Modified Anti-CD3 Therapy in Psoriatic Arthritis: A Phase I/II Clinical Trial

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ABSTRACT. ***Objective.*** Treatment of autoimmune diseases with therapies that tolerize pathogenic lymphocytes may obviate the need for longterm global immunosuppression. *In vitro*, non-Fc receptor binding derivatives of anti-murine CD3 monoclonal antibodies tolerize type 1 T cells and stimulate type 2 T cells. Recently, a humanized non-FcR binding derivative of the anti-human CD3 Mab OKT3, huOKT3γ1(ala-ala), has been described. We hypothesized that this Mab may be safe and efficacious in the treatment of type 1 T lymphocyte mediated chronic autoimmune diseases such as psoriatic arthritis (PsA).

Methods. In a Phase I/II trial, 7 patients with PsA were treated with escalating daily doses of huOKT3γ1(ala-ala) for 12 to 14 days. Number of tender and swollen joints and a visual analog pain scale were used to rate disease activity at entry and Day 30 and Day 90 after treatment.

Results. At Day 30, 6 of 7 patients had ≥ 75% improvement in the number of inflamed joints and an average 63% improvement on the patient pain scale. Two of 6 responders had sustained improvement at Day 90. No patient treated with an initial dose ≤ 1 mg had significant side effects, nor did they have detectable increases in serum cytokines. One patient treated with 4 mg without escalation developed mild cytokine release symptoms associated with elevation of interleukin 10. Transient T cell depletion occurred following treatment with the maximum dose of 4 mg, which resolved by Day 30. Antiidiotypic antibodies developed in 2 patients; however, there was no concurrent decrease in efficacy.

Conclusion. These data indicate that huOKT3γ1(ala-ala) may be useful in treating PsA. (J Rheumatol 2002;29:1907–13)

Key Indexing Terms:
PSORIATIC ARTHRITIS SPONDYLOARTHROPATHY MONOCLONAL ANTIBODY
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Ideally, autoimmune diseases would be treated with specific immunotherapeutics capable of reestablishing tolerance to the specific antigens driving the pathological immune process. One way to selectively inhibit or delete autoreactive T cell populations in the absence of a known antigen is to modulate the receptor/ligand interactions that initiate and maintain T lymphocyte activation[1,2]. Strategies targeting the T cell receptor (TCR) are one option to influence these autoreactive populations.

The most widely used anti-TCR complex monoclonal antibody is murine OKT3 (Mab OKT3), which recognizes the CD3 complex and is used for treating acute graft rejection in humans[3]. The murine OKT3 coengages Fc receptors (FcR) on adjacent cells, resulting in super-crosslinking of surface TCR and transient T cell activation prior to the onset of immunosuppression[4]. This can cause substantial toxicity in the form of cytokine release syndrome[5]. Further, OKT3 Mab therapy results in global nonspecific T cell suppression and generates a robust anti-Mab response, which makes repeated use impractical[6]. In rheumatoid arthritis (RA), signaling through the TCR is impaired, possibly due to low expression of signal transducing ζ chains in T lymphocytes of patients with RA[7,8]. However, TCR mediated signal transduction has not been studied in the seronegative spondyloarthropathies.

huOKT3γ1(ala-ala) is a modification of Mab OKT3 with decreased immunogenicity and inability to bind FcR, resulting in less toxicity than conventional OKT3. Rather than activating T cells, non-FcR binding anti-CD3 antibodies are thought to deliver a partial signal to the TCR, which has differing effects on the various T cell subsets[9]. Studies of the murine analog to huOKT3γ1(ala-ala), 2C11-IgG3, in mice revealed that this antibody causes type 1 T cells to become unrespon-

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Dr. Bluestone has a financial interest in the monoclonal antibody hOKT3gamma1 (ala-ala) consisting of a patent application and a commercial agreement with Centocor/Johnson & Johnson.

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sive to subsequent TCR stimulation, while type 2 T cells remain competent to proliferate and secrete interleukin 4 (IL-4)[10,11]. Studies of huOKT3γ1(ala-ala) in human graft rejection confirm much lower toxicity compared to conventional mOKT3[9,12,13]. Thus, modified anti-CD3 antibodies have little toxicity and restricted immunomodulatory effects, which make them promising agents to treat autoimmune diseases mediated by type 1 T lymphocytes.

Psoriatic arthritis (PsA) is a chronic seronegative arthritis that occurs in about 6 to 7% of individuals with the common dermatological disorder psoriasis[14]. PsA can be manifest by various patterns of joint involvement, including an asymmetrical oligoarthritis, spondylitis, distal interphalangeal joint arthropathy, or a rheumatoid-like polyarthritis. The majority of patients have cutaneous psoriasis[15] or a history of it. T lymphocytes have been implicated in PsA based on associations with MHC Class I[16] and on observations of elevated numbers of CD8+ T cells in PsA synovial fluid[17]. Psoriatic skin disease has been reconstituted in the SCID mouse by engraftment of uninvolved human skin and CD4+ T cells from patients with psoriasis, and appears dependent on resident CD8+ T cells contained in the skin graft[18,19]. The presence of type 1 associated cytokines in psoriatic synovium[20] suggests that type 1 T cells may be the primary effector cells in both the arthritis and the skin disease. Thus PsA appears to be an ideal candidate for immunomodulation with huOKT3γ1(ala-ala).

