**Treatment of Cutaneous T-Cell Lymphoma With Chimeric Anti-CD4 Monoclonal Antibody**

By Susan Knox, Richard T. Hoppe, David Maloney, Iris Gibbs, Sherry Fowler, Carol Marquez, P. JoAnne Cornbleet, and Ronald Levy

Chimeric anti-CD4 monoclonal antibody was administered intravenously as a single dose to eight patients with mycosis fungoides. The dose was escalated throughout the study between patient groups, and individual patients received 50, 100, or 200 mg per dose. Seven of eight patients responded to treatment with an average freedom from progression of 25 weeks (range, 6 to 52 weeks). The treatment was well tolerated, and there was no clinical evidence of immunosuppression. Following treatment, there was significant suppression of peripheral blood CD4 counts in all patients for 1 to 22+ weeks. Only one patient made a very low titer human antichimeric antibody response. All but two patients made primary antibody and T-cell proliferative responses to a foreign antigen administered 24 hours after antibody infusion. However, there was generally marked, but temporary suppression of T-cell proliferative responses in vitro to phytohemagglutinin (PHA), tetanus toxoid, and normal donor lymphocytes. We conclude that at the dose levels studied, this antibody (1) had clinical efficacy against mycosis fungoides; (2) was well tolerated; (3) had a low level of immunogenicity; (4) decreased T-cell proliferative responses in vitro, and (5) did not induce tolerance to a foreign antigen.

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**Mycosis Fungoides** (MF) is a cutaneous T-cell lymphoma (CTCL) that is composed primarily of CD4 positive cells. It is characterized by CD4 positive infiltrates in the skin and can eventually involve lymph nodes, visceral organs, and bone marrow. The management of recurrent, progressive, and often refractory disease can be a difficult problem. Once the disease involves sites other than skin, despite treatment with systemic chemotherapy, median survival is approximately two years. These patients are generally considered to be incurable, and new therapies are needed for this disease. Innovative therapeutic approaches have included the use of photopheresis, interleukin-2, fusion toxins, cyclosporine, interferons, retinoids, adenosine analogues, other novel biologic response modifiers or chemotherapeutic drugs, and monoclonal antibodies.

Clinical responses have been reported in studies using murine monoclonal antibodies (MoAb) directed against the T-cell antigen CD5, but the development of immune responses to the murine MoAb limited the effectiveness of this therapy. In a previous study using a chimeric (murine/human) anti-CD4 MoAb (SK3; anti-Leu3) in patients with MF, low level antibody responses against the mouse Ig variable region and human Ig allotypic constant region determinants were observed in two of seven patients, but were of no clinical significance. The antibody was well tolerated and had some clinical efficacy against MF. Given these encouraging results, we conducted a second Phase I clinical trial using a different chimeric anti-CD4 MoAb (chimeric M-T412) directed to a different epitope on CD4. Like chimeric SK3, the avidity and epitope specificity of the chimeric M-T412 is derived from the variable region of its murine counterpart antibody. Chimeric M-T412 has high-affinity binding to the CD4 antigen and depletes CD4+ T lymphocytes from the circulation via Fc mediated mechanisms unlike chimeric SK3. Chimeric M-T412 antibody contains human constant regions (IgG1, k) and murine variable (v) regions (anti-CD4). It was administered intravenously (IV) as a single dose. The dose was escalated throughout the study between patient groups, and individual patients received 50, 100, or 200 mg per dose. The objectives of the study were to: (1) monitor escalating doses of chimeric anti-CD4 for possible toxicity and define a maximally tolerated or optimal biologic dose, (2) measure the pharmacokinetics of chimeric anti-CD4, (3) determine the antigenicity of chimeric anti-CD4, (4) evaluate the immunosuppressive and tolerogenic properties of chimeric anti-CD4 by monitoring a variety of T-cell functions, and (5) assess the antitumor effects of chimeric anti-CD4 in patients with MF.

