Recombinant Therapies in Asthma

Donald W. Cockcroft, MD, FRCPC

Abstract

Numerous recombinant therapies are being investigated for the treatment of asthma. This report reviews the current status of several of these novel agents. Anti–immunoglobulin (Ig)E (omalizumab, Xolair) markedly inhibits all aspects of the allergen challenge in subjects who have reduction of free serum IgE to undetectable levels. Several clinical studies in atopic asthma have demonstrated benefit by improved symptoms and lung function and a reduction in corticosteroid requirements. Early use in atopic asthmatics may be even more effective. Several approaches target interleukin (IL)-4. Soluble IL-4 receptor has been shown to effectively replace inhaled corticosteroid; further studies are under way. Recombinant anti-IL-5 and recombinant IL-12 inhibit blood and sputum eosinophils and allergen-induced eosinophilia without any effect on airway responsiveness, allergen-induced airway responses, or allergen-induced airway hyperresponsiveness. Efalizumab, a recombinant antibody that inhibits lymphocyte trafficking, is effective in psoriasis. A bronchoprovocation study showed a reduction in allergen-induced late asthmatic response and allergen-induced eosinophilia, which suggests that it should be effective in clinical asthma. These exciting novel therapies provide not only promise of new therapies for asthma but also valuable tools for investigation of asthma mechanisms.

D. W. Cockcroft — Department of Medicine, University of Saskatchewan, Royal University Hospital, Saskatoon, Saskatchewan

Correspondence to: Dr. Donald W. Cockcroft, Royal University Hospital, Division of Respiratory Medicine, 103 Hospital Drive, Ellis Hall, 5th Floor, Saskatoon, SK S7N 0W8

History

As previously reviewed,[1] pharmacotherapy for asthma has changed dramatically in the past 100 years. At the turn of the century, therapy for acute asthma included mainly narcotics (eg, heroin, morphine) and sedatives (chloral hydrate), agents now considered contraindicated in acute asthma. Inhalants were also advocated for acute asthma, including amyl nitrate, ether, turpentine, ammonia, stramonium smoke, and even tobacco! The only pharmaceutical acting directly on the airways was atropine. Epinephrine, a nonselective α and β agonist, identified early in the 1900s and synthesized shortly thereafter, rapidly became the standard therapy for acute asthma administered subcutaneously at the rate of a minim a minute. Ephedrine, an old nonselective α and β agonist extracted from a Chinese herb, ma huang, was not widely used until well into the twentieth century, when it was usually combined with theophylline and barbiturates. Isoproterenol, a selective β (mixed β_1-β_2) agonist, proved to be an effective bronchodilator[2] and was used by inhalation (nebulization), as was racemic epinephrine. The introduction of the pressurized metered-dose inhaler (MDI) about 40 years ago revolutionized the management of asthma. Epinephrine and isoproterenol soon became available in an MDI, the latter most widely prescribed. Modifications to sympathomimetics resulted in increasingly long-acting increasingly selective β_2 agonists, the most widely prescribed of which was salbutamol, introduced in 1967. Further modifications have resulted in the ultra–long-acting inhaled β_2 agonists salmeterol and formoterol. Anticholinergics also have a long history of use in the Far East; atropine-containing tobaccos made from *Datura stramonium* were used for thousands of years in India. This remarkable

remedy was brought from India to the United Kingdom about 200 years ago. Atropine has been available for over 150 years and was mentioned in Osler's textbook 100 years ago; however, atropine seems never to have been very widely used for asthma.[3] In contrast, for the first half of the twentieth century, many different brands of asthma cigarettes and asthma burning powders were available for outpatient management of asthma. The development of topically active medium- and long-acting antimuscarinic agents (ipratropium and tiatropium, respectively) have resulted in useful pharmacologic therapy that is more valuable in chronic obstructive pulmonary disease than in asthma. Theophylline is a compound extracted from tea, another herbal remedy used for millennia as a stimulant in Asia. Theophylline first became widely available as a pharmaceutical in the form of the ethylene diamine salt known as aminophylline. It was initially used as a stimulant and diuretic but later was used intravenously and rectally as a bronchodilator. Oral preparations became available a little over 50 years ago and were often used alone or in combination with ephedrine and barbiturates. Yet another herbal remedy, khellin, extracted from *Ammi visnaga,* was a widely used Middle Eastern antispasmodic. The cromones sodium cromoglycate and nedocromil were modifications of this herbal remedy. Corticosteroids, the current cornerstone of asthma therapy, arrived on the scene relatively recently, having been available for a little over 50 years. Topically active corticosteroids have been available for inhalation therapy of asthma for almost 30 years now.

