HuMax-CD4

A Fully Human Monoclonal Anti-CD4 Antibody for the Treatment of Psoriasis Vulgaris

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Background: Psoriasis is characterized by infiltration with mononuclear cells. Especially activated memory CD4+ T cells are critical in the pathogenesis. Interaction between the CD4 receptor and the major histocompatibility complex class II molecule is important for T-cell activation.

Objective: To test safety and efficacy of a fully human monoclonal anti-CD4 antibody (HuMax-CD4) in the treatment of psoriasis.

Design: Multicenter, double-blind, placebo-controlled, randomized clinical trial.

Patients: Eighty-five patients with moderate to severe psoriasis.

Interventions: Subcutaneous infusions of placebo or HuMax-CD4 at doses of 20, 80, 160, or 280 mg once weekly for 4 weeks.

Main Outcome Measures: Psoriasis Area and Severity Index (PASI), investigators' and patients' overall response assessment, adverse events, laboratory assessment including total T-cell and subtype counts, CD4 receptor occupancy, and interleukin 2 receptor levels.

Results: At week 7, mean PASI was reduced in all treatment groups (95% confidence intervals are in parentheses): placebo, 8% (−3% to 19%); 20 mg, 12% (−6% to 27%); 80 mg, 14% (−14% to 35%); 160 mg, 16% (−4% to 33%); and 280 mg, 24% (−10% to 48%). At the highest dose level, 6 (38%) of 16 patients obtained more than 25% reduction of PASI and 3 (19%) obtained more than 50% reduction of PASI. A dose-dependent decrease in total lymphocyte count was seen and was parallel to a dose-dependent decrease in CD4+ T cells. This decrease was due to a decrease in the memory subset, whereas the naive subset was affected to a minor degree. Four weeks of treatment with HuMax-CD4 was safe and well tolerated.

Conclusions: Treatment with HuMax-CD4 led to a moderate, not statistically significant reduction in PASI. The efficacy results obtained after only 4 weeks of treatment suggest that longer treatment would lead to even further reduction of PASI.

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SORIASIS VULGARIS is a chronic, hyperproliferative inflammatory skin disease affecting about 1% to 3% of the Western population. The psoriatic lesions may be confined to certain predilection areas or may involve most of the skin. In addition to the skin lesions, about 10% of the patients have arthritis. The histologic appearance of psoriasis is characterized by epidermal hyperplasia and infiltration with mononuclear cells, including activated T cells and monocytes. The immune system, especially the activated T cells, has long been suggested to play an essential role in the pathogenesis of psoriasis. Observations supporting this hypothesis are numerous and include (1) association with particular HLA types, like many other autoimmune diseases; (2) invasion of the skin by mononuclear cells, especially activated T cells preceding epidermal hyperplasia; (3) release of lymphokines from T-cell clones derived from psoriatic skin, which can change phenotype and function of normal keratinocytes to that seen in psoriasis; and (4) significant clinical improvement with drugs and new biopharmaceutical agents (denileukin diftitox, alefacept, infliximab, and etanercept) that primarily or only affect the immune system and especially activated T cells.

Most patients with psoriasis have mild disease, which can be controlled by topical treatment including local corticosteroids or vitamin D analogues. However, 10% to 20% of the patients have moderate to severe disease and require ultraviolet irradiation, photochemotherapy, or systemic immunosuppressive therapy. These
treatments all have well-known severe adverse effects limiting their long-term use, including systemic suppression of bone marrow, liver toxic effects, kidney toxic effects, or increased cancer risk. The knowledge of the important role of T cells in psoriasis, combined with the current development in biotechnology, allows for design of more selective therapeutics potentially more effective and less toxic than the systemic therapies currently in use.

Monoclonal antibodies (mAbs) are among the most frequently used biopharmaceutical agents. Advances in mAb technology have allowed for production of mAbs directed at a variety of relevant antigens, but the safety profile of mAbs has been compromised by immunogenicity due to murine components of the mAbs. Now, however, it is possible to produce fully human antibodies that are less, if at all, immunogenic.

HuMax-CD4 (Genmab A/S, Copenhagen, Denmark) is a fully human anti-CD4 mAb, isolated from transgenic mice as a hybridoma clone but subsequently expressed in Chinese hamster ovary cells. The antibody is specific for the CD4 receptor expressed on a subset of T cells and on monocytes. The antibody is designed to prevent the interaction between the CD4 receptor and the major histocompatibility complex class II molecule, thereby interfering with T-cell activation.