We describe a Phase I/II study of the huOKT3γ1(ala-ala) Mab in PsA. Our observations suggest huOKT3γ1(ala-ala) is safe and may be efficacious in the treatment of PsA.

MATERIALS AND METHODS

This study was approved by the Federal Drug Administration of the United States (BB-IND 7191).

Patient selection. Patients between the ages of 18 and 65 were eligible for this study if they were diagnosed with PsA by a rheumatologist at the University of Chicago based on classic descriptions of PsA[15]. All patients had a current or previous history of cutaneous psoriasis. All patients had failed at least one remittive agent [methotrexate (MTX), sulfasalazine, or azathioprine], and were taking ≤ 10 mg/day prednisone. Patients discontinued remittive agents (MTX, sulfasalazine) at least 4 weeks prior to study entry but were allowed to continue stable doses of prednisone and nonsteroidal antiinflammatory drugs. Patients had to have at least 3 extraspinal joints with confirmed active synovitis at entry. The extent and activity of psoriasis were not part of the selection criteria. Patients were excluded if they were pregnant, had an active infection, had been treated with OKT3 previously, had a history of hypersensitivity to murine products, or had a history of cancer, leukopenia or significant cardiopulmonary disease.

Study drug. In a joint collaboration of the University of Chicago and Johnson and Johnson Laboratories, the Mab OKT3 was modified as described to produce huOKT3γ1(ala-ala)[9]. To reduce immunogenicity, the complementarity defining region (CDR) of Mab OKT3 was engrafted onto a human IgG1 backbone. Two additional alanine mutations (amino acids 234, 235) were then introduced to prevent FcR binding, resulting in the Mab huOKT3γ1(ala-ala).
Study design. This was an open label trial of daily infusions with escalating doses of huOKT3γ1(ala-ala). To explore the tolerance and safety of this agent, 8 patients were divided into 4 dosing protocols. The maximum dose in each treatment arm was 4.0 mg, with the initial dose ranging between 0.005 mg and 4.0 mg. Medication was administered intravenously in 25 ml normal saline over 5 min in the Clinical Research Center at the University of Chicago. Patients were assessed daily for toxicity during the infusion period by a physician (MRC).

Clinical measures. Physical examinations, number of tender and swollen joints, and psoriasis skin scores (PASI)[21] were performed at study entry, periodically during the infusion, and at 30 and 90 days by one physician (MRC). A visual analog scale for pain on a 10 cm line was completed by the patient daily at the time of each infusion and on Days 30 and 90.

Biological measures. Patient blood was drawn preinfusion and 1 h postinfusion. Complete blood counts, flow cytometric analysis of lymphocyte subsets, T cell coating, receptor modulation, and serum drug levels were assayed. Serum aliquots were stored at –80°C for later batch assay of cytokines.

T cell subsets, CD3 coating, and modulation. Peripheral blood was collected daily during the infusion period and at 30 and 90 days and was centrifuged at room temperature[13]. White blood cells were separated by standard methods and stained with antibodies to the following cell surface antigens: CD2, CD19, CD45, CD4, or CD8 or irrelevant isotype controls (Becton Dickinson). Data were collected using a FACScan flow cytometer (Becton Dickinson) and analyzed using CellQuest software (Becton Dickinson). Absolute number of each cell subset was calculated by first normalizing the percentage positive of each subset to the percentage of CD45 positive cells. Percentages were multiplied by the absolute lymphocyte count provided by the ABX Cobas Minos STL hematology analyzer (ABX Hematology, Garden Grove, CA, USA).

CD3 coating and CD3 modulation were calculated by staining leukocyte samples with FITC labeled OKT3 (Ortho Diagnostics) and OKT3D (R.W. Johnson) antibodies, which recognize distinct epitopes of the CD3ε molecule[22]. Analysis of patient and control cells using the CellQuest software provided daily mean fluorescence intensity (MFI) of OKT3-FITC and OKT3D-FITC staining for CD4+ and CD8+ subsets. Coating and modulation were then calculated as described[13]. In our assay, maximal inhibition of OKT3-FITC staining, as measured by prebinding with saturating huOKT3γ1(ala-ala), was only about 80% (data not shown). Thus, observed values approaching 80% inhibition in this assay reflect near saturation of the available receptor with huOKT3γ1(ala-ala).

Measurement of drug levels. huOKT3γ1(ala-ala) serum levels were determined using flow cytometry as described by Woodle[13]. Briefly, normal human peripheral blood cells were mixed with patient sera or with known concentrations of huOKT3γ1(ala-ala). OKT3-FITC was added, and a standard curve of OKT3-FITC fluorescence intensity versus drug concentration was generated. Drug levels of huOKT3γ1(ala-ala) in patient sera were then estimated by extrapolation to the standard curve generated with each assay.

Anti-huOKT3γ1(ala-ala) idiotypic antibody detection. Serum antibodies reactive with idiotype shared by murine OKT3 and huOKT3γ1(ala-ala) were detected by ELISA[23]. ELISA plates (Costar) were coated with OKT3 and blocked with 1% bovine serum albumin/phosphate buffered saline. Serial dilutions of patient or control sera were titered, washed, then incubated with peroxidase labeled anti-human Ig (antibody to human IgA, IgG, and IgM; Kirkegaard and Perry, Gaithersburg, MD, USA), then 2,2′-azino-di-3-ethylbenzthiazoline sulfonic acid (ABTS) substrate solution was added, and plates were read at 405 nm.

