Phase I Clinical Trial of a Monoclonal Antibody Against CD40-Ligand (IDEC-131) in Patients with Systemic Lupus Erythematosus

JOHN C. DAVIS Jr, MARK C. TOTORITIS, JAY ROSENBERG, THOMAS A. SKLENAR, and DAVID WOFSY

ABSTRACT. ***Objective.*** To investigate the safety and pharmacology of a humanized monoclonal antibody against CD40-ligand (IDEC-131) in patients with systemic lupus erythematosus (SLE).

Methods. Cohorts of 3 to 5 patients with symptomatic lupus each received 0.05, 0.25, 1.0, 5.0, or 15.0 mg/kg of IDEC-131 as a single intravenous infusion. Patients were followed for 3 months to evaluate toxicity and pharmacokinetics.

Results. This phase I, single dose, dose-escalating study was conducted in 23 patients at a single institution. All patients experienced at least 1 adverse event (AE) during a 3 month followup period, although 58 AE in 17 patients were considered possibly or probably related or of unknown relationship to treatment. No dose relationship in the distribution of AE was apparent. No infusion related cytokine-release syndrome was observed; no infusions were interrupted, and all patients completed treatment. Eight mild (grade 1 or 2) infections were reported in 8 patients. All infections were considered unrelated to drug administration and all resolved uneventfully. No patient developed detectable antibodies to IDEC-131. Flow cytometry revealed no apparent treatment related depletion of lymphocyte subsets. Pharmacokinetic analysis indicated that the maximum serum concentration and the area under the concentration curve of IDEC-131 were proportional to the dose administered. At doses between 1.0 and 15.0 mg/kg, the serum half-life ranged from 299 to 320 h. Efficacy was not formally evaluated in this single dose study.

Conclusion. IDEC-131 (humanized Mab against CD40L) administered in a single intravenous infusion at doses of 0.05–15.0 mg/kg is safe and well tolerated in patients with SLE. (J Rheumatol 2001;28:95–101)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS
CD40L (CD154) ANTIGEN
MONOCLONAL ANTIBODY
PHARMACOKINETICS

Systemic lupus erythematosus (SLE) is a prototypic autoimmune disease characterized by the development of autoantibodies to a defined set of nuclear antigens. Interaction between B and T lymphocytes has been shown to be required for the development of these antibodies. Recent studies in murine models of SLE have suggested new strategies for treating humans with SLE[1,2]. Several of these strategies are based on the observation that the activation of T cells, and their subsequent stimulation of other effector cells in the autoimmune process, requires at least 2 signals. The first of these signals is provided by the interaction between the T cell receptor and antigenic peptides in the context of class II major histocompatibility antigens. The second signal is provided by other receptor-ligand pairs on T cells and antigen-presenting cells (APC) and is referred to as T cell costimulation[3,4]. Specifically, the interaction between CD40 on APC and its ligand (CD40L) on T cells plays an important role in promoting T cell costimulation. CD40 is expressed on APC, and certain other cell types including B cells, dendritic cells, monocytes, macrophages, hemopoietic progenitor cells, endothelial cells, mast cells, and vascular smooth muscle cells[5]. CD40L is found predominately on activated CD4+ T cells, but its expression has also been reported on activated platelets[6], activated CD8+ T cells, stimulated mast cells, basophils, eosinophils, and B cells[5]. Expression of CD40L has also been described on vascular smooth muscle cells and endothelial cells[5]. The interaction between CD40 and CD40L has profound effects on B cell function by driving B cells into cell cycle entry, inducing germinal center formation, augmenting

From the Division of Rheumatology, University of California, San Francisco, California, and IDEC Pharmaceuticals Corp., San Diego, California, USA.

Supported by IDEC Pharmaceuticals Corp. and by the Rosalind Russell Medical Research Center for Arthritis at the University of California, San Francisco.

J.C. Davis, MD, MPH, Assistant Professor of Medicine, University of California; M.C. Totoritis, MD, Senior Director of Autoimmune and Inflammatory Diseases; J. Rosenberg, PhD, Associate Director of Preclinical Development and Clinical Immunology, IDEC Pharmaceuticals Corp.; T.A. Sklenar, BS, Clinical Research Associate, IDEC Pharmaceuticals Corp.; D. Wofsy, MD, Professor of Medicine, University of California, San Francisco.

Address reprint requests to Dr. J.C. Davis Jr, Division of Rheumatology, University of California, San Francisco, 533 Parnassus Ave., Box 0633, San Francisco, CA 94143.

Submitted March 23, 2000 revision accepted June 19, 2000.

