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A RANDOMIZED CLINICAL TRIAL OF OKT3 MONOCLONAL ANTIBODY FOR ACUTE REJECTION OF CADAVERIC RENAL TRANSPLANTS

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Abstract Since the murine monoclonal antibody OKT3 reacts with human T cells and blocks their function, we explored its effectiveness in treating T-cell-mediated rejection of renal allografts. In a prospective randomized multicenter trial, 123 patients undergoing acute rejection of cadaveric renal transplants were treated either with OKT3 daily for a mean of 14 days, with concomitant lowering of the dosage of other immunosuppressive drugs (63 patients), or with conventional high-dose steroids (60 patients). OKT3 reversed 94 per cent of the rejections — a figure that was significantly better ($P = 0.009$) than the 75

per cent reversal rate obtained with conventional steroid treatment. This superior reversal rate with OKT3 was reflected in an improved one-year graft survival of 62 per cent for the OKT3-treated group, as compared with 45 per cent for the steroid-treated group ($P = 0.029$), in patients who were all selected by virtue of having had acute rejection. We conclude that treatment with OKT3 (with concomitant lowering of the dosage of other immunosuppressive drugs) is an effective approach for acute renal-allograft rejection. (N Engl J Med 1985; 313: 337-42.)

DESPITE improvements in tissue matching and the introduction of newer immunosuppressive agents, acute rejection of the allograft remains a major impediment to the success of clinical renal transplantation. Conventional therapies include the use of high-dose steroid pulses and of antithymocyte globulins.¹⁻⁴ The use of high-dose steroids results in a high incidence of infection and other side effects. Antithymocyte globulins are more effective than steroids in reversing acute renal rejection, but difficulties in lot standardization, giving variations in efficacy and in the incidence of adverse reactions among lots, continue to be a major problem. OKT3 is a murine monoclonal antibody that is reactive with a 20,000-dalton molecule found only on the surface of thymocytes or mature human T cells.⁵ The structure recognized by OKT3 is linked to the T-cell antigen receptor^{6,7} and appears vital for the functioning of human T cells.⁸ Thus, OKT3 in vitro blocks both killing by cytotoxic

human T cells and the generation of other T-cell functions⁹⁻¹¹; furthermore, T-cell function is lost if OKT3 interacts with and causes the removal of the antigen T3 on the T-cell surface.^{12,13}

We have previously reported an open pilot study showing that OKT3 reversed acute renal-allograft rejection in all of 10 patients.¹⁴⁻¹⁶ We now present the results of a randomized prospective protocol comparing the safety and efficacy of OKT3 (with reduction in the dosage of concomitant immunosuppressive medication) with those of conventional steroid treatment in reversing acute renal-allograft rejection.

METHODS

Production of OKT3

OKT3 was produced from seed lots of the parent hybridoma. The immunoglobulin was purified from ascites and formulated, and ampules were filled under sterile conditions. Each batch was tested for purity and safety and conformed to the standards of the Food and Drug Administration.

Organization

This clinical trial was organized by the Immunobiology Division of the Ortho Pharmaceutical Corporation after a preliminary investigators' meeting at which a consensus was reached on protocol design. At each participating center an institutional review board approved the protocol and the informed-consent form and followed the progress of the study. All the patients were fully informed of the nature of the study and signed consent forms.

Eligibility Criteria

Patients had to be diagnosed as having their first rejection episode after cadaveric renal transplantation. Rejection criteria were documented and were those used by Shield et al.¹ To avoid cases of renal failure attributable to causes other than acute cellular rejection,

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entry was restricted to patients with rejections occurring from 6 to 93 days after transplantation.

Patients received a standard regimen of immunosuppression after transplantation. This comprised prednisone, starting at 2 mg per kilogram of body weight per day and tapering to 0.5 mg per kilogram per day by Week 9, and the maximal tolerated dose of azathioprine — approximately 100 to 150 mg per day.