Cytokine assays. Tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), IL-6, IL-2, IL-4, and IL-10 serum levels were quantitated using commercial ELISA kits (Beckman Coulter Immunotech) following manufacturer's instructions.

Statistical analysis. Two tailed paired t tests were used to evaluate changes in total and subset lymphocyte counts, T cell coating, TCR modulation, and patient pain scale scores. A paired Wilcoxon signed rank test was used to assess significant differences in the number of tender and swollen joints and PASI scores at Day 1 (or Preinfusion Day 0, if Day 1 not available), Day 30, and Day 90 due to non-normal data distribution. Data are expressed as mean ± SD unless otherwise specified. Stata 6.0 (Stata Corp.) was used for the statistical analysis.

Table 1. Patient characteristics at entry and clinical responses to huOKT3γ1(ala-ala). Eight patients with disease durations ranging from 3 to 14 years and who had failed methotrexate (MTX) and/or sulfasalazine (SSZ) were enrolled in one of 4 treatment arms based on rapidity of dose escalation. Shown are number of tender and swollen joints, visual analog pain scales (0–10 cm scale), and PASI skin scores at entry (Day 1) and at 30 and 90 days. Drug reaction and human anti-chimeric antibodies (HACA) are noted. Although all patients were diagnosed as having PsA at entry, Patient 5 evolved to polyarticular, rheumatoid factor positive arthritis after this trial. Patient 8 was withdrawn from the trial due to an adverse reaction.

Patient	Age, yrs	Sex	Duration, yrs	Previous Therapy	Dose Escalation Period, days	Tender Joint Number, Day			Swollen Joint Number, Day			VAS 10 cm, Day			PASI Skin Score Day			Drug Reaction	HACA
						1	30	90	1	30	90	1	30	90	1	30	90		
1	49	M	5	MTX	6	11	2	10	15	2	11	7.2	4.0	5.0	0.3	0	0	No	–
2	34	M	5	SSZ	6	9	2	7	10	0	8	3.3	1.1	2.0	0	0	—	No	–
3	31	M	3	SSZ	4	16	0	15	16	0	14	6.2	2.6	7.6	0.7	0.7	2.8	No	+
4	54	M	14	MTX	4	13	0	8	13	0	9	0.4	0.1	3.8	23.2	17.4	24.6	No	+
5	63	F	3	MTX	2	13	36	—	44	40	—	6.2	8.7	—	1.2	—	—	No	–
6	50	M	3	MTX	2	11	0	1	13	0	1	6.5	1.6	0.8	9.8	9.8	10.2	Minor	–
7	57	F	3	SSZ	2	4	0	0	4	0	0	7.1	1.9	5.9	0.4	0	0.4	No	–
8	71	M	12	MTX	0	0	—	—	18	—	—	4.0	—	—	9.6	—	—	Moderate	–

RESULTS

Clinical response and toxicity. Eight patients with PsA were enrolled in an open label phase I/II trial of huOKT3γ1(ala-ala) (Table 1). The average age at entry was 51 years and 6 patients were male. The average duration of disease was 6 years and all patients had failed at least one remittive therapy, most commonly MTX. Patients had small joint involvement of the hands, and additionally had variable degrees of large joint and lower extremity involvement. Four of 8 had involvement of the distal interphalangeal joints of the hands. At entry, all had active disease, with a mean number of 9.62 (± 5.23) tender and 16.62 (± 11.86) swollen joints. All patients had a history of cutaneous psoriasis, and 7 of 8 had active cutaneous psoriasis at study entry. Patients were enrolled sequentially into the 4 treatment arms. The first 2 patients received an initial dose of 0.005 mg/day and reached the maximum (4.0 mg) dose after 6 days. The next 2 patients started with 0.125 mg and escalated to 4.0 mg over 4 days, while the following 3 patients started with 1.0 mg and escalated to full dose after 2 days. Patient 8 received the full 4.0 mg on the first day without gradual escalation. All patients who completed the study received 8 to 10 days of treatment at 4.0 mg/day.

Of the 7 patients who completed the trial, 6 had dramatic improvement in their number of tender and swollen joints. Indeed, 5 patients had no swollen joints at 30 days (Table 1). By 90 days, 4 of 6 responding patients had a recurrence of joint activity but were still improved compared to disease activity at entry. Two of the 6 responding patients had no significant disease activity at 90 days.

For the 7 patients completing the trial, the mean number of tender joints at entry was 11.0 (± 3.79) and the mean number of swollen joints was 16.0 (± 12.86). By 30 days the mean swollen joint number was 6.0 (± 15.01; p = 0.02 relative to Day 1). The 30 day mean tender joint number decreased to only 5.71 (± 13.39; p = nonsignificant), due to a striking flare in tender joints in Patient 5, although the number of swollen joints decreased slightly in this patient (Table 1). Median tender and swollen joint number was 0. Patient 5, who had the flare in tender joints, later developed an elevated rheumatoid factor and rheumatoid nodules, and is now felt to have RA. Thus her response may not be representative of the response in PsA. In addition, the response of Patient 5 fulfills criteria for an outlier value ($p < 0.005$) if analyzed by Dixon's gap test[24].