Lymphocytes present in psoriatic lesions are both CD4+ and CD8+ memory effector T cells. However, the dominating cells are CD4+ T cells.2 The importance of CD4+ T cells in the pathogenesis of psoriasis is demonstrated in a severely compromised immunodeficient mouse xenotransplant psoriasis model, where injection of CD4+ T cells, but not CD8+ T cells, results in psoriatic plaque formation.3,4 Previously, 1 blinded and 3 open studies using murine or humanized anti-CD4 mAbs have demonstrated efficacy in the treatment of psoriasis vulgaris. These findings led us to perform a double-blind, randomized, placebo-controlled trial of HuMax-CD4 monotherapy in patients with moderate to severe psoriasis.

METHODS

A phase 2 multicenter study of HuMax-CD4 was conducted in 85 patients with moderate to severe psoriasis vulgaris. The study was conducted at 7 different departments of dermatology in Denmark (Copenhagen County Hospital, Gentofte; County Hospital, Roskilde; Bispebjerg Hospital, Copenhagen; Odense University Hospital, Odense; and Aarhus University Hospital, Aarhus), England (Hope Hospital, University of Manchester), and Scotland (Ninewell Hospital, Dundee), and 1 private dermatology practice in Denmark (Aalborg Hudklinik, Aalborg). The study protocol was identical for all study sites and was approved by the human research ethics committees for each of the study sites. All patients gave written informed consent before inclusion in the study.

STUDY DESIGN

This was a double-blind, placebo-controlled, randomized, multicenter safety and efficacy study of HuMax-CD4 at doses of 20, 80, 160, and 280 mg for treatment of psoriasis vulgaris. Randomization was stratified by study site. Patients were given subcutaneous infusions of placebo or HuMax-CD4 once weekly for 4 weeks and were followed up for 12 weeks thereafter. Assessment of the primary end point was at week 7, 4 weeks after the last drug administration.

PATIENT POPULATION

Adult patients with moderate to severe, stable plaque psoriasis vulgaris were enrolled in the study. The patients were enrolled from January 10, 2001, until August 1, 2001. Enrolled patients had a Psoriasis Area and Severity Index (PASI) of 10 or greater at the screening visit and had not responded adequately to topical treatment. Patients were otherwise in good general health. Patients who had used systemic antipsoriatic treatment or UV radiation during the previous 4 weeks or topical antipsoriatic treatment during the previous 2 weeks were excluded from the study. Previous treatment with anti-CD4 mAbs and simultaneous participation or participation within the previous 4 weeks in any other study involving investigational drugs also excluded patients. Although not an exclusion criterion, no patients had received alfacetap before participation in the study. Concomitant use of topical or systemic (UV radiation, etretinate, methotrexate, sulfa-salazine, and cyclosporine) antipsoriatic treatment was not allowed during the study. The only allowed concomitant treatment was moisturizing cream, which was provided to all patients.

Patients were excluded from the study for any of the following reasons: primary or secondary immunodeficiency or known positive serologic findings for human immunodeficiency virus; known alcohol or other drug abuse; active autoimmune disease other than psoriasis vulgaris requiring therapy; psoriasis arthritis requiring systemic treatment except nonsteroidal anti-inflammatory drugs; past or current malignancy; poorly controlled hypertension; acute illness or infection; chronic infectious disease; clinically significant cardiac disease; history of cerebrovascular disease; seizure disorder; CD4+ T-cell count less than 350/µL; or clinically significant laboratory abnormality. Pregnant or breastfeeding women were not enrolled in the study, and women of childbearing potential were to use either contraceptive pills or an intrauterine device.

During the study, patients were withdrawn from further administration of HuMax-CD4 if their CD4+ T-cell count dropped below 150/µL.

RESPONSE CRITERIA

Primary efficacy end point was percentage reduction of PASI from baseline to week 7. The PASI is a composite index rating the extent of the body surface involved and the intensity of erythema, infiltration, and desquamation characterizing the patients’ psoriatic lesions. The index ranges from 0 (no psoriasis) to 72 (most severe disease).7,8 Other efficacy end points were patients obtaining a 50% or 25% reduction in PASI, assessed at each visit, and investigators’ and patients’ overall response assessment, considering both extent and severity of psoriasis, quantifying individual patients’ clinical psoriasis status as compared with the baseline situation. Patient and investigator used the same scale for the overall assessment. Clinical laboratory measures were assessed at screening (2 weeks before first drug administration), at baseline (immediately before first drug administration), and at weeks 1, 2, 3, 4, 5, 7, 11, and 15. Study drug was infused at the baseline visit and at weeks 1, 2, and 3 thereafter. Clinical assessments included physical examination, vital signs, PASI scoring, and investigators’ and patients’ overall response assessment.