Randomization

Patients meeting the eligibility criteria were randomly assigned at entry to receive either OKT3 or steroid treatment, the randomization schedule being generated by computer for each center.

OKT3 Group

After a negative skin test (0.1 ml of a 1- μ g-per-milliliter solution intradermally), OKT3 was administered by intravenous push at a dose of 5 mg per day for 14 consecutive days (Fig. 1). Investigators had the option of continuing therapy, and 14 patients were treated for additional periods of 1 to 14 days. During OKT3 administration the dosages of concomitant immunosuppressive agents were reduced — azathioprine to 25 mg per day and prednisone to 0.5 mg per kilogram per day. These were raised to the continuing dosages on the day after OKT3 therapy was stopped, as if rejection had not

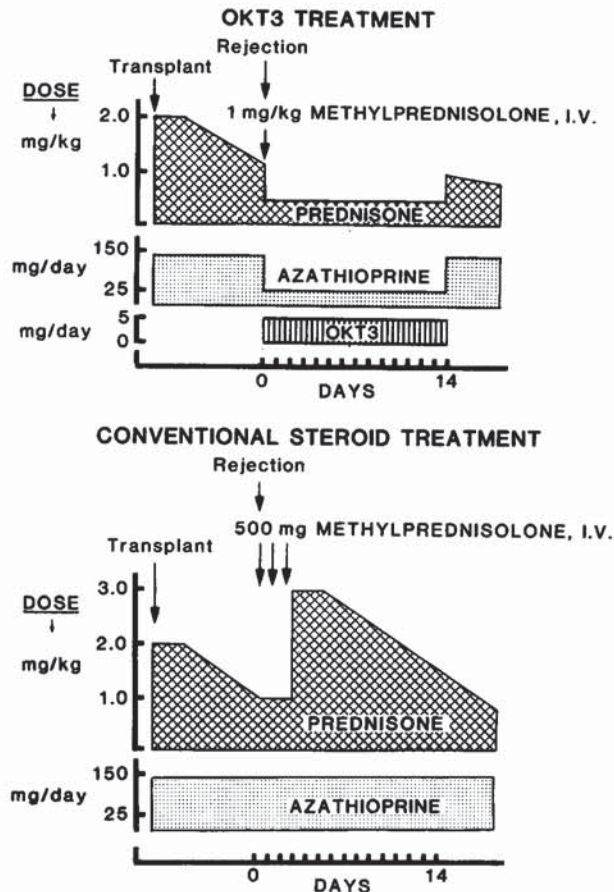


Figure 1. Plan of Daily Immunosuppressive Drug Regimens for Patients Randomly Assigned to OKT3 or Steroid Treatment for Acute Renal-Allograft Rejection.

During OKT3 treatment, dosages of steroids and azathioprine were reduced, with resumption of the pre-rejection tapered dosage of steroids and the azathioprine dosage when OKT3 was discontinued. By contrast, steroid treatment involved a high steroid dosage, with maintenance of the azathioprine dosage. I.V. denotes intravenous.

occurred. A bolus injection of 1 mg of methylprednisolone per kilogram and concomitant acetaminophen and antihistamines were permitted with the first dose of OKT3 to reduce the fever and chills that were known to accompany this first dose.

Conventional-Steroids Group

Azathioprine and prednisone were continued at pre-rejection levels. Methylprednisolone (500 mg per day) was given^{17,18} for a maximum of three days, after which prednisone could be given at a dosage of 3 mg per kilogram per day, if necessary, and tapered over the next seven days so that a dose of 1 mg per kilogram per day was achieved on the seventh day. The prednisone dosage was then tapered to what it would have been if rejection had not occurred (Fig. 1).

"Rescue" Treatment

Any patient whose serum creatinine level did not decrease on the sixth day or later and whose transplant rejection was judged not to have been reversed could be treated with additional conventional treatment (for the OKT3 group) or equine antithymocyte globulin (for the steroid group).