The five main classes of asthma drugs up to the late 1990s were all developed and modified from plant (ephedrine, atropine, theophylline, khellin) or animal (epinephrine, cortisone) sources. In the late 1990s, the first designer drugs for the management of asthma appeared in the form of various leukotriene modifiers, including lipoxygenase inhibitors and the more successful oral leukotriene receptor antagonists, such as montelukast. The currently available pharmaceutical armamentarium for the management of asthma is actually quite good. Appropriate and particularly early use of anti-inflammatory strategies (in addition to education and environmental control) is stressed by clinical practice guidelines.[4]

Nevertheless, numerous new pharmaceutical developments continue to be designed for asthma treatment, as summarized in a recent review.[5] Several of these pharmacotherapies have been developed using genetic recombinant technologies, including recombinant antibodies, interleukins (ILs), IL receptors, and IL receptor blockers. This review article covers several of these recombinant therapies, which involve immunoglobulin (Ig)E, IL-4, IL-5, IL-12, and lymphocytes. These exciting new agents provide potentially new therapeutic options for asthma and valuable tools for investigation of mechanisms in asthma.

Immunoglobulin E

Background

IgE antibody was identified as the cause of atopic sensitization and atopic allergic reactions about 35 years ago.[6] In the last 25 years, laboratory investigations identifying allergen inhalation as a cause of both airway hyperresponsiveness[7] and airway inflammation[8] have allowed the reclassification of allergens as important inducers of asthma.[9] This information has been supplemented by numerous epidemiologic studies, which now confirm that atopy is the most important single risk factor for the development of asthma,[10–12] and, thus, that IgE-mediated allergic airway inflammation is the most important *cause* of asthma. It is therefore logical to direct therapeutic strategies towards this end. Indeed, environmental control, where possible, is one of the cornerstones of asthma therapy and, for a single and completely avoidable allergen or sensitizer, such as in the occupational setting, can, in fact, be curative.[13] Sodium cromoglycate probably has its major effect in chronic asthma management as a prophylactically anti-inflammatory asthma therapy by preventing all aspects of the allergen-induced asthmatic response.[14] A number of approaches are available to address IgE and its interaction with effector cells. At this point, the most promising therapy, and that nearest marketing, is a monoclonal anti-IgE antibody, omalizumab (Xolair).

Anti-IgE Development

The development of anti-IgE antibodies is briefly outlined as a general background to the preparation of such agents. Initially, a series of clonal murine IgG antibodies directed against human IgE were developed. The clone demonstrating the ideal characteristics, namely reacting with or at least hiding the Fc component of the IgE molecule (ie, that area of the molecule that binds with the Fcε receptor on mast cells), was selected. The majority (about 95%) of this murine IgG antibody was then replaced with human IgG, leaving only a small amount of the antibody-specific variable area of the antibody as murine in origin.[15] The twenty-fifth antibody in the series, recombinant humanized murine monoclonal antibody E25 (rhuMAb-E25 [E25 for short], omalizumab, Xolair) had the desired characteristics, which included good tolerability, a reduction in free serum IgE to undetectable levels, inhibition of allergic reactions, a lack of mast cell degranulation (unlike polyclonal anti-IgE, which serves as a model to mimic allergic reactions), and a lack of immunogenicity (the latter the result of the 95% humanization).[16] Additionally, Fcε receptors are up-regulated in the presence of high serum IgE and down-regulated in the presence of low serum IgE[17]; therefore, omalizumab results in reduction in Fcε receptors, which may lead to reduced IgE synthesis[16]; this may allow at least the possibility of being able to lower the effective dose of omalizumab.