Because it became apparent that Patient 5 was aberrant in both her disease and her response, the data were reanalyzed excluding this patient. Such analysis revealed a strong, significant, and uniform clinical response in the remaining 6

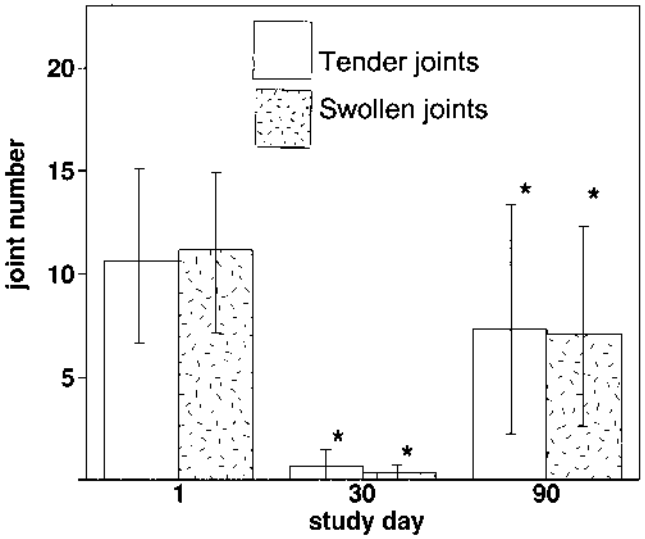

Figure 1. Clinical response as measured by tender and swollen joint number. Number of tender and swollen joints at 1, 30, and 90 days. Patient 5, who developed RA after the clinical trial, was excluded. Swollen joint number is significantly reduced at Day 30 (p = 0.02) and Day 90 (p = 0.04). Tender joint number is significantly reduced at Day 30 (p = 0.02) and at Day 90 (p = 0.03). *Statistically significant differences relative to Day 1.

patients in all variables between Day 0 and Day 30 (Figure 1). Mean swollen joint numbers improved from 11.33 (± 3.93) to 0.33 (± 0.82) on Day 30 (p = 0.02) and were still significantly improved at Day 90 (6.33 ± 4.63; p = 0.02). Tender joint counts improved from 10.67 (± 4.03) to 0.67 (± 1.03) by Day 30 (p = 0.03). Improvement persisted at Day 90 (6.63 ± 5.63; p = 0.03 relative to Day 1). Pain scale scores improved from 5.15 (± 2.80) at entry to 1.88 (± 1.33) at Day 30 (p = 0.009), but returned to 4.18 (± 2.52) at Day 90 (p = NS).

Six of 7 patients completing the trial had active cutaneous psoriasis at study entry (Table 1). No PASI score was available on Day 30 for Patient 5, or on Day 90 for Patient 5 and Patient 2. Two patients, both with minimal cutaneous disease at entry, had resolution of all lesions at Day 30; one patient remained in remission at 90 days, while the other relapsed. One additional patient (with very active cutaneous disease) experienced partial improvement at Day 30, and returned to baseline at Day 90. Mean PASI at entry was 5.08 (± 8.71) and 4.65 (± 7.34) at Day 30 (p = NS). At Day 90 PASI was 7.61 (± 10.3; p = NS relative to Day 1 or Day 30).

No patient treated in the 6 day and 4 day escalation arms had acute infusion related toxicities. Patient 6 (in the 2 day escalation arm) had mild symptoms (fever to 38.5°C and nausea) on Day 1, but recovered within 24 h and continued in the protocol without incident. Patient 8, who received 4 mg as his first dose, had significant toxicity, with nausea, vomiting, and fever to 40°C. His symptoms resolved within 24 h, but he was discontinued from the trial.

Immunological effects. Treatment with huOKT3γ1(ala-ala) induced a transient, dose dependent decrease in T lymphocyte counts from peripheral blood. While no substantial depletion was observed at lower doses (data not shown), significant decreases in both CD4 and CD8 peripheral T lymphocyte counts occurred after administration of the first 4 mg dose and these were maximal after the second or third dose of 4 mg (Figure 2). Absolute CD4 counts decreased from 960/μm^{-3} (± 627) at Day 0 to 270/μm^{-3} (± 171) at Day 3 (p = 0.02). Absolute CD8 counts decreased from 379/μm^{-3} (± 242) at Day 0 to 130/μm^{-3} (± 113) at Day 3 (p = 0.05). CD4+ and CD8+ T cells were depleted to similar degrees relative to pretreatment levels (62% vs 57% depletion at Day 3, p = NS). By Day 30 of the trial, or less than 3 weeks after the last dose of huOKT3γ1(ala-ala), lymphocyte counts had normalized in the periphery. By Day 90, the total number of lymphocytes was similar to that at entry, with a slight persistent elevation of CD8+ T lymphocytes (Day 90 CD8 count 830/μm^{-3} (± 595) (p = NS relative to Day 0). During and after therapy, we observed no significant changes in peripheral B lymphocytes, platelets, or red blood cells (data not shown).

T cell coating predictably increased with both dose and duration of administration of huOKT3γ1(ala-ala) (Figure 3A). Percentage T cell coating after 3 days of 4 mg huOKT3γ1(ala-ala) was 70.36% (± 10.83), and after 8 days of 4 mg huOKT3γ1(ala-ala) it was 79.71% (± 7.02). As the maximal