**MATERIALS AND METHODS**

**Patients**

Eight patients were treated in the study. Four of the patients were women and four were men, ranging in age from 41 to 77 with a mean of 57 years. The clinical profile of the patients including the extent of disease before treatment and their history of prior therapy has been summarized in Table 1. Seven patients had disease limited to the skin (six with plaque stage disease involving <10% of the total skin surface and one with plaque stage disease involving >10% of the total skin surface). One patient had pathologic adenopathy without measurable skin disease. All patients had failed at least one form of conventional therapy, with a mean of 2.4 prior therapeutic modalities (range, 1 to 5). Before entry on the study, patients had to meet the following eligibility criteria: (1) histologic diagnosis of MF with a CD4 positive phenotype; (2) advanced disease (persistent or progressive disease following conventional therapy), with at least one measurable or evaluable disease site, unlikely to require standard...
therapy during the 12-week study period; (3) serum creatinine less than 1.5 mg/dL; (4) SGOT within normal limits; (5) white blood cell count (WBC) >4,000/mm³; platelets >100,000/mm³; granulocytes ≥1,500/mm³; Hgb ≥10 g/mL and CD4 count >300/mm³; (6) human immunodeficiency virus (HIV) negativity; (7) physiologic age ≥20 and ≤70; (8) Karnofsky performance status ≥70% and life expectancy ≥15 wk; (9) no active infections or other concomitant active malignancy (except basal or squamous cell carcinoma of the skin); (10) no prior MoAb therapy; (11) at least 4 weeks since the last treatment with any other biologic agent, systemic chemotherapy (CTX), or topical CTX, radiation therapy, or ultraviolet (UV) therapy to any designated measurable or evaluable site(s) of disease; (12) no significant underlying cardiac or respiratory disease; and (13) no detectable tumor. A partial response (PR) was a reduction by at least 50% from baseline in overall tumor size of sentinel lesions (the sum of the products of three dimensions: height and the two largest perpendicular diameters of each of the sentinel lesions so designated before therapy), without the appearance of new lesions at any sites. A minor response (MR) was a decrease of at least 25%, but less than 50%, from baseline in overall tumor size of sentinel lesions without the appearance of new lesions. Progressive disease (PD) was defined as a 25% or greater increase in the size of any lesion as measured by the product of three dimensions or the appearance of any new lesion. Freedom from progression (FFP) was measured from the treatment date to the date that PD was first documented.

**Immunopathology**

Pretreatment biopsies were obtained from each patient for pathological review and immunophenotyping. Four- to 6-mm punch skin biopsies were obtained. Half of each biopsy was fixed in formalin and processed routinely for hematoxylin and eosin (H&E) stained sections. The remaining tissue was snap frozen for immunologic studies. Biopsies were stained with a panel of MoAb including: CD2 (leu 3), CD3 (leu 4), CD4 (leu 3), CD8 (leu 2), Ki-67, and BFI (alpha/beta T-cell receptor). Antibody binding was detected by a three-stage antibody-biotin-avidin method as previously described.16

**Peripheral Blood Immunophenotyping**

Blood was collected into EDTA (Vacutainers; Becton Dickinson, Rutherford, NJ) and was processed within 6 hours of collection. Flow cytometry was performed on the EDTA-anticoagulated whole blood using a FACScan (Becton Dickinson, Mountain View, CA) flow cytometer with LYSSIS II software. Cells, up to 1 × 10⁵, were stained at 4°C for 30 minutes in the dark, then lysed with ammonium chloride EDTA and analyzed between 5 and 20 minutes after incubation at room temperature. Anti-CD45 fluorescein isothiocyanate (FITC) and anti-CD14 R-phycocerythrin (PE) (Becton Dickinson, San
Jose, CA) were used to define the lymphocyte analysis gate, from which the percent positive cells was calculated. The leucocyte count and percent lymphocytes obtained from the Coulter STKS were used to compute the absolute number of positive cells. The panel included anti-CD3 FITC/anti-CD8 PE, anti-CD20 FITC/anti-CD16, and CD56 PE (Becton Dickinson), and a saturating concentration (1 μg) of M-T426 FITC (Centocor; murine IgG, anti-CD4 MoAb that does not competitively inhibit the binding of M-T412), along with appropriate murine isotype-matched controls. To assess the number of CD4-positive lymphoid cells coated with M-T412, washed buffy coat cells (up to 1 × 10⁶) were mixed with equal amounts of heat-inactivated rabbit serum and stained with 2.4 μg of FITC-conjugated polyclonal rabbit IgG antimurine M-T412 and matched rabbit isotype control (F(ab')², Centocor). To estimate the amount of chimeric anti-CD4 bound to the cells, an experiment was performed in which normal blood was incubated with M-T412 at a final concentration of 50 μg/mL. Mononuclear cells were prepared by density gradient separation on Ficoll Hypaque (Pharmacia KLB Biotechnology, Inc, Piscataway, NJ), then stained with M-T426 FITC and antimurine M-T412 FITC. Patient sample values were estimated from a standard curve.

