Allergic asthma and an anti-CD23 mAb (IDEC-152): Results of a phase I, single-dose, dose-escalating clinical trial

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Background: CD23, a cell-surface molecule, is involved in a variety of pathways likely to influence IgE production and inflammation in allergic disorders, such as allergic rhinitis and allergic asthma.

Objective: This study investigated the safety, clinical activity, and pharmacokinetic profile of IDEC-152, an IgG1 anti-CD23 antibody, in patients with mild-to-moderate persistent allergic asthma.

Methods: This single-dose, dose-escalating, placebo-controlled study involved 30 patients. Cohorts of 3 to 6 patients received single intravenous infusions of either placebo or IDEC-152 (0.05, 0.25, 1.0, 4.0, 10.0, or 15.0 mg/kg) on study day 1. Safety, clinical activity, and pharmacokinetics were assessed for 12 weeks after treatment.

Results: IDEC-152 was well tolerated. Adverse events (AEs) were mild, no grade 4 or serious AEs were reported, and no relationships were apparent between the dose of IDEC-152 and the frequency, severity, or type of event. The most common AEs in the IDEC-152 group included ecchymosis at the injection site, sinusitis, headache, arthralgia, cold syndrome, infection, throat irritation, and dysmenorrhea. Commonly reported AEs in the placebo group included headache, abdominal pain, and infection. Sustained and dose-dependent decreases in mean IgE concentrations were noted. The mean maximum concentration and area under the curve of IDEC-152 were proportional to the dose administered for the dose range 4.0 to 15.0 mg/kg. The serum half-life of the IDEC-152 antibody increased from 2 to 10 days with increasing doses. After single-dose administration of IDEC-152, no dose-dependent change in FEV1 was observed, and most changes in peak expiratory flow rate were within 10% of baseline values.

Conclusion: These data suggest that IDEC-152 is safe and has the potential for clinical activity in allergic asthma. (J Allergy Clin Immunol 2003;112:563-70.)

Key words: Allergy, asthma, B cells, CD23, IDEC-152, IgE, monoclonal antibody

Abbreviations used

AE: Adverse event
AUC: Area under the curve
Cmax: Maximum concentration
ICS: Inhaled corticosteroid
PEFR: Peak expiratory flow rate

Allergen-induced IgE synthesis is a central feature of allergic disorders. Subsequent interactions between IgE and allergen through a variety of mechanisms are directly related to allergy-associated symptoms. IgE production is regulated by CD23, a cell-surface molecule with a variety of activities.1-3 Also known as the low-affinity receptor for IgE (FcεRII),4 CD23 is a 45-kd C-type lectin that binds IgE, is expressed as a membrane receptor (mCD23) on several hematopoietic cell types5-10 and airway smooth muscle.11 and can be cleaved to a soluble receptor (sCD23) with possible cytokine properties. Other important activities of CD23 include presenting IgE-bound antigen to Tγδ2 cells.12,14 CD23 expression on antigen-presenting cells, such as dendritic cells and macrophages, might also play a biologic role in allergic inflammation. Activation of these cells by allergen-loaded IgE through the CD23 molecule can lead to production of pro-inflammatory cytokines, such as IL-1, IL-6, and TNF-α.15-18

The use of an anti-CD23 antibody can affect multiple aspects of allergic disorders. Several in vitro studies have demonstrated that cross-linking of mCD23 downregulates IgE synthesis.19-21 Thus an anti-CD23 antibody that crosslinks mCD23 might decrease the production of IgE, thereby lowering the serum concentration of the Ig. Interfering with CD23-mediated IgE-dependent antigen presentation to Tγδ2 cells could also reduce the immunologic response to allergens and decrease IgE synthesis by preventing class switching of B cells. In addition, anti-CD23 treatment could inhibit CD23-bearing B cells, macrophages, and dendritic cells from producing cytokines. Direct effects of anti-CD23 on airway smooth muscle cells are also possible. Consistent with these observations, the use of anti-CD23 mAbs in murine asthma models results in the suppression of lung eosinophil infiltration and reduction of airway hyperresponsiveness.22-26 On the basis of these observations, it is possible that CD23 antagonists, such as anti-CD23 antibodies, could be useful in the treatment of allergic rhinitis and allergic asthma.
This study assesses the safety, pharmacokinetic profile, and preliminary clinical activity of IDEC-152 for use in patients with mild-to-moderate persistent allergic asthma. IDEC-152 is designed to be structurally indistinguishable from human antibodies to prevent immune system rejection, the consequences of which could include decreased efficacy and increased allergic reaction. IDEC-152 is constructed as a PRIMATIZED (IDEC Pharmaceuticals, San Diego, Calif), IgG1, anti-CD23 mAb consisting of primate (cynomolgus macaque) variable regions and human constant regions to accomplish this. IDEC-152 has been shown to block synthesis of IgE from human B cells in vitro. A related antibody has been shown to prevent Ig class switching by inhibiting IL-4–stimulated germline Cε transcription and, consequently, total IgE production.