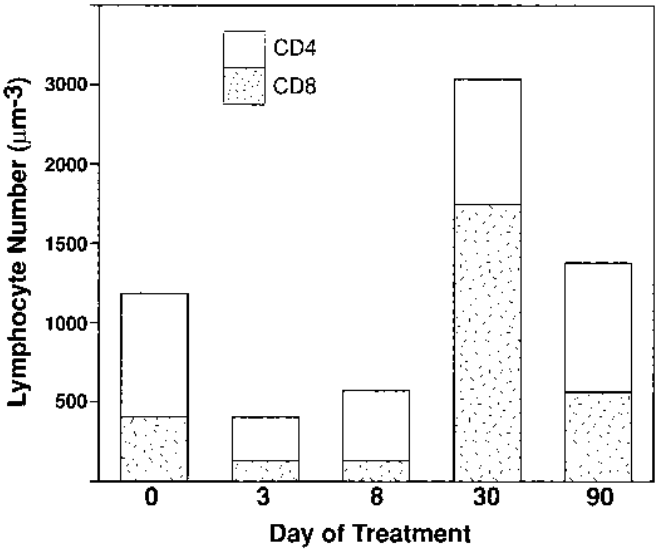

Figure 2. CD4/CD8 lymphocyte depletion following treatment with huOKT3γ1(ala-ala). CD4 and CD8 lymphocyte subsets at entry, after 3 and 8 days of daily 4 mg doses of huOKT3γ1(ala-ala), and at 30 and 90 days. Standard deviations are shown for the sum of CD4 and CD8 populations. Total lymphocytes are significantly depleted at Day 3 and Day 8 (each p < 0.02) but recover fully by Day 30. Day 30 and Day 90 counts are not significantly changed from Day 0. *Statistically significant lymphocyte depletion relative to Day 0.

binding in our assay plateaus at 80%, it is likely that most available CD3 epitopes were bound with repeated 4 mg doses of huOKT3γ1(ala-ala). T cell coating at both Day 3 and Day 8 of 4 mg huOKT3γ1(ala-ala) infusion was significantly greater than the coating after 1 mg or 2 mg infusions (p ≤ 0.02 for each comparison).

TCR modulation, the percentage internalization of surface TCR due to binding of huOKT3γ1(ala-ala), also occurred with higher doses of Mab (Figure 3B). After 3 days of 4 mg infusion, modulation was 31.71% (± 17.75), and after 8 days of 4 mg infusion it increased to 49.57% (± 10.26). Modulation was significantly increased after both 3 and 8 days of 4 mg huOKT3γ1(ala-ala) infusions relative to 1 mg and 2 mg doses (all p ≤ 0.001), and modulation was also significantly increased after 8 days of 4 mg huOKT3γ1(ala-ala) infusion relative to 3 days of 4 mg infusions (p = 0.005).

Nadir serum levels of huOKT3γ1(ala-ala) prior to each infusion were determined by flow cytometry. At peak lymphocyte depletion (Day 3), the average nadir serum concentration of huOKT3γ1(ala-ala) was 92.7 ng/ml (± 37.3). This increased to a nadir level of 237.6 ng/ml (± 109.3) after 8 days of daily 4 mg huOKT3γ1(ala-ala) infusion. The maximum nadir drug level detected, 586 ng/ml, occurred in Patient 7 after 10 days of 4 mg infusions of huOKT3γ1(ala-ala).

Cytokine assays for IL-2, IL-4, IL-6, TNF-α, and IFN-γ revealed no significant elevations with huOKT3γ1(ala-ala). Patient 8, who received the full dose huOKT3γ1(ala-ala) without gradual escalation, had a transient spike in serum IL-10,