**Human Antichimeric Antibody Responses**

Human antichimeric antibody (HACA) levels were determined using an enzyme-linked immunosorbent assay (ELISA). Ninety-six well microtiter plates were coated with chimeric anti-CD4 MoAb. Fifty microliters of the coat antigen solution (10 μg/mL) in carbonate buffer pH 9.6) was dispensed in each well of a flat-bottom microtiter plate (Dynatech [Immunon] Lab, Inc, Chantilly, VA). Plates were washed five times with 0.05% Triton X 100 in phosphate-buffered saline (PBS) before use. Nonspecific protein binding sites were blocked by filling wells with 2% bovine serum albumin (BSA) in PBS. Following incubation for 15 to 20 minutes at room temperature, plates were washed with 0.05% Triton X 100 in PBS. Serum samples were plated in serial dilutions in 2% BSA in PBS. Goat antimouse IgG (γ chain specific) MoAb (Sigma, St Louis, MO) was used as a positive control. Plates were incubated at room temperature for 1 hour and washed four times. Horseradish peroxidase (HRP)-conjugated chimeric anti-CD4 MoAb (final dilution 1/166) or HRP conjugated goat antihuman λ (Sigma) and κ (CalTag Lab, S. Francisco, CA) chain antibodies were added (50 μL) to each well at a final concentration of 1 μg/mL in 2% BSA-PBS. After a second incubation for 1 hour, plates were washed four times, and 100 μL of enzyme substrate solution (H₂O₂ 30% [U.T. Baker Chemical Co, Phillipsburg, NJ; 3.5 μL/10 mL], ABTS [2,2'-Azino bis (3-ethylbenzthiazoline sulfonylic acid) (Sigma, St Louis, MO; stock 15 mg/mL, 10 μL/mL) in citrate buffer, pH 4.0) was added to the plates. Plates were incubated at room temperature in the dark and read in an automatic ELISA kinetic micro plate reader (Molecular Devices, Palo Alto, CA) or ELISA microtiter plate reader (Dynatech) at optical density (OD) 405 nm.

**Tolerogenicity**

Patients were immunized with Pneumovac 23 (Merck and Co, Inc, Westpoint, PA) and in some cases with keyhole limpet hemocyanin (KLH) (Calbiochem, San Diego, CA) subcutaneously 24 hours after the first antibody infusion. An ELISA was used to monitor antipneumococcal Type III polysaccharide (Eli Lilly Laboratory, Indianapolis, IN) and anti-KLH responses. Plates were coated with KLH as above at a final concentration of 10 μg/mL or Type III pneumococcal polysaccharide at a final concentration of 1.0 μg/mL in 0.1 mol/L Hepes buffer pH 3.5. Undiluted serum of normal volunteers previously immunized with Pneumovac 23 and serum from a monokine immunized with KLH (at a dilution of 1:25 into patient pretreatment sera) were used as positive controls.

**T-Cell Functional Assays**

**Mixed lymphocyte culture.** Peripheral blood mononuclear cells from heparin anticoagulated blood were isolated by density gradient centrifugation using Histopaque-1077 (Sigma). Each one-way mixed lymphocyte reaction (MLR) was performed in triplicate in a microculture system using round-bottom plates with 7.5 × 10⁵ responder lymphocytes per well. In addition, each well contained 7.5 × 10⁵ stimulator cells (irradiated with 4,000 cGy), and 10% heat-inactivated fetal calf serum (Gemini Bioproducts, Inc, Calabasas, CA) serum in RPMI 1640 (Mediatech) culture medium supplemented with 20 mmol/L HEPES, 20 mmol/L L-glutamine, and antibiotics. After 120 hours of incubation (5% CO₂, 37°C) cultures were labeled with 1 μCi of L-thymidine (specific activity 5 Ci/mmol/L; Amersham, Arlington Heights, IL) for an additional 18 hours. The labeled cells were harvested onto glass fiber filters, dried, and counted in a liquid scintillation spectrometer. The responder capacity of the patients' lymphocytes was tested by incubation with stimulator cells obtained from two unrelated healthy donors. All results are expressed as the mean of the three stimulation indices (cpm stimulated culture/cpm background) on each sampling day to allow for comparison between groups and between sampling times. Whenever possible, cells from the same subjects were used as stimulators for each patient at each time point.

