

## Recombinant Products Show Promise in Treating Asthma

### IL-4R Treats the Cycle of Inflammation-Obstruction in Asthma



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When inflammatory cells infiltrate lung airways—and lead to epithelial disruption and mucosal edema—those airways become obstructed. It is this obstruction that directly results in the classic clinical symptoms of asthma: shortness of breath, chest tightness, labored breath-

ing and wheezing, increased sputum production and coughing, and feelings of suffocation. In addition, the initial inflammatory events also contribute to airway hyperresponsiveness. These inflammatory mechanisms then become intensified and perpetuate when other stimuli, such as common viral respiratory infections, air pollution, cigarette smoke or allergens, are present. This intensification results in a cyclic pattern of further airway inflammation and obstruction. At the same time, the asthma symptoms themselves can complicate the clinical picture by varying in severity, frequency and duration.

While both intrinsic and extrinsic causes of asthma are thought to exist, the role of allergens in triggering the inflammatory cycle has been well documented. Inhaled allergens are known to cause immediate obstructive reactions in the airways, as well as late bronchial obstruction. Research efforts have focused on the types of inflammatory cells found in the airways of asthma

patients, such as mast cells and eosinophils, whose products account for the abnormalities noted above.

### Asthma Treatment to Date: Countering Inflammation and Obstruction

Current asthma therapies counter the negative effects of inflammation-induced obstruction by reducing triggers and contributing factors such as sinusitis and gastric reflux. Pharmacologic management—with inhaled beta adrenergics that relax smooth muscle to open the airways—also forms a significant part of current asthmatic regimens. Other agents, such as cromolyn sodium, have been helpful in controlling airway hyperresponsiveness or “twitchiness.” Inhaled steroids make up the final step in typical therapies, as they reduce inflammation and thereby increase the effectiveness of the other medications.

### The Role of Interleukin-4 (IL-4) and IL-4R

Researchers have long examined the presence of T lymphocytes (T cells) and IgE production in asthma patients, because these T cells play a primary role in the inflammatory response. Previous studies have established interleukin-4 (IL-4)—a human protein for which T cells have a receptor—as a critical component in the development of allergic inflammation in asthma. The soluble recombinant human IL-4 receptor (IL-



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4R) has the ability to inhibit changes that lead to the inflammatory reaction in the T cells. IL-4R operates by binding the IL-4 before it can bind to the T cells and trigger those cells' immune response. In an effort to interrupt this underlying mechanism of asthma symptoms, researchers at the National Jewish Medical and Research Center have completed a pilot study of nebulized IL-4R. "All of the new understanding we have about the underlying mechanisms of asthma are now beginning to pay off," reports Harold Nelson, M.D., one of the study's investigators.

## The Pilot Study:

### A Unique Combination of Methods

The "Recombinant Human Interleukin-4 Receptor in Moderate Atopic Asthma" was a randomized, double-blind, placebo-controlled pilot study involving two unique methods. First, given the well-demonstrated efficacy of inhaled medications, the study, supported by a grant from the Immunex Corporation, was the first human study to use inhaled IL-4R. Second, while standard baseline tests were recorded, measurement of exhaled nitric oxide was used as a marker of inflammation. "This is considered 'cutting edge' in itself," comments Dr. Nelson. "This [test] is in response to the need for ways to measure the inflammatory process present in airways. Previously, inflammation could only be measured directly through biopsy or washing the airways during bronchoscopy...Exhaled nitric oxide is quite new."

With these two procedures available, 25 patients with moderate asthma requiring 4 to 8 puffs of inhaled corticosteroids per day were randomly assigned to receive a single dose of IL-4R 1500 µg, IL-4R 500 µg, or placebo. The study actually took place over a 29 day period, with a 10 day pre-study phase followed by the administration of IL-4R by nebulizer on Day 1. Because their corticosteroids were stopped the day of administration of the study drug, patients were closely monitored and carefully managed.

Although the intent was to evaluate safety of a single nebulized dose of IL-4R, there were secondary evaluations of the effect of IL-4R on spirometric measures, asthma symptoms, airway inflammation (the exhaled nitric oxide) and quality of life.

Measurements of total and specific IgE, anti-inflammatory studies and the Asthma Quality of Life Questionnaire were administered on designated days.

## The Future of Inhaled IL-4R

Patients in the pilot study tolerated IL-4R well and experienced no significant toxicity, respiratory complaints or spirometric compromise. A single dose of IL-4R appeared to be safe in moderate asthma, with the nebulizer offering practical administration. The data also indicated that the 1500 µg dose was just as safe as, but significantly more effective than, the 500 µg dose. Researchers based these conclusions on improved spirometric measurements—including FEV<sub>1</sub> (Figure 1), FEF<sub>25-75</sub> (Figure 2) and exhaled nitric oxide scores (Figure 3)—and patients' reports of significantly improved asthma symptoms and reduced use of beta agonists. "This is an interesting drug that has the promise of truly being exciting," notes study investigator Larry Borish, M.D., as it is conceivable that more prolonged therapy might provide long-term relief of symptoms. Because IL-4R has a prolonged half-life, study investigator Dr. Borish suggests, "there are indications that once a week therapy would be feasible. Weekly therapy could enhance patient compliance if it were administered at home. Or, it could be administered in the physician's office, considering that many asthma patients, as well as other allergic individuals, already make weekly visits for immunotherapy injections."