Reversal of Rejection

The therapeutic goal was reversal of renal-allograft rejection as judged by a three-day progressive fall in serum creatinine levels. The investigators judged that reversal had occurred in an additional three patients in the OKT3 group and eight patients in the steroid group, on the basis of clinical criteria alone, such as reduction in kidney swelling and tenderness, decreased fever, and resumption of diuresis.

Procedures

Before treatment for rejection, demographic data and a medical history were recorded for each patient. In addition, the patient underwent a complete pretreatment physical examination, with full clinical laboratory evaluation (blood-chemistry and hematologic studies and urinalysis) and chest radiography. During treatment for rejection, there were daily recordings of the serum creatinine level, body temperature, blood pressure, and white-cell count with differential cell count, and periodic measurement of other clinical laboratory indexes. On the termination of rejection therapy, all clinical laboratory measurements were repeated. Routine follow-up examinations were performed at 3, 6, 12, and 24 months after transplantation and included a determination of graft status and the same physical and laboratory examinations performed before rejection therapy. Throughout the trial, all adverse experiences and infections were recorded.

Statistical Methods

Fisher's exact test,¹⁹ Wilcoxon's rank-sum test,²⁰ or the extended Mantel-Haenszel chi-square test²¹ was used for pretreatment comparisons based on demographic and disease-history variables. Reversal of rejection was analyzed with stratification by investigators using the Mantel-Haenszel chi-square test.²² When reversal and graft-survival rates were being calculated, one OKT3-treated patient "rescued" with steroids was counted as constituting a treatment failure, as were 10 steroid-treated patients rescued with antithymocyte globulin. Steroid-treated patients rescued with additional steroids were considered treatment successes. Fisher's exact test was also used to compare the incidence rates in the two treatment groups for the following indexes: repeated rejection, adverse experiences, and infections. Life-table comparisons were performed with use of Breslow's test.²³

RESULTS

Patient Entry

In all, 123 patients — 63 in the OKT3 group and 60 in the steroids group — were treated with study medications. Summary data on demographic factors

and pertinent medical history for the study population are shown in Table 1. There were no statistically significant differences between the groups in any of these base-line characteristics, and the patients overall appeared representative of the population experiencing a first episode of acute renal-allograft rejection. However, 1 of the 63 patients treated with OKT3 was diagnosed in retrospect as having undergone a deterioration in renal function due to cytomegalovirus infection rather than acute renal rejection, and he was therefore excluded from the efficacy analysis.

Medication

OKT3 was administered intravenously at a dosage of 5 mg per day for a mean period of 14 days (range, 1 to 28). Increased amounts of steroids were also administered as rejection therapy in the control group for a mean of 14 days (range, 3 to 36). On the day before rejection, the mean daily doses of prednisone and azathioprine among patients entered into the OKT3 group were 1.07 mg per kilogram and 142 mg, respectively. During the period of OKT3 administration, the mean daily doses of prednisone and azathioprine were reduced to 0.56 mg per kilogram and 30 mg, respectively. Table 2 shows the cumulative doses of the conventional immunosuppressives for each group for the 28 days beginning with the day of rejection and indicates the marked steroid-sparing effect of the OKT3 regimen.

Reversal of Rejection

OKT3 reversed acute renal-allograft rejection in 58 of 62 patients (94 per cent) — a significantly higher reversal rate ($P = 0.009$) than that for conventional steroid treatment, which reversed rejection in 45 of 60 patients (75 per cent) (Table 3). If reversal was judged strictly according to the objective criterion of the occurrence of a progressive decrease in the serum creatinine level, the reversal rates became 55 of 62 (89 per cent) for the OKT3 group and 37 of 60 (62 per cent) for the steroids group ($P < 0.001$). The distribution of reversal results was generally consistent among investigators, and there was no statistically significant difference among the centers ($P = 0.36$). Among patients in whom rejection was reversed, the mean time to reversal was shorter in the OKT3-treated group (3.3 days) than in the steroid-treated group (4.9 days).