At all visits, patients were asked about occurrence of adverse events. Blood was sampled for safety laboratory assess-
Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Placebo (n = 17)</th>
<th>20 mg (n = 17)</th>
<th>80 mg (n = 18)</th>
<th>160 mg (n = 17)</th>
<th>280 mg (n = 16)</th>
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<td>Age, median (range), y</td>
<td>44 (27-68)</td>
<td>50 (22-62)</td>
<td>48 (21-73)</td>
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<td>Sex, No. M/F</td>
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<td>16/2</td>
<td>13/4</td>
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<td>Weight, median (range), kg</td>
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<td>85 (65-118)</td>
<td>90 (47-131)</td>
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<td>Race, No. white</td>
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<td>17</td>
<td>18</td>
<td>17</td>
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<tr>
<td>Duration of psoriasis, median (range), y</td>
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<td>23 (3-30)</td>
<td>16 (4-43)</td>
<td>22 (2-44)</td>
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<tr>
<td>Baseline PASI score, median (range)</td>
<td>16 (9-33)</td>
<td>21 (10-38)</td>
<td>19 (5-37)</td>
<td>16 (10-34)</td>
</tr>
</tbody>
</table>

Abbreviation: PASI, Psoriasis Area and Severity Index.
*Fully human monoclonal antibody against the CD4 molecule (Genmab A/S, Copenhagen, Denmark).
†Last observation carried forward.

Table 2. Disposition of Patients

<table>
<thead>
<tr>
<th>Placebo (n = 17)</th>
<th>20 mg (n = 17)</th>
<th>80 mg (n = 18)</th>
<th>160 mg (n = 17)</th>
<th>280 mg (n = 16)</th>
<th>Total (N = 85)</th>
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<tr>
<td>Discontinued during treatment</td>
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<td>0</td>
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<td>2</td>
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<tr>
<td>Discontinued during follow-up</td>
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<td>5</td>
<td>7</td>
<td>3</td>
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<tr>
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<td>15</td>
<td>17</td>
<td>15</td>
<td>14</td>
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<tr>
<td>Analyzed for primary end point†</td>
<td>17</td>
<td>17</td>
<td>18</td>
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<td>16</td>
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<td>Completed study</td>
<td>9</td>
<td>12</td>
<td>11</td>
<td>12</td>
<td>11</td>
</tr>
</tbody>
</table>

*Fully human monoclonal antibody against the CD4 molecule (Genmab A/S, Copenhagen, Denmark).
†Last observation carried forward.

RESULTS

PATIENTS

Eighty-five patients ranging in age from 21 to 74 years with moderate to severe psoriasis vulgaris (median PASI, 19) were included in the study. Seventeen were randomized to placebo, 17 to 20 mg, 18 to 80 mg, 17 to 160 mg, and 16 to 280 mg of HuMax-CD4. The patients’ baseline characteristics were similar across treatment groups (Table 1). Two patients had a baseline PASI below 10 (5 and 9). At the screening visit 2 weeks earlier, which was the basis for inclusion, their PASI values had been 14 and 13, respectively.

Six patients discontinued the study during the treatment phase (Table 2). Two discontinued placebo (deterioration of psoriasis after 3 infusions and patient refusal after 3 infusions), 2 discontinued 160 mg (deterioration of psoriasis after 2 infusions and rash after 2 infusions), and 2 discontinued 280 mg (influenza-like illness after 2 infusions and pneumonia and low CD4+ T-cell counts after 2 infusions). Fifty-five patients completed the full study, 9 (33%) of the patients in the pla-
cebo group compared with 46 (68%) in the 4 treatment groups.

**Efficacy**

All 85 patients were assessed for the primary end point, change in PASI at week 7, 4 weeks after the last treatment. Mean PASI was reduced in all treatment groups (95% confidence intervals are in parentheses): placebo, 8% (−3% to 19%); 20 mg, 12% (−6% to 27%); 80 mg, 14% (−14% to 35%); 160 mg, 16% (−4% to 33%); and 280 mg, 24% (−10% to 48%). There was no statistically significant difference between any of the active treatment groups and placebo (Figure 1). Twenty-one patients (25%) achieved at least a 25% reduction in PASI at week 7; of these, 11 (13%) achieved a reduction of 50%. The number of patients achieving a reduction in PASI at 25% or 50% increased with increasing dose (Figure 2). Nineteen of the 21 patients completed the study, and at week 15, 11 of the 19 patients still had at least a 25% reduction in PASI, 1 in the placebo group and 10 in the active treatment groups. Investigators’ and patients’ overall response assessment were secondary end points. At week 7, 3 patients, 1 in each of the 80-, 160-, and 280-mg groups, were clear or had marked improvement as assessed by the physician. In the placebo and the 20-mg groups, no patients were clear or had marked improvement.

