none of these strategies can cure the disease and many patients with asthma remain uncontrolled despite optimum drug treatment. Immunotherapy directed against common allergens in patients with asthma is not typically used in the UK, but US studies have shown that this treatment is disappointing in such patients and carries a small risk of serious adverse effects [40, 41]. Corticosteroids are the mainstay of anti-inflammatory treatment for asthma and provide an efficient therapy for disease control. These agents produce their effects on various cells by binding to intracellular glucocorticoid receptors, which in turn inhibit transcription factors that are normally activated by inflammation [42].

Many patients can be maintained on a low dosage of inhaled corticosteroid with minimal risk of adverse effects. Unfortunately, systemic effects can occur with long-term corticosteroids, in particular those administered by the oral route. These include hypothalamic-pituitary-adrenal axis suppression, osteoporosis, cataracts, hyperglycaemia, dermal thinning and growth retardation in children [43, 44].

Because of the central role it plays in atopic disease, inhibition of IgE with IgE antibodies represents a novel approach to improve IgE-mediated allergic reactions and to reduce the severity of asthma [45]. rhuMAb-E25, a humanized murine monoclonal antibody directed to the FcεRI binding domain of human IgE, inhibits the binding of IgE to mast cells without provoking mast cell activation. The ability to lower circulating free IgE levels is

desirable since most individuals are exposed to multiple allergens which they are sensitive to at any given time.

In clinical studies, rhuMAb-E25 exhibited a prolonged pharmacological effect without inducing anaphylaxis, blunted the early- and late-phase allergic response to inhaled allergen, reduced the symptoms of seasonal allergic rhinitis, reduced the symptoms of asthma (and improved some physiological measures of asthma) and reduced corticosteroid use. rhuMAb-E25 has been well tolerated in clinical trials to date. Thus, preliminary results with rhuMAb-E25 are encouraging, and late-phase clinical trials are under way to confirm and extend these findings.

One of the limitations of rhuMAb-E25 is that it is a protein that must be given by injection. Initially, twice weekly intravenous injections were used, but further studies may lead to less frequent or subcutaneous administration which would be less inconvenient in long-term management. rhuMAb-E25 is also likely to be expensive as are other antibody treatments, such as anti-TNF-α. Such a treatment, however, may be justified in patients with severe asthma who are only controlled on doses of oral corticosteroids that cause side effects [32]. Patients with severe atopic disease, in addition to asthma may also benefit. In the future it may be possible to develop small molecule IgG inhibitors, but in the meantime rhuMAb-E25 represents an important advance in the therapy of asthma.

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