Is there a role for treatment of asthma with omalizumab?

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The allergic response is distinct from other immune reactions in its reliance on IgE, its high affinity receptor, FcεRI, and the primary effector cell—the tissue mast cell. Positive skin tests or raised concentrations of specific immunoglobulin E (IgE) in the serum define IgE sensitisation or “atopy”. IgE participates both in immediate hypersensitivity response and in the induction of chronic allergic inflammation. It enhances allergen capture and Th2 cell activation, and may trigger other immunoregulatory pathways. Considerable effort in therapeutic research has focused on interference with IgE function because of its position high in the allergic cascade. Therapy with anti-IgE is one such approach that shows much promise.

Asthma, a most important cause of chronic disability in childhood, occurs with the highest prevalence in English speaking countries. Recent studies in Britain disclose a self reported rate of 23% in children aged 6–7 years and 21% in those aged 12–14. In the United States the prevalence of confirmed asthma in children rose from 3.1% in 1980 to 5.4% in 1994, but among impoverished residents of the inner city, the combined prevalence of diagnosed and undiagnosed asthma has been estimated at 26%. In the USA, deaths from asthma in children under 15 fell from 191 in 1996 to 154 in 1997. This decrease in mortality may reflect improved management, but it comes short of fulfilling our responsibility to our patients. About one third of children who die from asthma are judged to have mild disease prior to the fatal event. Preventable causes include inadequate assessment or therapy, poor adherence to therapy, and delay in seeking help.

PATHOGENESIS AND TREATMENT OF ASTHMA IN CHILDHOOD

A large proportion of all cases of asthma have their onset in the first years of life, but no more than a small minority of infants who wheeze have or will proceed to develop the disease. Atopy, or the expression of exaggerated IgE antibody responses against common environmental allergens, in early life strongly predicts future airway disease. The link between atopy and asthma lies in the development of persistent inflammation in the airway wall. As they grow older, those infants with early onset of wheezing who will develop asthma, suffer greater deterioration in lung function and greater persistence of symptoms. Thus, therapeutic strategies for children should include early anti-inflammatory therapy to prevent progression of the disease.

Asthma is a syndrome characterised by inflammation in medium and small airways that gives rise to constriction and hyperresponsiveness of the bronchial smooth muscle, oedema and disruption of the mucosa, and obstruction of the lumen by mucus. The inflammation may lead to airway remodelling with proliferation of airway smooth muscle and deposition of matrix proteins. There is emerging evidence that airway remodelling may be present very early in disease, even in infancy, and it may represent a risk factor for the persistence of symptoms and development of asthma. The bronchoconstriction, but not the inflammation, oedema, mucosal injury, or excessive mucus secretion, subsides temporarily after the administration of a bronchodilator. During the past decade national and international bodies, among them the British Thoracic Society, National Heart, Lung, and Blood Institute, and the Global Initiative for Asthma, have convened expert panels charged with developing guidelines to improve the detection and treatment of asthma. These panels expanded the definition of asthma to emphasise airway inflammation and airway hyperresponsiveness over the established focus on reversible obstruction and issued guidelines proposing that pharmacological management target these two processes.

Specific allergen reactivity and raised IgE are associated with persistent wheezing. The allergic response differs from other immune reactions by its dependence on IgE, its high affinity receptor, FcεRI, and the primary effector cell—the tissue mast cell. Atopy is manifested by positive skin prick tests or measurable specific serum IgE following exposure to a sensitising allergen. Non-atopic individuals, after a similar exposure, typically generate a response characterised by the production of IgG1 and IgG4 antibodies. Their lymphocytes react in vitro by secreting interferon γ by type 1 helper T (Th1) cells, rather than interleukin 4 (IL-4) and interleukin-5 (IL-5) produced by the type 2 (Th2) cells in patients with allergic disorders. The reactions following an antigen challenge of a sensitised individual have been designated as early and late phase allergic responses (EPR and LPR). IgE binds to FcεRI on inflammatory cells in the airways, the gut, and the skin. Cross linking by allergen molecules of a critical mass of IgE antibodies bound to the

Abbreviations: BDP, beclomethasone dipropionate; EPR, early phase allergic response; FEV1, forced expiratory volume in one second; ICS, inhaled corticosteroid; IL, interleukin; LPR, late phase allergic response.
OMALIZUMAB IN THE THERAPY OF ASTHMA

The avoidance of offending allergens remains a fundamental principle of therapy in patients with allergenic triggers. A pharmacological intervention at the stage of interaction of allergen with IgE first appeared achievable when anti-IgE antibodies were found to suppress both EPR and LPR in mice. Omalizumab lowered free IgE concentrations through the formation of immune complexes with the e3 domain of the Fc fragment of human IgE. This portion of the IgE molecule binds to the FcRI on inflammatory cells and is not accessible for cross linking on IgE attached to mast cells, a property necessary in order to avoid bridging of cell bound IgE and initiating the release of inflammatory mediators.