Laboratory Studies

The allergen challenge model is a useful method to study asthma pharmaceutical agents.[18] This would be particularly true for an agent designed to prevent IgE-mediated airway allergic responses. Omalizumab administered intravenously at a standard dose of 0.5 mg/kg/wk proved to be very effective in inhibition of the early asthmatic response (EAR) and the late asthmatic response (LAR).[19,20] Fahy and colleagues demonstrated a 63% reduction of the allergen-induced LAR after 10 weeks of intravenous therapy of omalizumab 0.5 mg/kg/wk.[19] The results are even more impressive when one takes into account that subjects receiving omalizumab actually received approximately twice as much allergen post-treatment as did those who received placebo. The second allergen challenge study involved an EAR model with the EAR reported as the allergen PC_{15}. The advantages of this model are that it allows study in a larger number of subjects and studies in subjects who are less severe and consequently more stable, and it allows better quantitation of therapeutic effect, particularly where the therapeutic effect is large. The disadvantage of this model is the inability to study the more important late consequences, including the LAR, allergen-induced increase in airway responsiveness, and allergen-induced airway inflammation. We demonstrated a marked and early shift of the allergen PC_{15} as early as 4 weeks.[20] After 10 weeks of treatment with 1 mg/kg for 2 weeks (the same total dose used in the Fahy and colleagues' study[19] but administered every 2 weeks), there was a 6.5-fold improvement in allergen PC_{15}.[20] In both allergen challenge studies, the drug was well tolerated, with the only important event being a single episode of first-dose urticaria, which is occasionally seen and does not recur on repeat exposure. No antiomalizumab antibodies developed. We observed that those subjects who were not protected against the antigen challenge were those in whom free serum IgE was not completely reduced to undetectable levels. Subsequently, studies have dosed E25 based not only on weight but also on total baseline serum IgE levels.[21] A third study investigated nebulized omalizumab in high dose (10 mg/d) and moderate dose (1 mg/d) for 8 weeks. Nebulized omalizumab had no effect on serum IgE levels and no effect on allergen challenge.[21] There was a single case of antiomalizumab antibodies developing via the inhaled route.

Clinical Studies

An early clinical study in ragweed allergic rhinitis served primarily to underscore the need for adequate omalizumab dosing based on serum IgE.[22] The first clinical asthma study examined two doses, 2.5 μg and 5.8 μg/kg/ng IgE, administered intravenously at two-weekly intervals.[23] There was improvement in lung function and symptoms in the active groups and, after

12 weeks, subjects on active therapy were able to reduce their corticosteroids by a larger amount than were those on placebo. These results were interpreted very optimistically. Recently, two large omalizumab trials of apparently identical design have been reported.[24,25] These parallel studies have involved more than 500 subjects receiving omalizumab compared with approximately the same number on placebo. The active patients received omalizumab 0.016 mg/kg IgE (IU/mL) every 4 weeks administered subcutaneously with doses administered every 2 or 4 weeks depending on the volume. During the 16-week steroid-stable phase, these asthmatic subjects, with a mean duration of asthma over 20 years, demonstrated reduced exacerbations, reduced symptoms, and improved lung function. In the subsequent corticosteroid reduction phase, over the next 12 weeks, the subjects on omalizumab were able to reduce their inhaled corticosteroids by a larger amount than were those on placebo. In all studies, omalizumab has been well tolerated, and there have been no instances of the development of antiomalizumab antibodies in any subject receiving parenteral omalizumab.

Hypothesis

Omalizumab has demonstrated statistically significant and clinically relevant improvement in allergic asthma in several studies. The marked success of omalizumab in the bronchoprovocation studies, however, suggested that omalizumab might have worked even better.