METHODS

Subjects

Eligible patients of at least 18 years of age were required to have an FEV1 of 60% to 90% of predicted normal value and a positive skin prick test response to at least one allergen, and, if taking long-term control medication, the dose was to have been stable for 30 days before treatment. Patients using leukotriene antagonists or inhibitors, methylxanthines, or inhaled corticosteroid (ICS) at doses greater than 800 µg of beclomethasone per day or an equivalent dose of other ICSs were excluded from enrollment. In addition, patients were excluded if they had a hospital admission or emergency department visit for asthma treatment within 4 weeks, had a respiratory infection within 4 weeks, smoked within 2 years, or had a significant pulmonary condition or disease other than asthma. All patients were required to provide written informed consent, and each participating clinical site had to obtain institutional review board approval to conduct this study.

Study design

This placebo-controlled, single-dose, sequential, dose-escalating study was conducted at 2 investigative centers in the United States. All patients, who were blinded to study treatment, received study medication (IDEC-152 or placebo) and completed a 12-week follow-up period, during which time they had 5 visits. Cohorts of 3 to 6 patients were treated with a single intravenous infusion of either placebo or IDEC-152 (0.05, 0.25, 1.0, 4.0, 10.0, or 15.0 mg/kg). The antibody was prepared according to methods described previously.

Study procedures

Safety evaluations included examination of clinical adverse events (AEs), hematologic and blood chemistry laboratory results, peripheral blood lymphocyte subpopulations, and serum concentrations of IDEC-152 and anti-IDEC-152 antibody. Toxicity was evaluated according to the National Cancer Institute Adult Toxicity Criteria (version 2.0). All AEs reported by the patient or observed by the investigator were collected from the case report form in predefined categories. An AE was defined as any adverse change from the patient’s baseline condition, irrespective of whether it was considered related to treatment. Peripheral blood lymphocyte subpopulations were monitored by using flow cytometry, and serum concentrations of IDEC-152 and anti-IDEC-152 antibodies were measured at IDEC Pharmaceuticals.

Pharmacokinetic analysis of IDEC-152 included calculation of the following parameters: the maximum concentration (C_max) was the observed value; the area under the curve (AUC) was calculated by using the linear-logarithmic trapezoidal method with time extrapolated to infinity; and serum half-life, clearance, and volume of distribution were determined by using noncompartmental linear regression. Data were to include all samples with detectable IDEC-152 concentrations (>8 µg/mL) obtained after study day 1 (ie, 24 hours after treatment).

Total serum IgE concentrations were monitored throughout the study at IDEC Pharmaceuticals by means of immunoassay with a UNICAP instrument. Assessment of a variety of clinical parameters were performed as an adjunct in this single-dose safety study, including FEV1, morning peak expiratory flow rate (PEFR), asthma and rhinitis symptom scores, nighttime awakenings caused by asthma, and use of on-demand β-agonists and asthma medications. Before FEV1 and PEFR measurements, use of inhaled β-agonists and ICS was proscribed for 6 hours, and use of long-acting β-agonists was proscribed for 24 hours. Patients were provided with diaries in which to record the severity of asthma (wheeze, shortness of breath, cough, chest tightness, and nighttime awakenings) and rhinitis (watery eyes, nasal congestion, sneezing, itchy nose, and runny nose) symptoms, nighttime awakenings, and use of on-demand β-agonists and asthma medications.

Clinical and safety assessments were performed, and pharmacokinetic samples were collected at baseline and on study days 2, 8, 15, 29, 57, and 85.

Statistical methods

Data presentation and statistical analyses were prepared by using the SAS software package, version 6.12. The sample size calculation was based on safety considerations: with a sample size of 24 patients, the study would be sensitive enough to detect AE rates of 3% or greater for the combined dose groups and 15% or greater for an individual dose group. Clinical activity analyses included all patients completing the infusion of IDEC-152 and having at least the study day 29 posttreatment evaluation. For all clinical activity measures, results were summarized through descriptive statistics. Individual data, means of raw data, and the mean change from baseline for variables were determined and plotted separately for each dose. The safety analysis included any patient who began an infusion. Summary descriptive statistics for laboratory data were analyzed, and abnormal laboratory findings (ie, those falling outside the appropriate normal range) were compared with the baseline (study day 1 before infusion) value. The incidence and frequency of all AEs observed during the study were summarized. Graphs were generated to explore any relationship between doses and safety variables.