B cell responsiveness to cytokines, and causing antibody isotype switching[7-9]. Additionally, the CD40–CD40L interaction can result in the production of antibodies to T cell dependent antigens, the protection of B cells from apoptosis, the induction of costimulatory molecules on B cells, and the activation of macrophages, endothelial cells, dendritic cells, keratinocytes, and T cells.

Mounting evidence implies that the interaction between CD40 and CD40L may play an important role in promoting disease activity in SLE. For example, in murine models, blockade of the interaction between CD40 and CD40L dramatically retards the progression of lupus nephritis and prolongs survival[2]. In humans with SLE, there is an increase in the absolute number of CD40L+ T cells as well as an increase in the cell to surface expression of CD40L[10-12]. After *in vitro* activation, T cells from patients with SLE show significantly prolonged expression of CD40L compared with T cells from healthy controls[10]. Additionally, patients with active SLE have elevated levels of soluble CD40L *in vivo*[13,14]. One mode by which the normal immune system maintains control is by regulating and permitting only transient expression of CD40L[9,15]. Persistent expression of CD40L in patients with SLE might disrupt this regulatory checkpoint and thereby promote autoimmunity.

IDEC-131 is a humanized monoclonal antibody (Mab) against CD40L comprising human gamma 1 heavy chains and human kappa light chains with murine complementarity determining regions. IDEC-131 binds to CD40L on T cells with high specificity and avidity thereby preventing CD40 signaling (Figure 1). In animal models, interruption of signaling through the CD40/CD40L pathway can block immune responses and, under some circumstances, can even induce antigen-specific tolerance[16]. Based on these observations, we conducted a phase I, single dose, dose-escalating trial of IDEC-131 in patients with SLE.

MATERIALS AND METHODS

Study design. This study was a phase I, single dose, dose-escalating clinical trial of IDEC-131 in patients with symptomatic SLE. Informed consent was obtained from all patients in accordance with the human subjects institutional review board of the University of California. Cohorts of 3 to 5 patients were treated with a single 2 h intravenous (iv) infusion of 0.05, 0.25, 1.0, 5.0, or 15.0 mg/kg of the Mab. Patients were evaluated over a 3 month followup period to assess pharmacokinetics, short term toxicity, and effects on peripheral blood lymphocytes, serum chemistries, complement levels, antinuclear antibodies (ANA), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR).

Patient selection. Study patients were required to meet at least 4 of the 11 criteria for the classification of SLE as defined by the American College of Rheumatology[17,18]. Patients were required to be at least 18 years of age and to have symptomatic SLE (e.g., fatigue, arthritis, rash, fever, oral ulcers, etc.) that required a stable dose of an accepted SLE therapy including prednisone, nonsteroidal antiinflammatory drugs (NSAID), hydroxychloroquine, or other agents. Steroids and NSAID were not to be stopped or started during the study and the dosage and frequency were to remain stable during the study. However, medications could be started, stopped, or modified during the study if the patient experienced a disease flare. In addition, patients were required to meet the following hematologic criteria for safety: hemoglobin > 9 gm/dl; WBC > 2000/mm^3; platelets ≥ 75,000/mm^3. Patients were excluded from the study if they had prior treatment with a Mab, other biologics, or cyclophosphamide. Patients with a history of recurrent or active infection, including human immunodeficiency virus, or another clinically significant condition were also excluded.