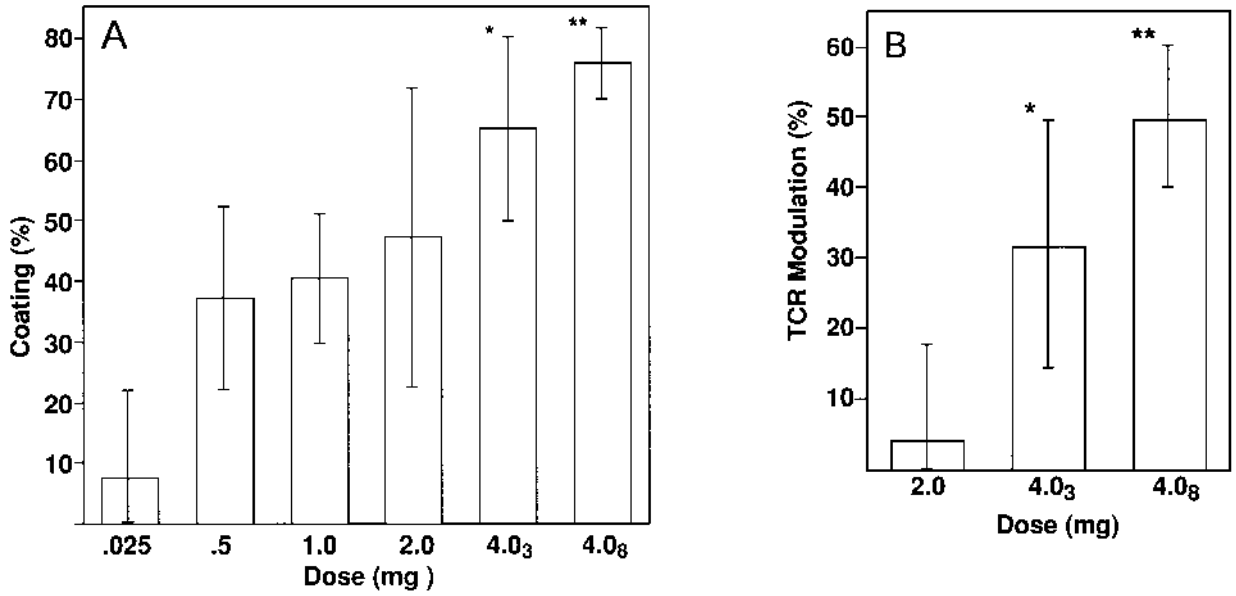

Figure 3. Coating and modulation of CD3 on peripheral T cells in response to huOKT3γ1(ala-ala). A. Percentage of CD3 coating with huOKT3γ1(ala-ala) increases with increasing doses of Mab. The coating observed at Day 3 (4.0_3) and Day 8 (4.0_8) of 4 mg huOKT3γ1(ala-ala) was significantly increased over coating observed at 1 mg or 2 mg doses ($p < 0.02$). B. TCR modulation is increased by Day 3 (4.0_3) and Day 8 (4.0_8) of 4 mg infusions of huOKT3γ1(ala-ala) relative to 2 mg huOKT3γ1(ala-ala). Significant modulation was only seen at the 4 mg doses ($p < 0.01$). *Statistically significant differences compared to doses < 4 mg per day huOKT3γ1(ala-ala).

from undetectable (< 80 pg/ml) pretreatment to 2800 pg/ml, associated with high fevers and vomiting. Patient 6 (who had mild symptoms after an initial infusion of 1 mg) had no detectable elevations in circulating cytokines.

The presence of antibodies to huOKT3γ1(ala-ala) was analyzed by ELISA at 30 or 90 days. Two patients treated in the 4 day escalation arm developed detectable antibodies, with titers > 10-fold above background at 30 days (data not shown). However, both these patients exhibited good clinical responses to huOKT3γ1(ala-ala).

DISCUSSION

PsA can be severe, unremitting, and poorly responsive to currently available therapeutics. Symptomatic improvement in PsA may occur with the use of medications such as MTX[25,26], but radiological progression may not be halted in these patients[27]. Recently, inhibitors of TNF such as etanercept or infliximab have shown promise for symptomatic control of PsA[28-30]. Although these agents appear to retard radiological progression in RA, their ability to prevent bone damage unique to PsA, such as osteolysis or ankylosis, remains to be determined. Patients that do respond must be treated chronically with immunosuppressives with concurrent increased risk of infection and other complications[31-33].

Non-FcR binding anti-CD3 antibodies, which anergize type 1 lymphocytes, have potential as relatively selective therapy in type 1 T lymphocyte mediated diseases such as PsA. We provide evidence that a single course of huOKT3γ1(ala-ala) may be safe and transiently efficacious in the treatment of PsA. Six of 7 patients who completed the protocol had ≥ 75% improvement in their affected joint number at 30 days, with median tender and swollen joint counts of 0. Symptoms did recur in a majority of patients by 90 days.

Although transient peripheral depletion of T cells occurred at the start of therapy, clinical responses were maximal at 30 days, when peripheral T cell counts had returned to normal levels. The population of T cells reappearing under huOKT3γ1(ala-ala) selection appears to be transiently incapable of mediating disease. This agent could ameliorate PsA by nonspecifically deleting effector T cells. However, studies of the analogous antibody in mice suggest differing effects on type 1 helper and type 2 T cells[10,11], which does support a relative specificity of action. Because the inciting antigen is not known in PsA, it is not possible to know if specific pathogenic clones or nonspecific clones were successfully deleted with this therapy. The precise immunomodulatory effects in human subjects will be investigated in a larger phase II study of huOKT3γ1(ala-ala) in PsA.

Despite remarkable initial clinical responses to huOKT3γ1(ala-ala), only 2 patients obtained lasting improvement. Because near maximal T cell coating and significant T cell depletion were obtained with the dose of 4 mg/day, this is not likely due to inadequate dosing. Rather, the failure of the majority of patients to gain a complete, persistent response may reflect heterogeneity of the T cell effector populations involved in autoimmune responses. Only committed and activated type 1 T cells are predicted to be sensitive to the anergizing potential of non-FcR binding anti-CD3 antibodies.

However, chronic autoimmune diseases, such as PsA, are mediated by asynchronous populations of lymphocytes that are at different stages of differentiation and activation. To affect all the lymphocytes involved in a chronic immune process, several rounds of treatment may be required[34].

Of the 6 patients who had active cutaneous psoriasis and who completed the trial, 3 had improvement in their skin disease. This did not achieve statistical significance. It is possible that larger trials of patients with more extensive cutaneous disease could demonstrate a significant effect of huOKT3γ1(ala-ala) on cutaneous psoriasis. This will be examined more closely in subsequent studies.

No patient in our study developed severe symptoms of cytokine release syndrome as seen in conventional mOKT3 therapy. However, Patient 8, treated with an initial dose of 4 mg without escalation, did develop symptoms suggestive of mild cytokine release syndrome. The weak activation of type 2 T cells seen in studies of the mouse analog 2C11-IgG3[10,11,35] might account for the relatively mild reaction observed in the patient treated without dose escalation, which was associated with the transient isolated release of the Th2 cytokine IL-10. Our results suggest that these side effects may be mitigated or avoided by using a dose escalation over at least 2 days prior to administration of full dose huOKT3γ1(ala-ala). However, as experience with this drug widens, more extensive data on toxicity will be obtained.

The treatment group appeared unusual in the predominance of swollen over tender joints. RA and PsA patients generally have more tender than swollen joints, although it has been observed that PsA patients are less tender than those with RA[15,36]. Most likely this distortion in the typical tender to swollen joint ratio is due to selection of PsA patients for this pilot study who have substantial objective synovitis, but whose pain level is low enough for them to be willing to discontinue their disease modifying agents.