Kidney Fate after Reversal of Initial Rejection

After the reversal of acute rejection by OKT3 or conventional steroid treatment, both groups were treated similarly with conventional therapy for both

Table 1. Clinical Characteristics of Patients Randomly Assigned to OKT3 or Steroid Treatment for Acute Renal-Allograft Rejection.

CHARACTERISTIC	TREATMENT GROUP*	
	OKT3	STEROIDS
Sex (M/F)	43/20	39/21
Median age (yr)†	38 (17–65)	36 (16–64)
Median weight (kg)†	67 (42–103)	66 (30–111)
Race (white/nonwhite)	50/13	49/11
No. with diabetes mellitus	20	14
No. with prior transplants (0/1/2)	55/7/1	52/6/2
No. with pretransplant transfusions (0/1–4/>4)	1/12/44	3/10/40
Acute tubular necrosis and dialysis at entry	12	9
Renal disease (glomerulonephritis)	23	18
Crossmatch (–/+)	63/0	59/1
Preformed antibodies (0–24%/26–100% positive)	44/10	39/18
Median time from transplant to rejection (days)†	10 (6–74)	11 (6–91)

*There were no statistically significant differences between the two groups in any of these indexes.

†Numbers in parentheses represent the range of values.

maintenance and repeated episodes of rejection. Because of the efficacy of OKT3 in reversing acute rejection there were more patients (58) in whom rejection had been reversed by OKT3 than by conventional steroid treatment (45). A second rejection was common in both groups, occurring in 38 of 58 patients (66 per cent) initially treated with OKT3 and 33 of 45 patients (73 per cent) initially treated with conventional steroids ($P = 0.52$). The incidence of kidney loss due to repeated rejection was also similar in both groups: 19 of 58 patients (33 per cent) initially treated with OKT3 and 17 of 45 (38 per cent) initially treated with conventional steroids lost a kidney ($P = 0.68$).

Patient and Kidney Survival

Two patients in the steroid-treated group were lost to follow-up. At one year, 53 of 62 patients (85 per cent) treated with OKT3 and 52 of 58 (90 per cent) of those treated with steroids were alive ($P = 0.47$) (Table 3). All 53 living patients treated with OKT3 and the 52 living patients treated with steroids were followed for one year. According to life-table anal-

Table 2. Mean Cumulative Dosage of Immunosuppressive Medications over the First 28 Days of Treatment for Patients Randomly Assigned to OKT3 or Steroids for Acute Renal-Allograft Rejection.

MEDICATION	OKT3		STEROIDS	
	NO. OF PATIENTS	MEAN CUMULATIVE DOSAGE mg	NO. OF PATIENTS	MEAN CUMULATIVE DOSAGE mg
Prednisone	63	1218	60	2042
Methylprednisolone sodium succinate	62*	965	60	2019
Azathioprine	63	1765	59*	2711

*One OKT3-group patient did not receive methylprednisolone, and one steroid-group patient received cyclophosphamide rather than azathioprine.

ysis, kidney survival rates for the OKT3 group and the steroid group were 62 and 45 per cent, respectively ($P = 0.029$) (Fig. 2).

Discontinuance of Initial Reversal Treatment

OKT3 was discontinued prematurely in 13 patients because of failure of reversal (two patients), a second rejection during treatment (one), adverse experiences (six, four of whom had already had reversal), or administrative error (four, all of whom had already had reversal).

Steroid treatment was discontinued prematurely in 15 patients because of its failure to reverse rejection; rescue with equine antithymocyte globulin was attempted in 10 of these cases, with reversal achieved in 7.