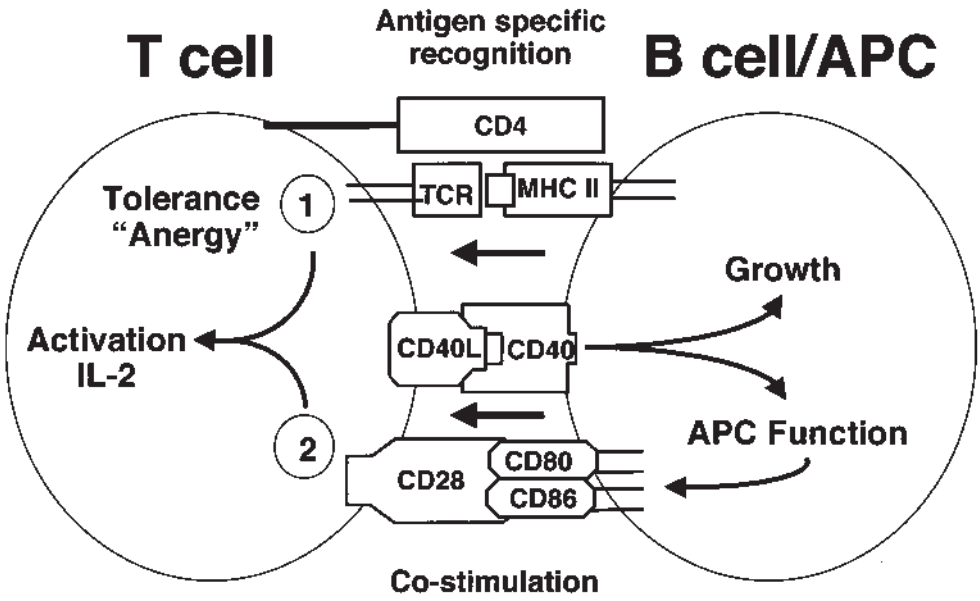

Figure 1. The 2 signal pathway required for T cell activation. The first signal (number one) is provided by antigen presentation to the T cell receptor in the context of an MCH Class II molecule. The second signal (number two) is provided by either (1) CD40Ligand/CD40 or (2) CD28/CD80+CD28/CD86 interaction. IDEC-131 binds to CD40L on T cells, blocking CD40 signaling in B cells. Interruption of this signaling can prevent the elaboration of the immune response (T and B cell activation and T cell mediated effector functions) and can potentially induce tolerance in an antigen-specific manner.

Mab against CD40L. IDEC-131 is a humanized Mab against CD40L. The antibody comprises human gamma 1 heavy chains and human kappa light chains with murine complementarity determining regions, and binds specifically to human CD40L, a membrane protein found predominantly on activated CD4+ T cells. IDEC-131 is produced by a Chinese hamster ovary (CHO) transfectoma containing the N5KG1 vector. This vector, encoding IDEC-131, was electroporated into the CHO cell line DG44. Clones secreting the IDEC-131 immunoglobulin were cultured in methotrexate-containing medium and high-producing clones were selected for use in the production of a master cell bank. The humanized Mab was produced by IDEC Pharmaceuticals Corp. (San Diego, CA, USA) and supplied under an Investigational New Drug Application.

Flow cytometry. Flow cytometry of peripheral blood was performed using fluorescent conjugated antibodies to determine the surface antigen expression of CD3+, CD4+, CD8+, and CD40L+ T cells and CD19+ B cells. Samples were obtained on Day 1 (pre- and postinfusion), Days 2, 3, 4, and 5, and at Weeks 2, 4, 6, 8, and 12. The anti-CD40L antibody used was TRAP1 (Pharmingen, San Diego, CA, USA), which does not compete with IDEC-131 for binding.

IDEC-131 pharmacokinetics. Serum IDEC-131 levels were determined using microtiter plates coated with a fusion protein consisting of the extracellular domain of CD40L linked to CD8. Serum was pipetted into the first well of the coated plate and then serially diluted. Known amounts of the IDEC-131 Mab were used to make a standard curve on each plate. Mouse Mab to human IgG conjugated with horseradish peroxidase was used as a detector. Color was developed by adding substrate to the wells, and absorbance was read by photometric colorimetry. Normal human serum was used as a negative control and, after addition of IDEC-131 Mab, for making the standard and positive control. The lower limit of detection of this assay is 27 ng/ml, and the lower limit of quantitation is 0.5 µg/ml in serum.

Measurement of the immune response to IDEC-131. Post-treatment sera from evaluations at 4, 6, 8, and 12 weeks were analyzed for the development of anti-IDEC-131 antibody response using microtiter plates coated with IDEC-131. Dilutions of the patient sera were added and, after washing, detected with biotin labeled IDEC-131 followed by streptavidin conjugated to horseradish peroxidase. The lower limit of detection of this assay is 96 ng/ml, and the lower limit of quantitation is 5 µg/ml.

Study assessments. Patients were evaluated for toxicity using the National Cancer Institute's Common Toxicity Criteria. Monitoring included history and examinations at Weeks 2, 4, 6, 8, and 12, as well as repeated analyses of hematology and serum chemistry profiles and periodic evaluations of lymphocyte subsets. Adverse events that were considered related were those that the investigators attributed as probably or possibly related to study drug or the relationship was unknown. Measurements of ESR, ANA, anti-dsDNA, serum complement levels (CH50 and C4), and CRP were conducted prior to treatment and at study exit.

Clinical activity. A formal evaluation of efficacy was not undertaken in this phase I study. Modified SLE Disease Activity (SLEDAI) scores were determined at baseline for the 2 highest dose groups (Group D: 5.0 mg/kg and Group E: 15.0 mg/kg) to more formally assess the baseline disease activity of these patients. Serial SLEDAI scores were not determined during the postinfusion followup period of the study.