One patient in this trial had a marked escalation in joint tenderness. Despite being seronegative for rheumatoid factor at the start of the trial, the patient later evolved to classic RA. Her joint flare improved after restarting MTX therapy. Two years later her rheumatoid nodules had disappeared, although rheumatoid factor was still positive. Radiography one year later did not reveal erosive disease. She was also found to have an aberrant response to infliximab, with exacerbation of synovitis after starting this therapy. It cannot be determined based on this uncontrolled study if huOKT3γ1(ala-ala) adversely affected her disease or whether the observed flare was due to MTX withdrawal in a patient unresponsive to the study drug. If future controlled studies reveal this type of flare, this might indicate adverse immunomodulation in a subset of patients with arthritis. Because this patient later evolved to RA, it is possible that huOKT3γ1(ala-ala) may have differing effects on PsA and other types of chronic polyarthritis, possibly due to abnormal TCR mediated signaling, as observed in patients with RA[7]. It seems much less likely that this therapy could have provoked the evolution of PsA into RA, a disease that differs substantially in clinical, genetic, epidemiological, and immunological features from PsA. To address this concern, future studies should follow rheumatoid factor status before and after therapy with huOKT3γ1(ala-ala).

Despite humanization of the anti-CD3 Mab, anti-huOKT3γ1(ala-ala) antibodies did occur by Day 30 in both patients on the 4 day escalation protocol. Although the development of antiidiotypic antibodies was not associated with a poor clinical response in our trial, their presence might limit the efficacy of repeated courses of huOKT3γ1(ala-ala). In parallel to our findings, antiidiotypic antibodies commonly develop against the therapeutic anti-TNF Mab infliximab, used to treat RA. However, antiidiotypic responses to infliximab can be minimized with rapid dose escalations and concomitant use of MTX[37,38]. None of the 3 patients treated in the 2 day escalation in this trial developed antiidiotypic antibodies, suggesting that rapid escalation may minimize antiidiotypic responses. Concurrent treatment with huOKT3γ1(ala-ala) and MTX has not yet been examined.

Our results suggest that huOKT3γ1(ala-ala) may offer a viable approach to the treatment of chronic type 1 T lymphocyte mediated autoimmune diseases such as PsA. Some patients in this small trial had clinical benefit that extended significantly longer than the period of active treatment. Recurrence of synovitis might be prevented by repeated exposures to huOKT3γ1(ala-ala), which would then more effectively modulate asynchronous populations of T lymphocytes[34]. By targeting specific lymphocyte subclasses driving the inflammatory process, the induction of drug-free remissions may be possible. Further studies are needed with this promising agent to assess the effect of cyclic exposures of huOKT3γ1(ala-ala) on lymphocyte populations and disease activity in type 1 T cell mediated chronic autoimmune diseases.

REFERENCES

1. Daikh DI, Wofsy D. Cutting edge: Reversal of murine lupus nephritis with CTLA4Ig and cyclophosphamide. J Immunol 2001;166:2913-6.
2. Abrams J, Kelley S, Hayes E, et al. Blockade of T lymphocyte costimulation with cytotoxic T lymphocyte-associated antigen 4-immunoglobulin (CTLA4Ig) reverses the cellular pathology of psoriatic plaques, including the activation of keratinocytes, dendritic cells, and endothelial cells. J Exp Med 2000;192:681-94.
3. Hong JC, Kahan BD. Immunosuppressive agents in organ transplantation: past, present and future. Semin Nephrol 2000; 20:108-25.
4. Woodle ES, Thistlethwaite JR, Ghobrial IA, Jolliffe LK, Stuart FP, Bluestone JA. OKT3 F(ab′)2 fragments — retention of the immunosuppressive properties of whole antibody with marked reduction in T cell activation and lymphokine release. Transplantation 1991;52:354-60.
5. Jeyarajah DR, Thistlethwaite JR. General aspects of cytokine-release syndrome: timing and incidence of symptoms. Transplant Proc 1993;25:16-20.
6. Jaffers GJ, Fuller TC, Cosimi AB, Russell PS, Winn HJ, Colvin RB. Monoclonal antibody therapy: Anti-idiotypic and non-anti-idiotypic