Adverse Experiences

The first and, to a lesser extent, second injections of OKT3 were associated with a symptom complex that did not occur with subsequent injections. This typically commenced 45 to 60 minutes after the first injection of OKT3 and lasted for several hours. It involved pyrexia (73 per cent), chills (57 per cent), tremor (10 per cent), dyspnea (21 per cent), chest pain and tightness (14 per cent), wheezing (11 per cent), nausea (11 per cent), and vomiting (13 per cent). This symptom complex was considered to be due to a physiologic response to mediators released from T cells after the initial OKT3 treatment, with resulting effects on temperature control, bronchial smooth-muscle tone, and the gastrointestinal tract. In one patient who was in a state of fluid overload before treatment, chills, bronchospasm, wheezing, shortness of breath, anxiety, increased blood pressure, and pulmonary edema developed after the first dose of OKT3. The patient was treated promptly and successfully with fluid reduction and steroids. The trial in one patient in the OKT3 group was discontinued because of renal-artery thrombosis. OKT3 was discontinued in four other patients because of high fever, rash and pruritus, thrombocytopenia, or profound weak-

ness; in all four cases reversal had already been established.

Infections

Infections occurred at comparable rates in both groups. During the first 45 days after the start of treatment, infection developed in 43 of 63 patients (68 per cent) and 39 of 60 patients (65 per cent) in the OKT3 and steroid groups, respectively. During this period, 11 patients in each group (18 per cent) had severe infections. In the follow-up period of one year, the incidence of infection continued to remain comparable for the two groups (54 and 50 per cent, respectively).

Skin Tests and Development of Antibodies

No patient had a positive skin test in response to OKT3. Antibodies to OKT3 developed in 80 per cent of the patients either during or after the second week of treatment with the drug. These antibodies were primarily of the IgG class, with titers from 1:100 to 1:1000 in the enzyme-linked immunosorbent assay system used for their detection. They did not affect the success of treatment, and there was no evident development of allergy, anaphylaxis, or serum sickness, although one patient acquired a rash and pruritus that were subsequently attributed to other medications.

DISCUSSION

The efficacy of reversal of rejection by OKT3 (94 per cent) was significantly better ($P = 0.009$) than that with conventional steroid treatment (75 per cent), and the high reversal rate with OKT3 was obtained with a significant reduction in the concomitant dosages of steroids and azathioprine. Once the reversal of rejection was achieved, patients in both groups were treated similarly with prednisone and azathioprine maintenance immunosuppression, and they were treated with high-dose steroids or antithymocyte globulin for repeated episodes of rejection. Both groups had similar subsequent rates of repeated rejection and consequent kidney loss, so that the number of kidneys saved as a result of a superior reversal rate with OKT3 was reflected in the higher numbers of functioning kidneys in this group at one year. Thus, in patients selected by virtue of having had acute rejection, one-year kidney survival according to life-table analysis was 62 per cent for the OKT3-treated group and 45 per cent for the steroid-treated group ($P = 0.029$). Since 15 to 20 per cent of the recipients of cadaver kidneys never have rejection, the overall kidney survival rates would be proportionately higher.

Patient survival and the incidence of infections were similar in both treatment groups. The main

Table 3. Efficacy of Treatment with OKT3 or Steroids for Acute Renal-Allograft Rejection.

	OKT3	STEROIDS	P VALUE
	incidence (%)		
Reversal of rejection (according to different criteria)			
Serum creatinine level plus clinical indexes	58/62 (94)	45/60 (75)	0.009
Serum creatinine level alone	55/62 (89)	37/60 (62)	<0.001
One-year follow-up			
Patient survival			
Actual	53/62 (85)	52/58* (90)	
Life table	— (85)	— (90)	0.47 (NS)†
Kidney survival			
Actual	36/53 (68)	25/52 (48)	
Life table	— (62)	— (45)	0.029

*Two patients were lost to follow-up.

†NS denotes not significant.