RESULTS

Clinical characteristics. Twenty-three patients with symptomatic SLE were enrolled between February and October 1998. Patient demographics are reported in Table 1. Of patients, 91% were female and 61% were Caucasian, with a mean age of 44 years (range 18 to 64). Mean modified SLEDAI score at baseline was 3.8 (range 0–8) and 4.6 (range 2–6) for Groups D and E, respectively. Clinical manifestations of SLE at baseline were considered to be mild to moderate and were as follows: synovitis in 9 patients (39%), lupus-specific rash in 9 (39%), nephritis in 3 (13%), pleuritis in 2 (9%), cytopenia in 2 (9%), and oral ulcers in one (4%). All patients were receiving at least one medication for SLE at study entry and continued stable doses of these medications throughout the trial. The most common therapies were NSAID (87% of patients), hydroxychloroquine (70%), prednisone (70%), and methotrexate (26%). Mean doses for hydroxychloroquine, prednisone, and methotrexate were 375 mg/day, 9 mg/day, and 10.4 mg/week, respectively. Prednisone doses were changed for 9 patients during the 3 month study. A decrease in dose was made for 5 patients, and an increase was made in one patient. Doses were initially increased then subsequently decreased for 3 patients.

Adverse events. All patients experienced at least 1 adverse event (AE). No clear dose relationship in the distribution of AE between the study groups was apparent (Table 2). Of 156 total AE reported (Table 2), only 58 events (37%) in 17 of the 23 patients (74%) were considered possibly or probably related or of unknown relationship to treatment (Table 3). The majority of these AE (84%) were mild or moderate (grade 1 or 2); nausea (43% of patients), dizziness (39%), and headache (26%) were noted most frequently. Nine study related AE were judged to be severe (grade 3): 1 event of chest pain was considered possibly related, while 3 events each of nausea and headache and 1 event each of asthenia (fatigue) and emesis were classified as unknown relationship. No maximal or life-

Table 1. Demographic features.

	Dose Group					
	0.05 mg/kg (n = 3)	0.25 mg/kg (n = 5)	1.0 mg/kg (n = 5)	5.0 mg/kg (n = 5)	15.0 mg/kg (n = 5)	Total (n = 23)
Age, mean ± SD	45.7 ± 18.2	38.6 ± 16.6	42.4 ± 9.3	44.4 ± 7.3	51.2 ± 12.2	44.3 ± 12.3
Female, n (%)	3 (100)	4 (80)	4 (80)	5 (100)	5 (100)	21 (91)
Race, n (%)						
Caucasian	1 (33)	2 (40)	3 (60)	4 (80)	4 (80)	14 (61)
Hispanic	2 (67)	0 (0)	0 (0)	0 (0)	1 (20)	3 (13)
African-American	0 (0)	2 (40)	1 (20)	0 (0)	0 (0)	3 (13)
Asian/Pacific Islander	0 (0)	1 (20)	1 (20)	1 (20)	0 (0)	3 (13)

Table 2. Most frequent* adverse events.

	Dose Group					
	0.05 mg/kg (n = 3)	0.25 mg/kg (n = 5)	1.0 mg/kg (n = 5)	5.0 mg/kg (n = 5)	15.0 mg/kg (n = 5)	Total n (%)
Any adverse event	18	30	35	42	31	156 (100.0)
Asthenia/fatigue	1	2	6	4	3	16 (10.0)
Nausea	3	3	4	1	2	13 (8.0)
Headache	1	1	6	3	1	12 (8.0)
Arthralgia	1	1	1	7	1	11 (7.0)
Dizziness	1	2	2	3	2	10 (6.0)
Rash	1	1	1	2	3	8 (5.0)
Diarrhea	1	1	1	3	1	7 (4.0)
Myalgia	0	1	1	2	1	5 (3.0)
Chest pain	0	3	0	1	1	5 (3.0)
Rhinitis	2	2	0	1	0	5 (3.0)
Infection	2	1	0	1	0	4 (3.0)
Throat irritation	1	1	0	1	1	4 (3.0)
Myasthenia	0	0	2	1	1	4 (3.0)
Amblyopia	0	0	1	0	2	3 (2.0)
Bronchospasm	0	3	0	0	0	3 (2.0)
Peripheral edema	0	1	1	1	0	3 (2.0)
Fever	0	0	0	0	3	3 (2.0)
Abdominal pain	0	1	2	0	0	3 (2.0)
Back pain	0	0	1	1	1	3 (2.0)
Vomiting	0	1	0	1	1	3 (2.0)

*Listed are events with a frequency > 1.0%.

