Published in final edited form as:

Nephron. 1987 ; 46(Suppl 1): 56–59.

Monoclonal Antibody Therapy with Ciclosporin and Steroids in Nonmatched Cadaveric Renal Transplants¹

Robert D. Gordon, Thomas E. Starzl, John J. Fung, Shunzaburo Iwatsuki, Carlos O. Esquivel, Andreas Tzakis, and Satoru Todo

Department of Surgery, University Health Center of Pittsburgh, University of Pittsburgh, and the Veterans Administration Medical Center, Pittsburgh, Pa, USA

Abstract

Thirty-six ciclosporin-prednisone-treated recipients of nonmatched cadaver renal allografts were given a course of Orthoclone OKT3 monoclonal antibody for steroid-resistant cell-mediated rejection. Although side effects were common, only 2 patients had to be withdrawn from therapy and there were no deaths related to therapy. Twenty-three (63.9%) allografts were rescued with OKT3 therapy and 21 (58.3%) of the grafts have continued to function well. We conclude that OKT3 is an effective agent for the treatment of steroid-resistant cell-mediated rejection and that rebound rejection can be prevented in most patients if adequate therapy with ciclosporin-prednisone is maintained.

Keywords

Kidney transplantation; Allograft rejection; Immunosuppression; Monoclonal antibody

Introduction

Antilymphocyte globulin for the treatment of steroid-resistant rejection was introduced into clinical practice by Starzl et al. [1] and its value has been proved in the treatment of steroid-resistant allograft rejection. The limitations of therapy with this heterologous polyclonal agent are summarized by Fung et al. [2] elsewhere in this symposium. Orthoclone OKT3 is a monoclonal reagent directed against a specific T-cell antigen receptor complex known to be important in both antigen recognition and T-cell activation [3,4]. The development of such a refined biologic product offers an attractive alternative to the treatment of acute cellular allograft rejection with conventional antilymphocyte preparations.

The first successful clinical trials with OKT3, which were conducted by Cosimi et al. [5,6] at the Massachusetts General Hospital, provided convincing evidence of the increased effectiveness of this agent compared with traditional treatment with high-dose steroids. However, there was a significant incidence of recurrent rejection after resumption of maintenance therapy with azathioprine and prednisone.

Since 1981, ciclosporin low-dose prednisone therapy has been the standard form of immunosuppression for cadaveric renal transplants at the University of Pittsburgh. In August 1985, we began a pilot trial of OKT3 therapy for the treatment of steroid-resistant

¹Supported by research grants from the Veterans Administration, by NIH Research Project Grant No. AM-29961, and by a grant from the Competitive Medical Research Fund-Richard King Mellon Foundation.

Dr. Thomas E. Starzl, Department of Surgery, 3601 Fifth Avenue, Room 218, Falk Clinic, Pittsburgh, PA 15213 (USA).

rejection in cadaveric renal and hepatic allografts under ciclosporin-steroid therapy. We report here our results for the first 36 consecutive renal allograft recipients treated in this trial.

Materials and Methods

Case Material

Between August 15, 1984, and December 15, 1985, 40 recipients of cadaveric renal allografts were treated with OKT3 monoclonal antibody. Four of the patients also received a simultaneous pancreas transplant, and they are excluded from this report. Thirty-six recipients of a renal allograft alone have been followed for 2–20 months since transplantation.

The 36 patients included in this series ranged in age from 9 to 63 years (mean 36.9 ± 13.5 SD). There were 22 males and 14 females. Twenty-three patients received a primary graft and 13 patients received a second graft. The causes of renal failure were known in all but 7 patients and are summarized in table I. There were 7 diabetics in the series.

Tissue Matching

Cytotoxic antidonor antibodies were avoided with conventional cross-match techniques using current recipient sera. Otherwise, matching was random in all cases. HLA antigen matches at the A and B loci averaged 0.7 ± 0.3 SD, and at the DR locus, 0.3 ± 0.5 SD. Current panel-reactive antibody (PRA) was less than 30% in 26 patients. In 4 of the 10 patients with a current PRA greater than 30%, the PRA was above 60%. Eighteen patients had a historical PRA of less than 30%. Fourteen of the 18 patients with a historical PRA greater than 30% had a peak PRA above 60%.

Immunosuppression

Several hours before operation, 17.5 mg/kg of ciclosporin was given orally. If tolerated, this dose was continued on a daily basis for 2 months postoperatively before being reduced. Earlier reductions were made in the event of toxic side effects [7] or if whole-blood ciclosporin levels were excessive. If blood levels were inadequate or oral intake was interrupted, oral ciclosporin was supplemented or replaced by 2 mg/kg i.v. ciclosporin twice a day.