According to the patients’ assessment, a total of 7 patients in the 80-, 160-, and 280-mg groups had marked improvement at week 7. In the placebo group, 1 patient had marked improvement and no patients in the 20-mg group had marked improvement.

No patients had flare or rebound of psoriasis after cessation of HuMax-CD4 treatment, and in some patients the effect was long lasting. One patient, a 46-year-old woman in the 280-mg group with a baseline PASI of 16, had an excellent response, and this clinical improvement has now lasted for more than 11/2 years (Figure 3).

**Safety**

Adverse Events

HuMax-CD4 therapy was well tolerated. Fifty-eight (68%) of the 85 patients had 134 adverse events, which were mostly mild or moderate. There were 3 serious adverse events, 2 considered not related to HuMax-CD4 (prostate cancer and traumatic ulcer). One serious adverse event was judged by the investigators to be related to HuMax-CD4. This was an allergylike rash after the second infusion of the study drug in a patient receiving 160 mg of HuMax-CD4. A deterioration of the psoriasis was noted and the patient was reported to have clinically infected psoriasis on the hands and face. The following adverse events occurred in more than 5% of the patients (5 or more of the randomized 85 patients): influenzalike illness, injection site pain, pruritus, headache, and decrease of CD4+ T-cell count (below 150/µL). Influenzalike illness seemed to occur more frequently in the high-dose groups (160 and 280 mg, 8 patients) than in the low-dose (20 and 80 mg, 2 patients) and placebo (2 patients) groups. Decreased CD4 counts were seen only in the high-dose groups: 2 patients in the 160-mg group and 3 patients in the 280-mg group. Eleven of 85 patients reported an infection. The only infections reported by more than 1 patient were influenza (4 patients in 4 different treatment groups, including placebo) and nasopharyngitis (2 patients, 160- and 280-mg groups). No infections were serious.

**Laboratory Findings**

Treatment with HuMax-CD4 led to a dose-dependent decrease in total lymphocyte count (test for trend, P=.01) (Figure 4). The decrease was due to a decrease in CD3+ T cells. No decrease in the number of monocytes was observed. The decrease in CD3+ T cells was caused mainly by a decrease in CD4+ T cells (P<.001), whereas the number of CD8+ T cells was unchanged. The reduction of CD4+ T cells was primarily in the memory cell subset (CD3+CD4+CD45RO+). Only a minor decrease in the naive cell subset (CD3+CD4+CD45RA+) was observed. No correlation between reduction in CD4+ lymphocyte counts and decrease in PASI was found.
Eighteen patients had CD4+ T-cell counts below 250/µL on 1 or more occasions, and in 5 of the patients the CD4+ T-cell counts were below 150/µL. The lowest values measured in these patients were 96, 92, 76, 89, and 74/µL. In 1 patient, the CD4+ T-cell count went below 150/µL during treatment and treatment was held. In the rest of the patients, the CD4+ T-cell counts were below 150/µL after the end of treatment. Six of the patients with CD4+ lymphocyte counts below 250/µL were in the 280-mg HuMax-CD4 group. There was a slow increase in the CD4+ T-cell count during the follow-up period. At the end of the study, 21 patients had CD4+ T-cell counts below the inclusion level of 350/µL. In some cases the counts were slow to normalize, and by August 2002 (9 months after end of the study) 6 of the 21 patients had CD4+ T-cell counts below 350/µL.

There was a dose-dependent increase in occupancy of the CD4 receptors by HuMax-CD4, but there was no correlation between the degree of occupancy and the decrease in PASI (Figure 5). In parallel, there was a dose-dependent decrease in CD4 expression in patients receiving 20 to 280 mg of HuMax-CD4, which was back to normal at week 5 in most of the patients. As a marker for T-cell activation, we measured soluble interleukin 2 receptor concentration in serum. We found a decrease in soluble interleukin 2 receptor from baseline to week 7, which was correlated to the reduction in PASI (P = .006).

The standard safety panel of serum chemistry and hematology indicated no impact of HuMax-CD4 treatment. There was no development of anti–HuMax-CD4 antibodies in any of the patients.