Table 3. Adverse events probably, possibly, or unknown relationship to treatment*.

	n (%)	Event (%)
Any adverse event	17 (74)	58 (100)
Nausea	10 (43)	11 (19)
Dizziness	9 (39)	9 (16)
Headache	6 (26)	7 (12)
Asthenia/fatigue	4 (17)	5 (9)
Diarrhea	4 (17)	4 (7)
Chest pain	3 (13)	3 (5)
Amblyopia	2 (9)	2 (3)
Arthralgia	2 (9)	3 (5)
Bronchospasm	2 (9)	2 (3)
Vomiting	2 (9)	2 (3)

n: number of patients.
*Listed are events with a frequency > 2%.

threatening AE (grade 4) were reported. Thirteen of the 23 patients experienced an AE on the day of infusion (Table 4). These AE were all mild or moderate and consisted primarily of lightheadedness, nausea, or headache. No infusions were interrupted, and all patients completed treatment.

Eight infections occurred in 8 patients during the course of the 3 month followup period. They included 4 upper respiratory tract infections, 2 urinary tract infections, 1 case of herpes simplex (cold sore), and 1 case of dermatitis after an insect bite. No infection was considered related to the study drug, and all patients recovered without complication.

Table 4. Adverse events occurring within 24 hours of infusion*.

	n (%)	Event (%)
Any adverse event	13 (57)	38 (100)
Dizziness	8 (35)	8 (21)
Headache	7 (30)	7 (18)
Nausea	6 (26)	6 (16)
Asthenia/fatigue	4 (17)	4 (11)
Amblyopia	3 (13)	3 (8)

n = number of patients.
*Listed are events with a frequency > 5%.

Anti-IDEC-131 antibody response. No patient developed detectable antibodies to IDEC-131.

Flow cytometry. Treatment did not deplete lymphocytes. In peripheral blood, fluctuations in mean absolute T cell (CD3, CD4, and CD8) and B cell (CD19) counts were observed throughout the treatment period (Figure 2, Table 5), and were seen equally in all dose groups.

Clinical laboratory assessments. Measurements of hepatic, renal, and hematologic function showed no evidence of treatment related toxicity in any patient.

IDEC-131 pharmacokinetics. Serum concentrations of the IDEC-131 antibody increased proportionally with dose. Patients in the 0.25 mg/kg dose group exhibited a mean maximum serum concentration (C_{max}) of 7.7 ± 3.2 µg/ml, while patients treated with 1.0 mg/kg of IDEC-131 exhibited a mean