There are increasing data to support the view that early use of anti-inflammatory therapeutic strategies may improve the natural history of asthma. It was first shown that the late introduction of corticosteroids, even in a survival population treated with β_2 agonist alone for the first 2 years of asthma, did not allow catch-up to those individuals who started on corticosteroids early.[26] This has been confirmed by other studies.[27] This issue related to early therapy is likely more relevant for prophylactic anti-inflammatory therapies such as environmental control, as has been best demonstrated with occupational asthma in which early environmental control frequently resulted in a cure, whereas delayed environmental control, although helpful, was associated with persistent asthma airway hyperresponsiveness and airway inflammation.[13] The anti-inflammatory effects of omalizumab should be, to a large extent (perhaps completely), analogous to environmental control. One could hypothesize that omalizumab might be particularly effective, therefore, when introduced early in subjects with allergic asthma. This testable hypothesis would require studies of omalizumab targeting children and adolescents with recent-onset atopic asthma.

Interleukin-4

Background

IL-4 is regarded as the most important cytokine underlying the development of the allergic type of inflammation by a number of mechanisms, including IgE production, up-regulation of Fcε receptors, induction of adhesion molecules, and differentiation of lymphocytes towards the T helper 2 (Th2) phenotype, which favours maintenance of the allergic type of airway inflammation.[28] Therapeutic strategies designed to block the effect of IL-4 should therefore be effective in asthma and other atopic allergic disorders. Recombinant pharmaceutical agents targeting IL-4 include soluble IL-4 receptor (IL-4R),[29] an IL-4/13 receptor blocker,[30] and anti–IL-4 antibodies.[31] All of these are in various stages of investigation. Soluble IL-4R, effective in a murine allergen challenge model,[29] has the most reported data in humans.

Soluble IL-4R

Recombinant soluble IL-4R is a relatively low-molecular-weight protein representing the extracellular component of the cell membrane IL-4R. Soluble IL-4R reduces the effect of IL-4 in tissues by competing with membrane-bound IL-4Rs, thus reducing the biologic activity of IL-4. There are two clinical studies in humans in which nebulized IL-4 was shown to have some effect.[32,33] In a preliminary small placebo-controlled study,[32] two different doses of nebulized IL-4R (500 and 1,500 μg) were administered in a single dose on day 1. Inhaled corticosteroids were stopped on day 0, and the subjects were followed closely. The drug was well

tolerated; this was primarily a safety study. No antibodies developed. The nine subjects receiving the high dose of IL-4 demonstrated stable symptoms, quality of life, and lung function compared with significant deterioration in the eight subjects receiving placebo and the eight subjects receiving the low dose. A subsequent double-blind, placebo-controlled, dose-ranging study was carried out over 12 weeks assessing weekly nebulized doses of 750, 1,500 and 3,000 μg in approximately 15 subjects each.[33] All subjects were demonstrated to be dependent on inhaled corticosteroids, which were stopped abruptly at the beginning of the trial. Once again, efficacy was demonstrated for soluble IL-4R, particularly in the highest-dose group, who demonstrated less decline in lung function, less increase in symptoms, and less requirement for rescue medications. IL-4R was demonstrated to be safe, although one subject in this study did develop non-neutralizing antibodies to IL-4R.[33] Much as was hypothesized for omalizumab, the maximum benefit from this (or any other anti-IL-4) strategy should occur with early use.

Interleukin-5

Airway eosinophilia is a ubiquitous feature in asthma, and eosinophil levels correlate with disease activity. Airway eosinophilia, along with the LAR and airway hyperresponsiveness, can be induced by exposure to allergen.[7,8] Eosinophilia, LARs, and airway hyperresponsiveness are all inhibited by inhaled corticosteroids.[34] Consequently, it has been assumed that airway hyperresponsiveness and the LAR may somehow be caused by the eosinophilia or other airway inflammatory cells. IL-5 is the major cytokine responsible for the differentiation and production of eosinophils.[35] Consequently, IL-5 has become a potential target for new asthma therapies.