COMMENT

Psoriasis is a chronic inflammatory skin disease in which T cells are of major importance. Subcutaneous infusion of the fully human mAb against the CD4 molecule, HuMax-CD4, resulted in a dose-dependent increase in occupancy of the CD4 receptor. In the present study, we demonstrated safety and a moderate, not statistically significant, therapeutic response after 4 weeks of treatment with HuMax-CD4. Reduction in PASI at week 7, 4 weeks after the last treatment, increased with increasing doses of HuMax-CD4. In the group receiving the highest dose of HuMax-CD4, ie, 280 mg once a week for 4 weeks, we saw a 24% reduction in PASI compared with an 8% reduction in the placebo group. The reduction in PASI was correlated to decreased T-cell activation as measured by circulating interleukin 2 receptor levels. It is important to note that we treated the patients for only 4 weeks. A 12-week clinical trial with weekly intravenous administration of alefacept showed similar efficacy after 4 weeks of treatment at the highest dose level. The Ophthalmic and Dermatologic Advisory Board under the Food and Drug Administration recently recommended alefacept for approval.

HuMax-CD4 was well tolerated, and we found few adverse events in this short-term study. The only ad-
verse events that were seen more often in the active treatment groups than in the placebo group were influenza-like illness and decrease in CD4+ T-cell count. The decrease in the number of circulating CD4+ T cells was caused primarily by a decrease in the memory cell subset (CD3+CD4+CD45RO+). One patient with low CD4+ T-cell counts developed pneumonia; other than that, we did not see an increased occurrence of infections or any other adverse effects associated with the decrease in the number of circulating CD4+ memory T cells during the study or follow-up period. Potential long-term adverse effects of the treatment are not known, but, because of the more selective target, one would expect fewer adverse effects than for the systemic therapies currently in use.

The decrease in the number of circulating CD4+ T cells may be caused by compartmentalization, apoptosis, or cell lysis. Compartmentalization may be caused by binding of the HuMax-CD4–coated lymphocytes to cells in the reticuloendothelial system via the Fc receptor. Apoptosis may be caused by activation-induced cell death after the antibody’s binding to the receptor or by antibody-dependent cell death, which may also lead to cell lysis.

The decrease in memory T cells may be due to higher expression of CD4 molecules on the memory T cells compared with naive T cells and therefore increased binding of HuMax-CD4. Another explanation may be that memory T cells are more predetermined to undergo apoptosis because of a higher activation level. The decrease in memory T cells may be of special benefit in psoriasis because memory T cells are the main inflammatory cells in the skin lesions. A marked decrease in naive T cells could be potentially harmful because naive T cells are the important cells in the primary immune response against new infections.

From experimental studies and especially clinical trials with denileukin difitox, it is known that activated T cells play a central role in psoriasis. A potential mechanism of action for HuMax-CD4 could be inhibition of T-cell activation. HuMax-CD4 may inhibit T-cell activation by (1) decreasing the memory T-cell count, (2) blocking the interaction between the T-cell and the major histocompatibility complex class II molecules on the antigen-presenting cells, (3) modulating the CD4 molecule on the T cells, and (4) inducing tolerance. This study showed a reduction of the number of circulating memory T cells. Binding of HuMax-CD4 to the CD4 molecule on the T cells blocks the interaction between the T-cell and the major histocompatibility complex class II molecules on the antigen-presenting cells, resulting in inhibition of T-cell activation and proliferation. This is supported by the data presented in Figure 4 and Figure 5.
by in vitro data, clearly demonstrating that HuMax-CD4 inhibits alloantigen- and antigen (tetanus toxoid)–induced activation of peripheral-blood mononuclear cells (data on file, Genmab A/S). Data from a phase 1-2 clinical trial with HuMax-CD4 against rheumatoid arthritis demonstrated a dose-dependent decrease in the expression of CD4 receptors on the cell surface, which may be due to modulation of the receptor (data on file, Genmab A/S). The maximum decrease was observed 24 hours after administration of HuMax-CD4. In the present study, we did not measure the CD4 expression until 1 week after drug administration, but still we found a dose-dependent decrease in CD4 expression. In some of the patients, treatment with HuMax-CD4 led to long-lasting reductions in PASI. A possible mechanism for this long-term effect may be induction of tolerance. In mouse models of transplantation and autoimmune diseases, short courses of a non-lytic anti-CD4 antibody have induced long-term peripheral T-cell tolerance in primed and unprimed mice.22

In conclusion, this study has demonstrated safety and a moderate, not statistically significant, therapeutic effect after treatment with a fully human mAb against the CD4 molecule. The efficacy results obtained after just 4 weeks of treatment suggest that longer treatment would lead to even further reduction of PASI.

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