Omalizumab interferes with allergic responses in several ways. (1) It attaches to the FcRI binding domain of free IgE, rendering it unavailable to mast cells to set off EPR. (2) It prevents IgE from interacting with FcεRI on monocytes, cosinophils, dendritic cells, epithelial cells, and platelets, thus interfering with mediator/cytokine release and LPR. (3) It prevents IgE from interacting with FcεRII on antigen presenting cells. (4) It indirectly causes a notable down-regulation of FcεRI on basophils and in all probability other cells. (5) The effects of IgE–anti-IgE complexes are particularly interesting and potentially beneficial. The non-immunogenic complexes with a half life of about 40 days persist in circulation for a prolonged time. These complexes have unoccupied antigen binding sites and are able to remove from circulation those allergens against which the patient’s IgE is directed.

In early trials, omalizumab reduced free serum IgE concentrations by more than 90%, considerably suppressed cosinophilia in induced sputum, and blunted both EPR and LPR. Three published studies involving 1388 patients aged between 11 and 76 years with moderate to severe asthma evaluated treatment with omalizumab using double blind, randomised, placebo controlled clinical protocols. Two of the studies enrolled patients who remained symptomatic despite treatment with systemic or inhaled corticosteroids and bronchodilators and at the same time enhanced the control of asthma. In each study the observations were supported by improvement in quality of life measurements.

Omalizumab treatment was also evaluated in children who were well controlled on inhaled corticosteroids and as-needed bronchodilators. Three hundred and thirty four children aged 6–12 years, with moderate to severe allergic asthma, were treated with subcutaneously administered placebo (n = 109) or omalizumab (n = 225) at a dose based on body weight and initial serum IgE concentration (0.016 mg/kg/IgE per week). Beclomethasone dipropionate (BDP) dose (initial range 168–420 mg/day) was kept stable for 16 weeks (stable steroid phase), reduced over eight weeks to the minimum effective dose (steroid reduction phase), and maintained constant for the final four weeks. More subjects in the
omalizumab group were able to reduce their BDP dose (p = 0.002), compared to those treated with placebo (median reduction 100% v. 66.7%, p = 0.001). BDP was withdrawn completely in 55% of patients treated with omalizumab versus 39% of patients treated with placebo (p = 0.004). The incidence and frequency of asthma exacerbations requiring treatment with doubling of BDP dose or systemic corticosteroids were lower in the omalizumab group. The treatment differences were statistically significant during the steroid reduction phase, when fewer subjects in the omalizumab group had asthma exacerbation episodes (18.2% v. 38.5%, p < 0.001), and the mean number of episodes per patient was smaller than with placebo (0.42 v. 0.72, p < 0.001). Five asthma exacerbations requiring hospitalisation all occurred in the placebo group. Over the entire treatment period, patients in the omalizumab group missed a mean of 0.65 school days, compared to a mean of 1.21 days in the placebo group (p = 0.040). The mean number of unscheduled medical contacts for asthma related medical problems was significantly smaller in the omalizumab group than in the placebo group throughout the treatment period (0.15 v. 0.35, p = 0.001). Median reduction in serum free IgE was 95–99% among omalizumab patients. Omalizumab treatment was well tolerated. There were no serious treatment related adverse events. The frequency and types of all adverse events were similar in the omalizumab and placebo groups. Treatment with omalizumab has been free of serious complications among more than 3000 patients treated to date. One patient who received inhaled therapy developed antibodies to omalizumab, and this mode of delivery has been abandoned. Among patients receiving intravenous therapy, 4% developed urticaria, usually during the first infusion. With the subcutaneous technique the occurrence was reduced to 2%, no longer limited to the first dose. In October 2000, there were reports of thrombocytopenia in juvenile cymolmonkeys treated with omalizumab at doses up to 27 times greater than recommended for clinical use. There were two deaths in animals treated with a more potent anti-IgE antibody that has never been used in clinical trials. However, a search for thrombocytopenia through the records of more than 2000 study patients did not disclose any cases.

CONCLUSION

We already know that omalizumab is effective for the treatment of allergic rhinitis, 15 16 and most likely for the therapy and prevention of anaphylaxis, food allergy, and atopic dermatitis. Although atopy may be a parallel rather than sequential factor in the pathogenesis of asthma, 17 there is sound evidence that manifestation of the disease is associated with specific IgE antibodies. Omalizumab decreases free IgE, suppresses both early and late phase allergic reactions, improves symptoms, stabilises lung function, and reduces the need for corticosteroids. However, longer term studies are needed to determine the best selection of patients for treatment and the duration of beneficial effect, and, most importantly, to answer the question whether omalizumab arrests disease progression. Current pharmacotherapy decreases inflammation and provides symptomatic relief, but it does not entirely suppress the underlying disease, and new approaches are still needed. Further, there are some patients for whom existing medical regimens are not satisfactory. Omalizumab should be evaluated in the treatment of children who require unacceptably high doses of oral or inhaled corticosteroids and those who are suffering from steroid induced side effects. In certain patients uncontrolled asthma is associated with reduced glucocorticoid receptor binding within the inflammatory cells. 18 Frequent exacerbations and increased mortality have been documented in patients who do not adhere to their treatment regimen. 19 20

“As for the future our task is not to foresee it but to enable it” (St Exupery)

REFERENCES


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_Arch Dis Child_ 2003 88: 71-74
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