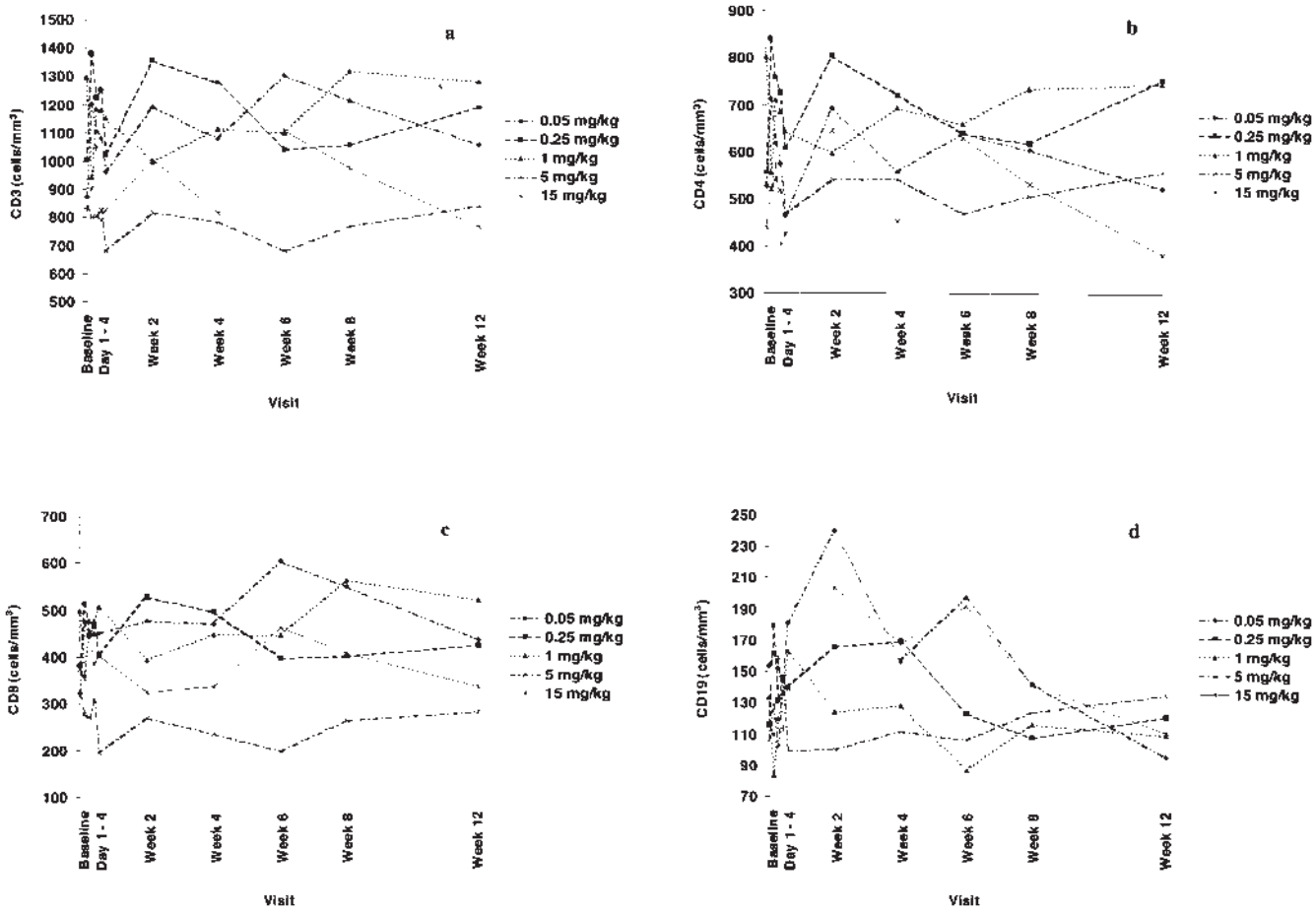

Figure 2. CD3, CD4, CD8, and CD19-bearing lymphocytes were measured at baseline, on Days 1+4, and at Weeks 2+12. Mean absolute counts for CD3 (a), CD4 (b), CD8 (c), and CD19 (d) are presented for each dose group.

Table 5. Mean absolute CD3+, CD4+, CD8+, and CD19+ cell counts*.

	CD3+ Count (cells/mm^3)		CD4+ Count (cells/mm^3)		CD8+ Count (cells/mm^3)		CD19+ Count (cells/mm^3)	
	Low	High	Low	High	Low	High	Low	High
Dose group (mm/kg)								
0.05	873.7 ± 685.0	1301.3 ± 1255.0	466.5 ± 574.9	713.7 ± 592.2	322.7 ± 240.1	602.3 ± 596.2	95.3 ± 86.3	240.0 ± 48.5
0.25	1002.8 ± 312.7	1382.2 ± 532.0	556.2 ± 257.3	805.2 ± 434.7	381.6 ± 92.3	527.6 ± 239.4	107.8 ± 87.9	169.2 ± 185.2
1.0	945.0 ± 611.7	1315.6 ± 776.9	556.6 ± 403.7	801.8 ± 434.5	361.4 ± 238.3	561.2 ± 416.9	83.8 ± 23.9	163.2 ± 82.0
5.0	677.2 ± 90.9	837.2 ± 228.4	466.5 ± 138.0	560.8 ± 90.0	194.0 ± 45.2	317.6 ± 143.4	100.0 ± 31.7	145.4 ± 78.2
15.0	758.0 ± 397.1	1106.2 ± 600.5	383.0 ± 189.5	645.8 ± 397.2	324.5 ± 249.0	459.4 ± 335.5	109.2 ± 91.0	204.0 ± 69.7

*Mean counts any time during the study period.

C_{max} of 45.4 ± 3.0 µg/ml. Patients in the 5.0 and 15.0 mg/kg dose groups exhibited a mean C_{max} of 207.1 ± 46.8 µg/ml and 887.5 ± 358.1 µg/ml, respectively. The mean C_{max} was proportional to the dose administered (Figure 3a). A noncompartmental analysis of the serum level data yielded mean area under the concentration curve (AUC) values ranging from 816 ± 447 µg-h/ml for the 0.25 mg/kg dose group to 137,322 ± 38,758 µg-h/ml for the 15.0 mg/kg dose group. The mean AUC was proportional to the dose administered (Figure 3b). The half-life of the IDEC-131 antibody was consistent between the 1.0, 5.0, and 15.0 mg/kg dose groups and was determined to be 303.6 ± 101.9 h, 319.7 ± 64.7 h, and 298.7 ± 51.2 h, respectively. Similarly, the clearance rate of the antibody was consistent between these 3 dose groups, yielding respective values of 0.09 ± 0.03, 0.12 ± 0.04, and 0.12 ± 0.05 ml/h-kg. However, the half-life and clearance rate for the 0.25 mg/kg dose group differed substantially from the higher dose groups. This dose group exhibited a serum half-life of 123.0 ±