**T-cell proliferation assay.** Peripheral blood lymphocytes were obtained as above. Peripheral blood cells, 5 × 10⁶ were placed into a flat-bottom 96-well microtiter plate. The culture medium consisted of RPMI 1640 supplemented with 10% heat-inactivated fetal calf serum, 2 mmol/L glutamine, 100 U/mL penicillin, and 10 μg/mL streptomycin. Triplicate assays were performed using KLH (Sigma) at 100 μg and 10 μg/mL, tetanus toxoid (Connaught Laboratories Limited, Willowdale, Toronto, Canada) at a final concentration of 1/1000 and 1/1500, 7.5 μg phytohemagglutinin/well (PHA; Sigma) and Pneumococcal polysaccharide Type III at 5.8 and 11.5 μg/well. Cultures were pulsed with 1 μCi of tritiated thymidine at 96 hours and harvested 16 hours later. The mean cpm of thymidine incorporation was calculated for triplicate cultures. All responses were calculated as stimulation indices.

**Assessment of Baseline Immunocompetence**

Pretreatment mixed lymphocyte culture (MLC) and T-cell proliferation assay results using PHA and tetanus toxoid, as well as skin tests to measure delayed type hypersensitivity to Tuberculin Purified Protein Derivative (PPD) (Connaught, Willowdale, Ontario, Canada), mumps (Connaught, Swiftwater, PA), candida (Miles Inc, Elk- hart, IN), trichophyton (Berkeley Biologicals, Berkeley, CA) and coccidioidin (Berkeley Biologicals, Berkeley, CA) were used to assess the general level of the immunocompetence of the patients before treatment.

**Results**

**Clinical Responses**

The clinical responses for patients treated with 50 to 200 mg of chimeric anti-CD4 MAB are shown in Table 2. The dose administered (expressed in terms of mg and mg/kg) is shown for each patient as well as the subsequent best response and FFP in months measured from the treatment date to the date that PD was first documented or reported. The clinical responses consisted of decreased size and/or induration of the skin lesions. All patients with skin lesions had
decreased erythema of their lesions, but it is not possible to quantitate this in a reliable way. Therefore, the scoring of clinical responses was based entirely on tumor size. Five of eight patients had a PR and two patients had an MR, resulting in an overall response rate of approximately 88%. The FFP ranged from 6 to 52 weeks, with an average of 25 weeks. Patient no. 3 had an MR with FFP of 34 weeks with two site dependent PRs out of five sentinel lesions. Patient no. 6 had an excellent MR with a 49% decrease in tumor volume posttreatment compared with baseline tumor volume measurements. Only patient no. 4, who was treated on a compassionate use basis and had extensive and progressive adenopathy at the time of treatment, failed to show any improvement and continued to have PD. Although the sample size is small, there does not appear to be a significant correlation between dose and clinical response. However, the data suggest that tumor burden is inversely related to response.

Toxicity

All of the patients tolerated the treatment well without any significant problems or complications. Nevertheless, some patients complained of fatigue postinfusion and others reported symptoms that included myalgias, headache, nausea, chills, and fever. The adverse events observed following administration of the chimeric anti-CD4 MoAb have been summarized in Table 3. All of these with the exception of a skin reaction that occurred in patient no. 5 2 days after treatment and a headache that occurred in patient no. 7 12 days after treatment were thought to be either possibly or probably related to administration of the MoAb. There was no Grade 3 or 4 toxicity. All reported symptoms responded to acetaminophen, antihistamines and/or nonsteroidal anti-inflammatory drugs as indicated. There was no clinical evidence of immunosuppression. There were also no significant changes in any routine laboratory parameters (serum chemistries, urine analyses and red blood cell and platelet counts) attributable to the MoAb therapy following treatment.