In adults, a 5-day burst of steroids was given, beginning with 200 mg methylprednisolone or prednisone on the day of operation in four divided doses. The dose was reduced by 40 mg/day until a daily maintenance dose of 20 mg was reached. Further reductions in the dose of prednisone were dictated by the clinical course. Rejections were treated with a 1-g bolus of methylprednisolone, followed by a repeat of the 5-day cycle of high-dose prednisone. In the 1 child in this series, the steroid doses were adjusted downward in accordance with weight.

In the event of steroid-resistant or accelerated early rejection, a 10- to 14-day course of OKT3 was administered by giving a 5-mg i.v. bolus each day. The protocol for administration of OKT3 is described in greater detail by Fung et al. [2] elsewhere in this symposium. Patients were premedicated with hydrocortisone and antihistamines to minimize side effects. The decision to treat for rejection was based on clinical criteria (fever, graft tenderness, oliguria with rising serum creatinine), radionuclide scans demonstrating a significant reduction in renal blood flow, or percutaneous needle biopsy showing mononuclear cell infiltrates and edema characteristic of acute cellular rejection.

A major objective of this study was to maintain optimal blood levels of ciclosporin during the course of OKT3 therapy. Downward adjustments of ciclosporin at the start of therapy were often necessary to minimize nephrotoxicity, but restoration of normal blood levels was sought before completion of therapy with OKT3 in an effort to minimize the risk of rebound rejection.

Successful reversal of rejection was characterized by a significant fall in serum creatinine, restoration of urine output, improved renal blood flow as determined by radionuclide scanning, and, in selected cases, by demonstrable improvement in needle-biopsy histology within 2 weeks of treatment with OKT3. A temporary response was defined as one in which some or all of these parameters showed only transient improvement.

Results

Mortality

One (2.8%) of the 36 patients, a 50-year-old diabetic, died of a myocardial infarction 2 months after transplantation. The patient died at home, and there was no apparent relationship between his death and treatment with OKT3. His graft was functioning well at the time of death (serum creatinine, 1.6 mg/dl).

Response to OKT3

Twenty-three (63.9%) allografts treated with OKT3 were successfully rescued. Three (8.3%) grafts improved transiently but were eventually lost. At their request, 2 patients were withdrawn from therapy after a few doses of OKT3 because of side effects. One of them lost his graft to rejection, but the other recovered.

The relationship between time of therapy after transplantation and outcome of treatment is summarized in table II. Twenty-six patients were treated within 30 days of transplantation, and treatment was successful in 17 of those who received a full course of therapy. Six of the 10 patients treated beyond the first month after transplantation were successfully rescued, including 2 patients treated more than 240 days after transplantation.

Nineteen (73.1%) of the 26 patients with a current PRA less than 30% were successfully reversed. Only 4 (40.0%) of the patients with a current PRA greater than 30% were reversed, including 2 of the 4 patients with a current PRA greater than 60%. Thirteen (72.2%) of the 18 patients with a historical PRA less than 30% were reversed compared with 10 (55.5%) of 18 patients with a historical PRA greater than 30%. Seven (53.8%) of 13 patients with a historical PRA greater than 60% were rescued. There is no statistical significance to these results for high- and low-PRA patient groups. However, the results suggest the possibility of a difference between current high- and low-PRA patients ($p < 0.10$) that may achieve statistical significance in a larger patient sample.

Biopsies were available for review in 16 of the 36 patients. Fourteen biopsies showed evidence of cellular rejection. Eight (57.1%) of these grafts were rescued. Two biopsies showed only ischemic injury, but treatment was instituted because of failure to recover function and diminished renal blood flow observed on radionuclide scanning. One of these grafts recovered. Fourteen (70%) of the 20 grafts for which biopsies were not available recovered function.

Twenty-two of the grafts treated in this series produced urine immediately or within 10 days of transplantation. Fourteen (63.6%) of these grafts were rescued from rejection with OKT3. Eight of the grafts treated had delayed function, presumably due to acute tubular necrosis, for 10–30 days after transplantation. Six (75%) of these 8 grafts were rescued. Three grafts

failed to function for between 30 and 90 days after transplantation, but all recovered function, although 2 of them did not recover function for more than 2 weeks after treatment with OKT3. Three grafts never functioned and were removed.

Graft Survival

Twenty-one (58.3%) of the 36 grafts treated in this series are still functioning with a mean serum creatinine of 2.1 mg/dl, 0.8 SD. Fourteen (38.8%) of the grafts have been lost to rejection. One graft was lost by death of a patient due to myocardial infarction.

Eighteen (69.2%) of the 26 grafts in patients with a PRA less than 30% at the time of transplantation are still functioning, compared with only 3 of the 10 grafts in patients with a PRA greater than 30%. Fourteen (77.8%) of the 18 grafts in patients with a historical PRA less than 30% are functioning, compared with 7 (38.9%) of the 18 grafts in patients with a historical PRA greater than 30%. These differences are not statistically significant.