RESULTS

Patients

Twenty-four patients receiving IDEC-152 and 6 patients receiving placebo were treated at 2 study sites. Patient characteristics (Table I) were similar among dose groups: patients were predominantly white (88% of patients receiving IDEC-152; 100% of patients receiving placebo); there was no bias as to sex (58% of patients receiving IDEC-152 and 50% of patients receiving placebo were female); and the median age was 39.5 years (range, 19.0-63.0 years) for patients receiving IDEC-152 and 48.0 years (range, 21.0-57.0 years) for patients receiving placebo. Median time from initial diagnosis to study entry was approximately 22.5 years and ranged from 1 year to 54 years in patients receiving IDEC-152 and 2 to 53 years in patients receiving placebo. Patients had abnormal spirometry results at baseline, with a mean...
FEV\textsubscript{1} of 78% ± 8% for patients receiving IDEC-152 and 77% ± 11% for patients receiving placebo. Each patient received a single intravenous infusion of placebo or IDEC-152 at 0.05, 0.25, 1.0, 4.0, 10.0, or 15.0 mg/kg. No patient discontinued treatment or required dose reduction. All patients completed the trial and were evaluable for safety and efficacy analyses.

**Safety**

AEs were primarily mild and transient; the incidence (>10% of patients receiving either IDEC-152 or placebo) is listed in Table II. The overall incidence of AEs was similar between treatment groups: 36 AEs were reported in 17 (70.8%) of 24 patients receiving IDEC-152, and 28 AEs were reported in 4 (66.7%) of 6 patients receiving placebo. No relationship was apparent between IDEC-152 dose and either the frequency or severity of AEs, and no grade 4 or serious AEs were reported in patients receiving either IDEC-152 or placebo. One patient receiving IDEC-152 (1.0 mg/kg dose group) with sinusitis experienced an unrelated grade 3 allergic reaction to amoxicillin on study day 71; the patient recovered with...
medication and was not hospitalized. Through a clinical review of the data, 10 (41.7%) patients receiving IDEC-152 and 3 (50.0%) patients receiving placebo were identified as having infections; all infections were grade 1 or 2, and none were considered study related in either treatment group. Infections were predominantly respiratory: among patients receiving IDEC-152, 3 patients had sinusitis, 2 had cold syndrome, and 1 each had bronchitis, pneumonia, otitis media, upper respiratory infection, and viral infection; among patients receiving placebo, 1 patient had an upper respiratory infection, 1 had cold syndrome, and 1 had a head cold, bronchitis, and sinusitis. No cytokine-mediated or infusion-related syndrome was apparent, and no patient had an anti-IDEC-152 antibody response.

Pharmacologic effect on IgE concentration

A dose-dependent decrease in mean IgE values was noted (Fig 1). For all patients receiving IDEC-152, mean IgE concentration began to decrease by study day 8, decreasing 30.4% from baseline by study day 57 and returning to 24.5% less than baseline by study day 85. For patients receiving the lowest dose (0.05 mg/kg), mean IgE concentration began to decrease by study day 2, decreasing 15.1% from baseline by study day 8 and remaining 2.4% less than baseline on study day 85. For patients receiving the highest dose (15 mg/kg), mean IgE concentration began to decrease by study day 8, decreasing 39.2% less than baseline by study day 85. IgE concentrations in the placebo group ranged from 5.3% less than baseline to 10.4% greater than baseline over the course of the study.

Pharmacokinetics

The serum half-life of IDEC-152 ranged from 2 days in patients receiving 0.25 mg/kg IDEC-152 to 10 days in patients receiving either the 10.0 or 15.0 mg/kg dose. Mean $C_{\text{max}}$ was proportional to the dose administered for the dose range of 4.0 to 15.0 mg/kg and ranged from 171 ± 14.5 to 658 ± 56 mg/mL, respectively (Fig 2, A). A non-compartmental analysis of the serum level data yielded mean AUC values ranging from 38.1 µg·d·mL⁻¹ for patients receiving 0.25 mg/kg to 6261.6 µg·d·mL⁻¹ for patients receiving 15.0 mg/kg. The mean AUC was proportional to the dose administered for the dose range 4.0 to 15.0 mg/kg (Fig 2, B). No marked difference was noted in either clearance rate (median range, 2.7-6.2 mL·d⁻¹·kg⁻¹) or volume distribution (median range, 20.9-38.2 mL/kg).
among dose groups. Serum IDEC-152 concentration was less than the lower limit of detection (8 ng/mL) in the majority of samples from patients who received 0.05 mg/kg, and therefore $C_{\text{max}}$ was the only pharmacokinetic parameter determined for this dose group.