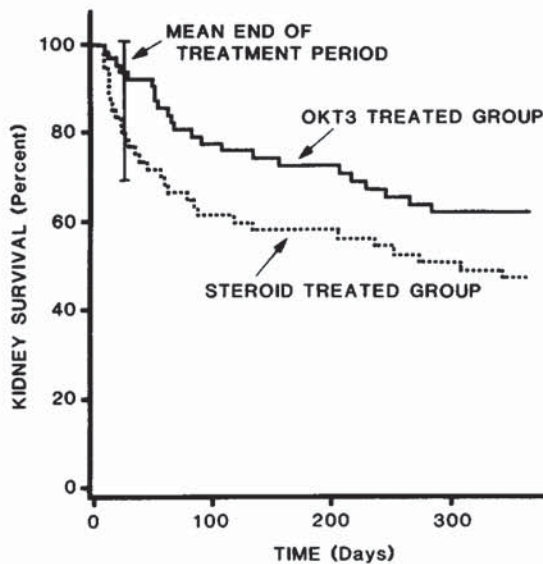


Figure 2. Life-Table Analysis of Kidney Survival in Patients Randomly Assigned to OKT3 or Steroid Treatment for Acute Renal-Allograft Rejection.

All 53 living OKT3-treated patients were followed for one year. In the steroid-treated group, two patients were lost to follow-up, and all 52 remaining living patients were followed for one year. The end of the treatment period is shown by the vertical bar.

adverse reaction attributable to OKT3 was a symptom complex involving fever and pulmonary and gastrointestinal symptoms and occurring 45 to 60 minutes after the initial dose. We attribute these symptoms to mediators released from T cells opsonized by OKT3 and localized in the reticuloendothelial system.²⁴ These first-dose symptoms were not due to hypersensitivity, since they occurred in almost all the patients (with no previous exposure to mouse immunoglobulin), the skin tests before OKT3 administration were uniformly negative, and symptoms were absent with later injections of OKT3.

One case of pulmonary edema occurred in this study after a first injection of OKT3 in a patient in a state of fluid overload. Four additional cases of pulmonary edema have occurred after the initial injection of OKT3 for acute renal-allograft rejection in other studies, and two of those patients died of anoxic sequelae (Ortho Pharmaceutical: unpublished data). It is noteworthy that in all cases there was evidence of fluid overload, as judged by weight gain and chest-film changes before OKT3 injection. No cases of pulmonary edema have occurred in 136 patients treated for conditions other than acute renal rejection, and no cases have occurred in 197 patients treated for acute renal-allograft rejection who did not have fluid overload, as judged by chest films and a weight gain of less than 3 per cent in the week preceding treatment. We conclude that the pharmacologic effects of the mediators released after the first dose can impose a left ventricular strain and cause pulmonary edema, but only in patients with impending left ventricular failure due

to fluid overload; patients should be brought to appropriate fluid balance before treatment with OKT3 is initiated.

Other monoclonal antibodies have been used therapeutically for acute renal-allograft rejection.²⁵⁻²⁷ Although these antibodies have resulted in the removal of circulating T cells, they have not produced the striking reversal rate obtained with OKT3; it may well be that the pharmacologic effect of OKT3 in blocking T-cell function is essential for its therapeutic efficacy.

Host antibodies to the murine immunoglobulin OKT3 frequently developed shortly after treatment with OKT3 was stopped.^{28,29} These antibodies did not result in hypersensitivity, anaphylaxis, or serum sickness. OKT3 administered in the presence of these antibodies may be consumed and rendered unavailable for binding to T3 antigen on T cells.³⁰ Thus, if OKT3 is to be used for the treatment of subsequent episodes of rejection after successful reversal of initial rejection, it will be necessary to develop protocols for preventing antibody formation or to give sufficient amounts of OKT3 to consume the host antibody and establish adequate levels of free OKT3 in the circulation.

Our results were achieved in patients receiving conventional azathioprine and prednisone therapy. Preliminary studies in patients treated with cyclosporine and prednisone show similar high reversal rates and give promise that even better overall rates of kidney survival may be attainable.

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