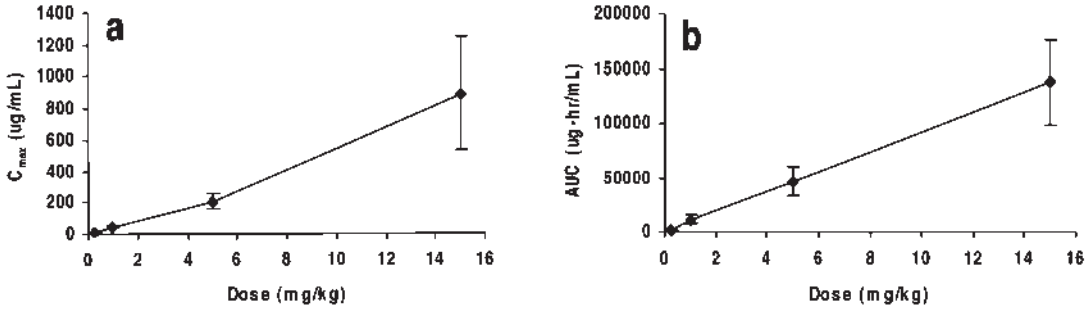

Figure 3. Serum concentrations of the IDEC-131 antibody were determined for samples obtained throughout the study. Mean C_{max} and AUC were calculated for all but the lowest dose group (0.05 mg/kg). (a) Mean C_{max} ranged from 7.7 ± 3.2 to 887.5 ± 358.1 mg/ml. (b) A noncompartmental analysis of the serum concentration data yielded mean AUC values ranging from 816 ± 447 to 137,322 ± 38,758 mg-h/ml.

29.7 h and a clearance rate of 0.38 ± 0.20 ml/h-kg, indicating that the IDEC-131 antibody cleared more rapidly in these patients compared with higher dose groups. Moreover, the volume of distribution for the 0.25 mg/kg dose group was much higher than that of the 1.0, 5.0, or 15.0 mg/kg groups.

Clinical activity and serologic studies. Based on the results of studies in murine models for SLE, it was not anticipated that the single dose regimen employed in this study would produce demonstrable serologic or clinical benefit. No clinically significant changes in serologic variables were observed, including complement CH50, complement C4, ESR, CRP, ANA, and DNA antibodies. It should be noted that abnormal baseline values for some of these variables were present in only a small number of patients. A nonvalidated patient global assessment of their overall condition (5 point scale ranging from very poor to very good) did not reveal an apparent clinically significant change after treatment. A formal evaluation of disease activity including serial SLEDAI scores was not conducted.

CD40 ligand expression. CD40L expression was measured during the study. There was no demonstrable expression of CD40L on T cells in any dose group. Specifically, less than 1% of cells expressed this cell surface molecule, which was below the level of detection for our assay. Consequently, it was not possible to assess CD40L saturation by IDEC-131.

DISCUSSION

The primary objective of this phase I study was to assess the short term toxicity and to evaluate the pharmacokinetics of IDEC-131. All 23 patients completed the study, and overall a favorable safety profile was observed. The majority of AE were classified as mild or moderate (grade 1 or 2) and appeared to be a consequence of lupus disease activity rather than from treatment with IDEC-131. The most common AE experienced were asthenia/fatigue, rashes, nausea, headaches, and arthralgia, all potential disease related manifestations of SLE. There was no relationship between the dose of IDEC-131 and the number, severity, or type of AE reported. AE that occurred on the day of infusion were not characteristic of a cytokine mediated, infusion related syndrome that has been observed with some other anti-T cell antibodies. It should be emphasized, however, that clinical trials of a different anti-CD40L Mab have apparently been suspended due to thrombotic complications (unpublished report). Therefore, future studies should monitor closely for the development of thrombosis. Overall, there were no unanticipated AE in this study.

Based on the role of CD40L in immune function, it is conceivable that blocking the CD40 pathway may increase the risk of infection[19]. However, there were no apparent infectious complications in this short term study. Eight infections were reported in 8 patients, but no infection was considered related to study treatment. All infections were mild or moderate, and all the patients recovered without complications. Study participation occurred during the winter and spring months, and the upper respiratory infections observed during the study appeared to be those expected for this population of patients.

No patient treated with IDEC-131 developed a detectable immune response to the administered Mab. This lack of antibody response to the study drug may allow patients in future studies to receive repeated treatments without the development of an antibody response.

Previous studies have reported both an increased and prolonged expression of CD40L on the surface of T cells in patients with lupus. The reason for our inability to detect increased expression in this population is unclear. In particular, CD40L was expressed on < 1% of lymphocytes (data not shown). One possible explanation is that the patients in this study may not have had active enough disease. Another possibility is that peripheral measurements of CD40L expression may not accurately reflect the degree of immune stimulation taking place in other compartments of the immune system.