**Effect on lymphocyte subsets**

Mean counts for CD19+, CD3+, CD4+, and CD8+ cells were generally within normal ranges (Fig 3). Over the course of the study, mean B-cell count decreased from baseline in patients receiving the 3 higher doses of IDEC-152 (Fig 4); however, a clear dose response was not observed.

**Clinical activity**

No dose-dependent change in $\text{FEV}_1$ was observed (Fig 5), and most changes in $\text{PEFR}$ were within 10% of baseline values (data not shown). There were no apparent relationships between dose groups and the mean number of asthma or rhinitis symptom-free days per week, the number of nighttime awakenings caused by asthma, or the use of on-demand (rescue) $\beta$-agonist or asthma medication (data not shown). Variability was noted both within and between patients. Baseline variability could not be verified because baseline data were not obtained.

**DISCUSSION**

This was a phase I trial intended to evaluate the safety of the 152-01 antibody administered as a single dose. A favorable safety profile was observed in the 24 patients who received single doses of IDEC-152 (0.05-15.0 mg/kg). No significant toxicity was reported, and no relationships between the dose of IDEC-152 and the fre-
The infection rates were similar between patients treated with either IDEC-152 or placebo. Although 3 (12.5%) of 24 patients receiving IDEC-152 had ecchymosis at the injection site, these patients did not have abnormal platelet counts or bleeding times. The absence of a similar rate of ecchymosis in patients receiving placebo is most likely due to the small sample size of 6 patients.

Sustained and dose-dependent decreases in mean IgE concentrations were demonstrated in all IDEC-152 dose groups. Moreover, these decreases were sustained for longer periods of time with increasing doses of antibody. This reduction of serum IgE concentration after a single dose of IDEC-152 is consistent with preclinical data on the effects of anti-CD23 antibodies. CD23 is expressed on a fraction of normal B cells. Thus the slight reduction in B cells, as measured by CD19+ cell count, is consistent with the potential effects of an anti-CD23 antibody. A small and transient reduction in B-cell levels is likely to have no adverse effect and might even be beneficial if the reduction is due to specific elimination of B cells destined to produce IgE. The clinical significance of this B-cell reduction will be understood only in the context of multiple-dose studies.

Results showed that Cmax and AUC were proportional to the administered dose for the higher dose range, and half-life of IDEC-152 increased with increasing dose. These data demonstrate that a weekly or monthly dosing schedule will be feasible for multiple-dose studies. Experiments with an anti-IgE antibody demonstrate that patients are able to tolerate profound reduction in free IgE concentration without adverse effects. The overall encouraging safety results of this small trial suggest that more prolonged use of an anti-CD23 mAb might be well tolerated.
In this study baseline asthma medications were not modified, and patients were not required to demonstrate bronchodilator-induced FEV₁ reversibility before study entry. For these reasons, it is not surprising that clinical activity of single-dose administration of IDEC-152 was not observed. Taken together, these findings are consistent with a potential for clinical improvement when multiple doses of IDEC-152 are used. Long-term reduction of IgE concentrations through the use of an anti-CD23 mAb is likely to be beneficial in allergic asthma. Other mechanisms for potential improvement with anti-CD23 therapy also are possible. These would include reduction in cytokine production by targeting B cells, macrophages, and dendritic cells, as well as a direct effect on CD23-bearing airway smooth muscle cells.

On the basis of pharmacologic activity of a single dose of IDEC-152 and an overall favorable safety profile, multiple-dose studies are warranted. In addition to potentially more profound effects on IgE concentrations when multiple doses of IDEC-152 are used, the direct anti-inflammatory actions of an anti-CD23 mAb might contribute to clinical activity. The mechanism of action of an anti-CD23 mAb is clearly distinct from that of anti-IgE mAb. The favorable safety profile and reduction in serum IgE concentration indicate that targeting of CD23 by mAbs might provide a positive clinical effect in patients with allergic asthma.

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REFERENCES