There is one double-blind, randomized, placebo-controlled study in which two different single doses of intravenous humanized anti–IL-5 antibody (2.5 and 10 mg/kg) were compared with placebo.[36] The eight subjects with asthma in each group were then followed for 16 weeks. As expected, there was a marked effect on both blood and sputum eosinophils. The suppressive effect was greater and longer lasting for the high dose. The anti-IL-5 antibody suppressed allergen-induced eosinophilia in allergen challenges done 9 and 30 days after the dose. There was no effect, however, on airway responsiveness to histamine, the allergen-induced EAR, the allergen-induced LAR, or the allergen-induced increase in airway responsiveness to histamine. Although this parallel study was not adequately powered to detect small differences in allergen-induced airway responses, examination of the data confirms that there was not even a trend for a difference.

These results have been interpreted as surprising by many. They provide convincing evidence that airway eosinophilia and airway hyperresponsiveness may not be as closely linked as had been previously assumed. This is one way in which these new recombinant therapies have given us some remarkable and unsuspected insight into mechanisms. This, of course, raises important questions as to the relevance of eosinophils in the pathogenesis of clinical asthma. Further studies with this novel therapy, if pursued, may provide valuable answers.

Interleukin-12

IL-12 is a cytokine involved in the Th1-Th2 balance. IL-12 has been reported to favour the Th1 as opposed to the Th2 phenotype. IL-12 is effective in animal allergen challenge models in inhibiting airway eosinophilia and airway hyperresponsiveness.[37]

Recombinant IL-12 was administered subcutaneously in increasing doses (0.1, 0.25, and 0.5 μg/kg) weekly in 19 individuals compared with placebo in 20 individuals.[38] IL-12, like anti-IL-5, had a profound effect on eosinophils but no effect on airway responsiveness or the allergen-induced LAR. There was a marked reduction in blood and sputum eosinophilia and a reduction in the magnitude of allergen-induced eosinophilia. IL-12 does not appear to have been terribly well tolerated because flu-like symptoms were reported in the majority of individuals.

Lymphocytes

Lymphocytes play an important role in the pathogenesis of allergic inflammation. Efalizumab is a humanized murine monoclonal antibody directed against CD11a. This antibody interferes with lymphocyte integrin 1 and intercellular adhesion molecule and blocks T-lymphocyte activation and trafficking.[39] Efalizumab is effective in the treatment of psoriasis.[40] Efalizumab was investigated in the human allergen challenge model in a double-blind, parallel study with 2:1 randomization active:placebo and 2:1 randomization dual asthmatic:early asthmatic responders. After a conditioning dose, seven weekly doses of 2 mg/kg were administered subcutaneously. Allergen challenges were done before and 4 and 8 weeks after starting treatment. The allergen-induced EAR was not affected. There was a reduction in the allergen-induced LAR expressed as the maximum percent fall in forced expiratory volume in 1 second ($p = .09$) and the area under the curve ($p = .06$) when compared with placebo.[41] In a subset of patients, we did demonstrate a significant ($p < .05$) reduction in allergen-induced sputum eosinophilia.[41] There was a significant prevalence of flu-like syndromes with early dosing. Although not severe, this drug was not as well tolerated as, for example, omalizumab.

The trend towards inhibition of the allergen-induced LAR and the definite reduction in eosinophils points to the importance of lymphocytes and the pathogenesis of the clinically important late allergen-induced sequelae. This is another example of the value of these new recombinant medications in further clarifying mechanisms of allergen-induced asthma. The potential role of efalizumab in the therapy of asthma remains to be determined.

Conclusion

Recombinant therapies that inhibit IgE, which inhibit (IL-4, IL-5) or mimic (IL-12) ILs and which block lymphocyte trafficking, are currently being investigated in asthma. Undoubtedly, other recombinant approaches are in developmental stages. These exciting new agents hold promise for the treatment of asthma and provide valuable tools for the understanding of mechanisms in asthma.

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