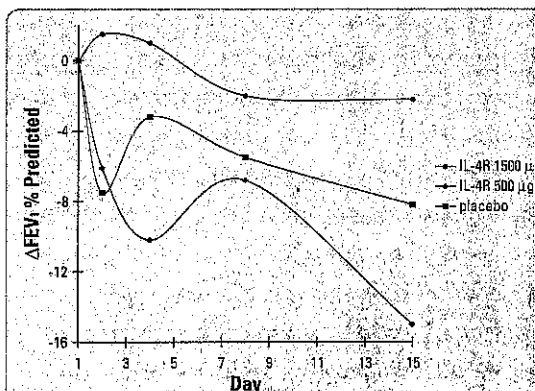


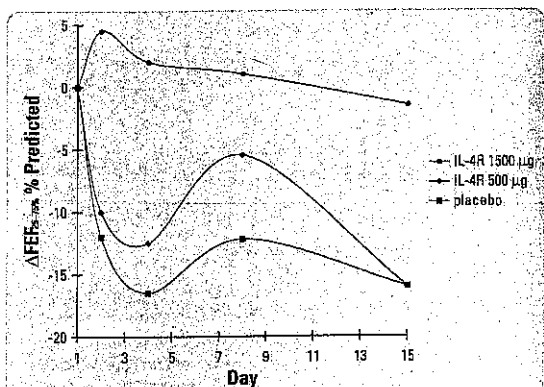
Figure 1. Percent of Predicted Forced Expiratory Volume in One Second (FEV<sub>1</sub>) change from baseline. Through Week 2, FEV<sub>1</sub> was at least maintained at baseline levels following acute discontinuation of inhaled corticosteroids with IL-4R 1500 µg while steady declines in FEV<sub>1</sub> were seen with IL-4R 500 µg and placebo. On Day 4, the difference between the IL-4R 1500 µg group and the placebo group was statistically significant (P = 0.048). At two hours and on Days 2 and 15, the differences between the IL-4R 1500 µg and 500 µg groups were statistically significant (P = 0.008 for each time point).

## A New Study of the Effects of rhuMAb-E25 on Allergic Asthma

Based on epidemiologic studies, IgE-driven allergic reactions cause much asthma, but particularly in children. The anti-IgE recombinant humanized monoclonal antibody rhuMAb-E25 may interrupt such allergic responses in allergic asthma patients. rhuMAb-E25 could accomplish this task by reducing the concentration of free IgE antibody in the bloodstream. To date, however, there have been no definitive studies to indicate the extent to which patients' symptoms can be relieved if IgE is removed in this manner. In theory, it also is possible that symptoms due to a specific allergen, such as cat, could be essentially eliminated.

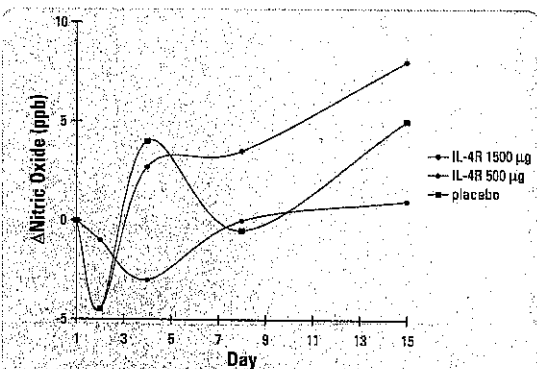
To begin to understand the practical application of rhuMAb-E25 in asthma treatment, researchers at the National Jewish Medical and Research Center are now enrolling adolescents and adults with moderate to severe allergic asthma in a new 12-month multicenter study. While researchers hope to see a reduction in asthma symptoms, especially the number of exacerbations, they will also examine the pharmacokinetic and pharmacodynamic effects of this recombinant product, including long-term safety and tolerability. The study includes measures of the use of rescue medication, as well as lung function and quality of life. "It will be over a year before results are available to meet these study objectives," says principal investigator, Harold Nelson, M.D.

Because rhuMAb-E25 operates by removing IgE from the bloodstream, Dr. Nelson explains, "[the antibody] has to be injected and the frequency of injections is dependent upon individual patient levels of IgE." Because rhuMAb-E25 does not remove IgE from mast cells on which it is carried, it will take several months to optimally reduce symptoms." Therefore, Dr. Nelson concludes, "it's not three shots and you're cured for the rest of your life."



**Figure 2.** Percent of Predicted Forced Expiratory Flow at 25 to 75% of Forced Vital Capacity (FEF<sub>25-75%</sub>): change from baseline. Through Week 2, FEF<sub>25-75%</sub> was improved from baseline levels with IL-4R 1500 µg while steady declines were seen with IL-4R 500 µg and placebo. On Days 2 and 4, the differences between the IL-4R 1500 µg and placebo groups were statistically significant (P = 0.014 for each time point). At two hours and on Days 2 and 4, the differences between the IL-4R 1500 µg and 500 µg groups (P = 0.011, P = 0.008 and P = 0.048, respectively) were statistically significant.

The findings suggest that IL-4R could be equally effective in patients with non-allergic forms of asthma. Other atopic disorders, such as allergic rhinitis and atopic dermatitis, may also respond. Both Drs. Nelson and Borish confirm that further studies are warranted and they anticipate large scale studies, including multiple doses and trials in children. Dr. Nelson states, "we are now discovering drugs that are designed to interrupt the mechanisms that cause asthma, not just counter the effects." Dr. Borish is equally enthusiastic: "This is the first drug that has a real crack at using biotechnology to treat asthma [or,] if we're really lucky, a course of therapy to eliminate asthma."



**Figure 3.** Exhaled Nitric Oxide: change from baseline. Through Week 2, exhaled nitric oxide levels (ppb) appeared to decrease relative to baseline in the IL-4R 1500 µg group. On Day 4, the difference between the IL-4R 1500 µg group and the placebo group was statistically significant (P = 0.026).

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