Peripheral Blood Immunophenotyping

Pretreatment and nadir CD4 and CD8 counts are shown for each patient in Table 4. The time of onset and duration are shown as well. As can be seen, there was significant suppression of CD4 counts in all patients. In general, there was greater suppression of CD4 counts with increasing doses of anti-CD4 MoAb, with the nadir occurring 24 hours after infusion in all patients. The duration of suppression ranged from 1 week to 22+ weeks. There was not a clear relationship between dose and duration of count suppression. As expected, there was an associated decrease in the absolute lymphocyte and CD3 counts (data not shown). The magnitude of the suppression of CD8 counts was less than that observed for CD4 counts. The nadir of CD8 counts occurred 24 hours postinfusion, and in all but one patient (no. 4) persisted for only 1 week. There was some waxing and waning of counts during and after the recovery period. The two patients treated with 200 mg had transient decreases in CD14 (macrophage) counts and one patient treated with 100 mg and both patients treated with 200 mg had transiently decreased CD20 (B lymphocyte) counts that returned to normal or pretreatment levels within 1 week of treatment (data not shown). All eight patients had depressed CD16 counts (NK cells) 24 hours postinfusion (data not shown). Again, there was no obvious dose response relationship, and all CD16 counts had returned to normal or pretreatment levels 1 week posttreatment, with the exception of patient no. 3's counts which took 3 weeks to recover. Antibody coated cells were transiently detectable at very low levels 24 hours postinjection in three of four patients treated with 50 mg of antibody. Maximal numbers of antibody coated cells were detected in the other dose groups 24 hours postinjection, with staining of an average of 24% and 41% of peripheral blood mononuclear cells with antichimeric anti-CD4 idiotype MoAb in patients treated with 100 and 200 mg, respectively. Antibody coated cells were still detectable 1 and 3 weeks posttreatment in patients treated at these two dose levels (data not shown).
**Table 4. Peripheral Blood Immunophenotyping**

<table>
<thead>
<tr>
<th>Pt No.</th>
<th>MoAb Dose (mg)</th>
<th>Pretreatment CD4</th>
<th>Nadir CD4</th>
<th>Onset Duration CD4</th>
<th>Pretreatment CD8</th>
<th>Nadir CD8</th>
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<td>300</td>
<td>24</td>
<td>550</td>
<td>270†</td>
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* CD4 and CD8 counts are expressed in units of cells/μL. The normal range for CD4 is 540 to 1,660/μL. The normal range for CD8 is 270 to 930/μL.
† Total time required for recovery of counts to within approximately 10% of the pretreatment level (if counts pretreatment were below normal)
‡ The patient had progressive disease and died before the counts returned to pretreatment levels.
§ The patient developed progressive disease and required other therapy before the count returned to the pretreatment level.
‖ Lost to follow-up with CD4 count of 350/μL.

**Pharmacokinetics**

Mean serum levels ± standard deviation (SD) of the chimeric anti-CD4 MoAb are shown in Table 5 as a function of dose. Higher serum levels of MoAb were achieved with higher doses of administered MoAb, although there was not a linear relationship between administered dose and subsequent serum levels. By 1 week postinfusion at the highest dose level, the level of MoAb remaining in the serum was <1 μg/mL.

**Antibody Responses**

Antibody responses to the chimeric anti-CD4 MoAb, KLH and type III pneumococcal polysaccharide (PPS III) were measured and are summarized in Table 6. Only one patient (no. 5) made a significant, but very low titer HACA response that was only detectable 3 weeks posttreatment. All patients were immunized with a pneumococcal vaccine, and five were also immunized with KLH 24 hours after antibody infusion to determine whether the chimeric anti-CD4 would induce tolerance to a coadministered antigen. Six patients made an antibody response to one or both antigens. Patients no. 4 and no. 8 failed to make antibody responses and were either anergic or poorly responsive to a variety of skin test antigens before therapy (Table 7).

**T-Cell Function**

To assess potential interference of chimeric anti-CD4 on in vitro immunoreactivity, the responder capacity of patient lymphocytes was measured in MLR and T-cell proliferative assays using a panel of normal donor lymphocytes, tetanus toxoid, and KLH (with which the patients had been previously immunized). The results of the studies are summarized in Table 8. Most patients had a temporary suppression of these responses. The level of reactivity in these assays generally returned to baseline levels within 1 to 6 weeks posttreatment. There was no direct relationship between dose or the extent of duration of the suppressed responses. In addition, in two patients with pretreatment reactivity to pneumococcal polysaccharide, there was also suppression of their proliferative responses to this antigen following treatment. Despite the fact that preexisting responses to pneumococcal antigens were suppressed by the anti-CD4 antibody, five patients were able to make new T-cell proliferative responses.
to pneumococcal immunization or to Pneumovac 23 and four patients made T-cell proliferative responses to KLH. Thus, chimeric anti-CD4 depressed the MLR and preexisting T-cell proliferative responses to tetanus toxoid and PPS III, but was not tolerogenic at the dose levels studied, and did not suppress the ability of patients to mount an immune response to a coadministered antigen.