antibodies to OKT3 arising despite intense immunosuppression. Transplantation 1986;41:572-8.
7. Mirza NM, Relias V, Yunis EJ, Pachas WN, Dasgupta JD. Defective signal transduction via T-cell receptor-CD3 structure in T cells from rheumatoid arthritis patients. Hum Immunol 1993;36:91-8.
8. Matsuda M, Ulfgren AK, Lenkei R, et al. Decreased expression of signal-transducing CD3 ζ chains in T cells from the joints and peripheral blood of rheumatoid arthritis patients. Scand J Immunol 1998;47:254-62.
9. Alegre ML, Peterson LJ, Xu D, et al. A non-activating "humanized" anti-CD3 monoclonal antibody retains immunosuppressive properties in vivo. Transplantation 1994;57:1537-43.
10. Smith JA, Tso J, Clark MR, Cole M, Bluestone JA. Nonmitogenic anti-CD3 monoclonal antibodies deliver a partial T cell receptor signal and induce clonal anergy. J Exp Med 1997;185:1413-22.
11. Smith JA, Bluestone JA. T cell inactivation and cytokine deviation promoted by anti CD3 mAbs. Curr Opin Immunol 1997; 9:648.
12. Woodle ES, Bluestone JA, Zivin RA, et al. Humanized, nonmitogenic OKT3 antibody, huOKT3γ1(ala-ala): Initial clinical experience. Transplant Proc 1998;30:1369-70.
13. Woodle ES, Xu D, Zivin RA, et al. Phase I trial of a humanized Fc receptor nonbinding OKT3 antibody, huOKT3γ1(ala-ala) in the treatment of acute renal allograft rejection. Transplantation 1999;68:608-16.
14. Shbeeb M, Uramoto K, Gibson L, O'Fallon W, Gabriel S. The epidemiology of psoriatic arthritis in Olmsted County, Minnesota, USA 1982-91. J Rheumatol 2000;27:1247-50.
15. Moll JM, Wright V. Psoriatic arthritis. Semin Arthritis Rheum 1973;3:55-78.
16. Gladman DD, Anhorn KAB, Schachter RK, Mervart H. HLA antigens in psoriatic arthritis. J Rheumatol 1986;13:586-92.
17. Costello P, Bresnihan B, O'Farrelly C, Fitzgerald O. Predominance of CD8+ T lymphocytes in psoriatic arthritis. J Rheumatol 1999; 26:1117-24.
18. Nickoloff B, Wrone-Smith T. Injection of pre-psoriatic skin with CD4+ T cells induces psoriasis. Am J Pathol 1999;155:145-9.
19. Nickoloff BJ. The immunologic and genetic basis of psoriasis. Arch Dermatol 1999;135:1104-10.
20. Ritchlin C, Haas-Smith SA, Hicks D, Cappuccio J, Osterland C, Looney RJ. Patterns of cytokine production in psoriatic synovium. J Rheumatol 1998;25:1544-52.
21. Fredriksson T, Pettersson U. Severe psoriasis — oral therapy with a new retinoid. Dermatologica 1978;157:238-41.
22. Woodle ES, Thistlethwaite JR, Jolliffe LK, Fucello AJ, Stuart FP, Bluestone JA. Anti-CD3 monoclonal antibody therapy. An approach toward optimization by in vitro analysis of anti-CD3 antibodies. Transplantation 1991;52:361-8.
23. Woodle ES, Thistlethwaite JR, Jolliffe LK, et al. Humanized OKT3 antibodies: successful transfer of immune modulating properties and idiotypic expression. J Immunol 1992;148:2756-63.
24. Bliss CI. Statistics in biology, Vol. 1. Statistical methods for research in the natural sciences. New York: McGraw-Hill; 1967.
25. Jones G, Crotty M, Brooks P, and the Psoriatic Arthritis Meta-anlysis Study Group. Psoriatic arthritis: a quantitative overview of therapeutic options. Br J Rheumatol 1997;36:95-9.
26. Willkens RF, Williams HJ, Ward JR, et al. Randomized, double-blinded, placebo controlled trial of low-dose pulse methotrexate in psoriatic arthritis. Arthritis Rheum 1984;27:376-81.
27. Abu-shakra M, Gladman DD, Thorne JC, Long J, Gough J, Farewell VT. Longterm methotrexate therapy in psoriatic arthritis: clinical and radiological outcome. J Rheumatol 1995;22:241-5.
28. Ogilvie AL, Antoni C, Dechant C, et al. Treatment of psoriatic arthritis with antitumor necrosis factor-alpha antibody clears skin lesions of psoriasis resistant to treatment with methotrexate. Br J Dermatol 2001;144:587-89.
29. Yazici Y, Erkan D, Lockshin MD. A preliminary study of etanercept in the treatment of severe, resistant psoriatic arthritis. Clin Exp Rheumatol 2000;18:732-4.
30. Mease PJ, Goffe BS, Metz J, VanderStoep A, Finck B, Burge DJ. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomized trial. Lancet 2000;356:385-90.
31. Gladman DD. Natural history of psoriatic arthritis. Baillieres Clin Rheumatol 1994;8:379-99.
32. Gladman DD, Shuckett R, Russell ML, Thorne JC, Schachter RK. Psoriatic arthritis — an analysis of 220 patients. Q J Med 1987;62:127-41.
33. Torre Alonso JC, Rodriguez Perez A, Arribas Castrillo JM, Ballina Garcia J, Riestra Noriega JL, Lopez Larrea C. Psoriatic arthritis: a clinical, immunological and radiological study of 180 patients. Br J Rheumatol 1991;30:245-50.
34. Coffman RL, Mocci S, O'Garra A. The stability and reversibility of Th1 and Th2 populations. Curr Top Microbiol Immunol 1999; 238:1-12.
35. Smith JA, Tang Q, Bluestone JA. Partial TCR signals delivered by FcR non-binding anti-CD3 monoclonal antibodies differentially regulate individual Th subsets. J Immunol 1998;160:4841-9.
36. Buskila D, Langevitz P, Gladman DD, Urowitz S, Smythe HA. Patients with rheumatoid arthritis are more tender than those with psoriatic arthritis. J Rheumatol 1992;19:1115-9.
37. Antoni C, Kalden JR. Combination therapy of the chimeric monoclonal anti-tumor necrosis factor alpha antibody (infliximab) with methotrexate in patients with rheumatoid arthritis. Clin Exp Rheumatol 1999;17 Suppl 18:S73-77.
38. Maini R, Breedveld F, Kalden JR, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. Arthritis Rheum 1998;41:1552-63.