No evidence of treatment related T cell or B cell depletion was observed from a single iv infusion of IDEC-131. The absence of treatment related lymphocyte depletion was expected, because the CD40L antigen is expressed on only a small percentage of activated T lymphocytes. Pharmaco-

kinetic analyses determined that the C_{max} and AUC values were proportional to the dose administered. At doses between 1.0 and 15.0 mg/kg, the serum half-life was about 13 days.

Given the complexity of SLE outcome measures, and the low likelihood of clinical efficacy from a single dose, a formal evaluation of the efficacy of IDEC-131 was not undertaken in this phase I single dose study. However, this study provides the first demonstration of anti-CD40L monoclonal antibody administration in patients with SLE. This has clinical relevance because it demonstrates the feasibility of administering specifically targeted immunosuppression, and thereby possibly reducing toxicity of treatment for autoimmune disease. Based on our finding that a single dose of IDEC-131 was safe and well tolerated in patients with SLE, a multidose phase II study has been initiated in which the effect of IDEC-131 on SLE disease activity is being assessed using validated disease activity indices.

ACKNOWLEDGMENT

The authors thank Susan Cairelli for editorial assistance in the preparation of the manuscript and Dr. David Daikh for thoughtful review of the manuscript.

REFERENCES

1. Daikh DI, Finck BK, Linsley PS, Hollenbaugh D, Wofsy D. Long-term inhibition of murine lupus by brief simultaneous blockade of the B7/CD28 and CD40/gp39 costimulation pathways. J Immunol 1997;159:3104-8.
2. Mohan C, Shi Y, Laman JD, Datta SK. Interaction between CD40 and its ligand gp39 in the development of murine lupus nephritis. J Immunol 1995;154:1470-80.
3. Janeway C Jr, Bottomly K. Signals and signs for lymphocyte responses. Cell 1994;76:275-85.
4. Jenkins M. The ups and downs of T cell costimulation. Immunity 1994;1:443-6.
5. Grewal I, Flavell R. CD40 and CD154 in cell-mediated immunity. Annu Rev Immunol 1998;16:111-35.
6. Henn V, Slupsky J, Grafe M, et al. CD40 ligand on activated platelets triggers an inflammatory reaction of endothelial cells. Nature 1998;391:591-4.
7. Armitage R, Fanslow W, Strockbine L, et al. Molecular and biological characterization of a murine ligand for CD40. Nature 1992;357:80-2.
8. van Essen D, Kikutani H, Gray D. CD40 ligand-transduced co-stimulation of T cells in the development of helper function. Nature 1995;378:620-3.
9. Noelle R, Ledbetter J, Aruffo A. CD40 and its ligand, an essential ligand-receptor pair for thymus-dependent B-cell activation. Immunol Today 1992;13:431-3.
10. Koshy M, Berger D, Crow MK. Increased expression of CD40 ligand on systemic lupus erythematosus lymphocytes. J Clin Invest 1996;98:826-37.
11. Datta SK, Kalled SL. CD40-CD40 ligand interaction in autoimmune disease. Arthritis Rheum 1997;40:1735-45.
12. Desai-Mehta A, Lu L, Ramsey-Goldman R, Datta SK. Hyperexpression of CD40 ligand by B and T cells in human lupus and its role in pathogenic autoantibody production. J Clin Invest 1996;97:2063-73.
13. Kato K, Santana-Sahagun E, Rassenti L, et al. The soluble CD40 ligand sCD154 in systemic lupus erythematosus. J Clin Invest 1999;104:947-55.
14. Vakkalanka R, Woo C, Kirou K, Koshy M, Berger D, Crow M. Elevated levels and functional capacity of soluble CD40 ligand in systemic lupus erythematosus sera. Arthritis Rheum 1999; 42:871-81.
15. Foy T, Aruffo A, Bajorath J, Buhlmann, Noelle R. Immune regulation by CD40 and its ligand GP39. Ann Rev Immunol 1996;14:591-617.
16. Durie F, Foy T, Masters S, Laman J, Noelle R. The role of CD40 in the regulation of humoral and cell-mediated immunity. Immunol Today 1994;15:406-11.
17. Tan EM, Cohen AS, Fries J, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271-7.
18. Hochberg M. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus [letter]. Arthritis Rheum 1997;40:1725.
19. Grewal I, Borrow P, Pamer E, Oldstone M, Flavell R. The CD40-CD154 system in anti-infective host defense. Current Opin Immunol 1997;9:491-7.