**DISCUSSION**

In this dose escalation study of single doses of 50 to 200 mg of chimeric anti-CD4 MoAb in patients with MF, five of eight patients had a PR and the overall response rate was approximately 88%. The FFP ranged from 6 to 52 weeks, with an average of 25 weeks. This response rate is superior to response rates reported for therapy of CTCL with multiple doses of unlabeled murine MoAb with brief response durations of ≤4 months, and is also better than response rates obtained in CTCL patients following radioimmunotherapy.

This relatively high response rate may be due in part to the relatively low tumor burden in the group of patients treated in this study. Interestingly, there was no obvious dose response relationship.

Although clinical responses of fairly short duration have been reported in patients with CTCL treated with murine MoAb, these responses were limited in part by the development of antimouse Ig antibodies as well as antiidiotypic antibodies in approximately 50% to 100% of the patients. In the study reported here, only one patient made a significant, but very low level HACA response. The rate of HACA formation (12.5%) was lower than previously observed in a similar study using a different chimeric anti-CD4 MoAb.

The antibody infusions were well tolerated. The mild side effects (eg, fever, fatigue, and nausea) reported are not uncommon during or after antibody infusions. Importantly, there was no dose-limiting toxicity observed at any of the dose levels studied. This is in contrast to other unlabeled MoAb studies in which more significant toxicities were observed, and to radioimmunotherapy studies in which myelosuppression is the dose-limiting toxicity unless bone marrow or peripheral stem cell reinfusion is used. Although there was a marked temporary reduction in CD4 and CD8 counts and in vitro T-cell proliferative responses following treatment, there were no clinical indications of myelosuppression. Specifically, none of the patients developed opportunistic infections, whereas two of seven patients previously treated with a different chimeric anti-CD4 MoAb developed opportunistic infections (although in one of these patients, the infections in retrospect predated the MoAb therapy). Interestingly, the extent and duration of CD4 and CD8 count suppression in this study in this patient population was considerably less than that previously observed in multiple sclerosis and rheumatoid arthritis patients treated with similar doses of the same antibody (personal communication, Dr. Richard McCloskey, May 1995). As previously reported in a similar patient population treated with a different chimeric anti-CD4 MoAb, treatment with chimeric anti-CD4 MoAb (cT412) was not tolerogenic at the dose levels studied and did not suppress the ability of patients to mount an immune response to a new antigen administered 24 hours after MoAb infusion.

The results reported here are encouraging and demonstrate that this chimeric MoAb was safe, well tolerated, and efficacious in the patients studied. These results suggest that the epitope specificity of the MoAb is an important determinant of toxicity and efficacy, and that this chimeric anti-CD4 MoAb may be useful for the treatment of CD4 positive lymphoid malignancies. This MoAb might be even more efficacious if administered as multiple doses or radiolabeled. It is the least immunogenic of any chimeric MoAb studied to date in patients with CTCL, but a direct comparison with murine anti-CD4 against the same epitope is needed to make a definitive statement about relative immunogenicity. Future studies are needed to determine the relative immunogenicity of this chimeric anti-CD4 compared with the murine version of the antibody, to better define an optional biologic dose, to optimize the treatment regimen, and to elucidate the mechanism of action of anti-CD4 MoAb in patients with CTCL.

**Table 7. Skin Test Reactivity**

<table>
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<tr>
<th>Patient No.</th>
<th>PPD</th>
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**Table 8. T-Cell Functional Assays**

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</table>

Abbreviations: (+), Positive pretreatment; NR, nonreactive (stimulation index < 2); NA, not applicable; ND, not done.

* Transient increase (generally at 24 hours after MoAb administration) only in the stimulation index, followed by suppression of these responses.

**ACKNOWLEDGMENT**

The authors thank Centocor for provision of the chimeric anti-CD4 monoclonal antibody and Dr Gerald Schiffman for provision of purified pneumococcal polysaccharide Type III. The authors also thank Dr Roger Warnke for assistance with immunophenotyping of biopsy specimens, Dr Shoucheng Ning and Bill Sutherland for technical assistance with the ELISAs, Dr Richard Siegel at Centocor for performing the PK assays, and Sharon Clarke for assistance with preparation of the manuscript.
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