The relationship of ultimate graft survival to the time after transplantation of OKT3 therapy is summarized in table III. Actuarial survival for the 36 grafts treated in this series is shown in figure 1. One-year survival is 59.8% and 2-year survival is 35.9%. Figure 1 also shows the survival of grafts reversed with OKT3. For this group, 1-year survival is 81.3%, and 2-year survival is the same.

Side Effects

Side effects were common but generally well tolerated (table IV). Only 2 patients requested that therapy be discontinued, and none were withdrawn on the initiative of an attending physician. Gastrointestinal complaints (nausea, vomiting, diarrhea, abdominal cramps) were the most common side effects, followed by hemodynamic changes (tachycardia, transient alterations in blood pressure) and fever. There was no major anaphylactoid reaction (defined as a reaction requiring intensive respiratory support, including intubation).

Infections

There were two major infections (1 case of *Pneumocystis carinii* pneumonia and 1 of cytomegalovirus pneumonia). Both patients recovered with reduction of steroids. There were four minor infections, all oral or genital herpes lesions treated with acyclovir and moderate reduction in steroid therapy.

Discussion

The population of cadaver kidney transplant recipients treated in this pilot series of 36 cases represents a special high-risk subset of the overall transplant-recipient population. Nearly all of these patients demonstrated a high immunologic responsiveness to their allografts, which was resistant to conventional steroid therapy. Thus, it is not surprising that actuarial graft survival for the entire series is only 60% at 1 year and 36% at 2 years posttransplantation. Nevertheless, 23 (63.9%) of the 36 grafts treated with OKT3 in this study were rescued, and 21 (58.3%) of the 36 grafts have continued to function well. Thus, the incidence of rebound rejection after successful treatment with OKT3 has been low in our experience, provided careful attention is paid to adequate maintenance therapy with ciclosporin-prednisone.

Two patients in this series had renal biopsies at the start of therapy that showed ischemia (acute tubular necrosis) without rejection. Other grafts with a long interval of delayed function and evidence of concurrent rejection recovered function after treatment with OKT3. It has been recently reported in a large regional study in the United States that grafts with delayed function are at greater risk of loss to rejection than are grafts with prompt function

[8]. It can be difficult to diagnose accurately rejection in grafts with delayed function, and this may lead to undertreatment. Antilymphocyte globulin therapy has been used in the past to protect grafts with delayed function, and OKT3 may be equally useful in this role now that both its efficacy and safety appear to be established.

Although side effects of OKT3 were common in this series of patients, they rarely limited therapy, and the drug was better tolerated with each successive dose. There were no deaths or significant morbidity attributable to use of OKT3 in this series of 36 patients.

Conclusion

We conclude that OKT3 is a safe and effective biologic agent for the treatment of acute cell-mediated rejection of cadaveric renal allografts. When combined with proper maintenance therapy with ciclosporin and low-dose prednisone, a favorable response can be expected in the majority of patients treated, and recurrent rejection can be expected in 20% or less of the grafts rescued.

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Fig. 1.
Graft survival after OKT3 monoclonal antibody therapy for acute rejection.

Table I

Causes of renal failure (36 patients)

Cause	Patients	
	n	%
Unknown	7	19.4
Diabetes	7	19.4
Glomerulonephritis	6	16.7
Polycystic disease	4	11.1
Hypertension	2	5.6
Analgesic nephropathy	2	5.6
Congenital nephritis	1	2.8
Buerger's disease	1	2.8
Hypoplastic kidneys	1	2.8
Interstitial nephritis	1	2.8
Lupus nephritis	1	2.8
Nephrosclerosis	1	2.8
Obstructive uropathy	1	2.8
Scleroderma	1	2.8

Table II

Time of treatment and outcome of treatment

Days after transplantation	Outcome of treatment			
	failed	temporary	reversed	withdrawn
0–30	7	1	17 (65.4%)	1
30–60	0	1	2	0
60–180	0	1	2	0
240–300	0	0	2	1
> 300	1	0	0	0

Table III

Time of treatment and graft survival

Days after transplantation	Graft survival			
	death	nonfunctioning	functioning	rejected
0–30	1	1	17 (65.4%)	7
30–60	0	0	1	2
60–180	0	0	1	2
240–300	0	0	2	1
> 300	0	0	0	1

Table IV

Side effects of OKT3 therapy

Side effect	Patients	
	n	%
Gastrointestinal	28	77.8
Hemodynamic	24	66.7
Fever	24	66.7
Chills	10	27.8
Dyspnea	9	25.0
Minor infection	4	11.1
Major infection	2	5.6
Anaphylaxis	0	0.0