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Preliminary Communication

Kidney Transplantation Under FK 506

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The experimental immunosuppressive drug FK 506 was given to 36 renal transplant recipients, many of whom were highly sensitized. Ten were undergoing kidney retransplantation, 10 also underwent liver transplantation at an earlier time (6 patients) or concomitantly (4 patients), and 2 patients received a third organ (heart or pancreas) in addition to a liver and kidney. With follow-ups of 4 to 13 months, all but 2 of the 36 patients are alive, 29 (81%) are dialysis free, and most have good renal function. Twenty of the 29 dialysis-free patients are receiving no or low-dose (2.5 to 5.0 mg/d) prednisone therapy. Only one kidney was lost to cellular rejection. However, patients who had antidonor cytotoxic antibodies in current or historical serum samples had a high rate (3 of 9) of irreversible humoral rejection. A low incidence of posttransplant hypertension was noteworthy. Hirsutism and gingival hyperplasia were not observed. Serum cholesterol levels in patients who took FK 506 were unexpectedly low, and the effect on the level of uric acid was minimal. The side effects of FK 506 therapy include nephrotoxicity, neurotoxicity, and potential induction of a diabetic state. These are similar to the side effects of cyclosporine use, but probably less severe. The seeming safety, efficacy, and relative freedom from side effects of FK 506 encourage further trials in kidney transplantation.

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ENCOURAGING clinical trials in liver transplantation have been reported with the new immunosuppressive agent FK 506,[1-3] which is produced by the fungus *Streptomyces tsukubaensis*.[4,5] Although the molecular structure of FK 506 is unrelated to cyclosporine and has a different cytosolic binding site,[6,7] the two drugs have similar effects on the immune system.[8,9] We report here a trial of FK 506 in kidney recipients, of whom the majority had complex clinical problems or were at high risk because of adverse medical or immunologic factors.

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METHODS

Recipient Case Material

Complexity factors in the 36 patients included concomitant or prior liver transplantation (29%), previous kidney transplantation (29%), and causes of renal failure that increase the risk of transplantation (Table 1). The only child in the series (10 years old) had hemolytic uremic syndrome. Hemolytic uremic syndrome is a known complication of cyclosporine use[10] that has been treated successfully with FK 506.[11] Five patients were older than 60 years.

Donor Features

Cadaveric kidneys were used in 34 recipients, with son-to-mother and father-to-daughter donation in the other 2. Five of the cadaver donors were 57 to 64 years old, and 8 infants who were 4 to 26 months old donated en bloc kidneys. The cold ischemia time for the cadaveric grafts was 32 ± 10 (SD) hours. Twenty-eight (82%) of 34 cadaveric grafts as well as the 2 living donor grafts had primary function as defined by early diuresis and freedom of the recipient from dialysis for the first postoperative week.

Immunologic Matching

There were no good HLA matches (defined as four or more antigen matches), and multiple mismatches were present (Table 2). Almost one third of the recipients had cytotoxic antibodies (Table 3). In 9 of 36 patients, the transplantation was carried out despite a positive (+) or equivocally positive (±) cytotoxic crossmatch (Table 4) after the dithiothreital treatment of stored or current recipient serum, which removes IgM antibodies that can cause false-positive crossmatches.[12] Transplantation under these circumstances is dangerous[13-15] but has been justified in highly sensitized patients whose wait for a kidney otherwise can be endless.[16,17]

Immunosuppression

A 4-hour intravenous infusion of 0.075 mg/kg of FK 506 is given every 12 hours until starting oral doses of 0.15 mg/kg twice daily. Oral doses were increased when indicated by suspected rejection or reduced in size or frequency if a toxic reaction to a drug was suspected. Plasma concentrations of FK 506 were measured once or twice a week by the two-step monoclonal enzyme immunoassay technique of Tamura et al.[18]

Prednisone therapy was started at 200 mg on the first postoperative day and reduced in daily 40-mg steps to a daily maintenance dose of 20 mg by day 6. Further reductions were made quick-

Table 1.—Clinical Features of 36 Kidney Recipients (March 27, 1989, to January 3, 1990)*

	No. of Organs	No. of Recipients
Complexity Factors		
Primary kidney transplant only	...	16
Previous kidney transplant		
Patients	...	10
Kidneys	12	...
Previous liver transplant		
Patients	...	6
Livers	9	...
Simultaneous liver transplant	...	4
Liver only	2	...
Liver-pancreas	1	...
Liver-heart	1	...
Total	...	**36**
Causes of Renal Failure		
Glomerulonephritis	...	8
Cyclosporine toxicity	...	7
Diabetes mellitus	...	7
Chronic renal rejection and cyclosporine toxicity	...	4
Hypertension	...	3
Polycystic disease	...	2
Hemolytic uremia syndrome	...	2
Focal glomerulosclerosis	...	1
Lupus nephritis	...	1
Sickle-cell disease	...	1
Total	...	**36**

*Age, 40 ± 14.4 (SD) years; range, 10 to 67 years. Sixteen patients were men and 20 were women. Transplantation dates are shown in Table 5.

Table 2.—HLA Antigen Matches and Mismatches in 34 Patients*

	No. (%) of Patients	
Antigen No.	**Matches**	**Mismatches**
6	0 (0)	5 (14.7)
5	0 (0)	7 (20.9)
4	0 (0)	13 (38.2)
3	4 (11.8)	8 (23.5)
2	11 (32.3)	1 (2.9)
1	10 (29.4)	0 (0)
0	9 (26.5)	0 (0)
Total	**34 (100)**	**34 (100)**

*Incomplete data for two other patients.

Table 3.—Panel Reactive Antibody (PRA) With Testing Against Lymphocytes of 62 Volunteers

	No. (%) of Volunteers	
% PRA	**Historical**	**Current**
40-100	7 (19.4)	4 (11.1)
10-36	4 (11.1)	7 (19.4)
0-9	25 (69.4)	25 (69.4)
Total	**36**	**36**

Table 4.—Cytotoxic Crossmatch After Treating Recipient Serum With Dithiothreital[12]*

Historical Serum	Current Serum	No. (%) of Cases
+	−	2 (5.6)
±	−	4 (11.1)
+/±	±	3 (8.3)
−	−	27 (75.0)

*+ indicates 20% to 40% killing; ±, 10% to 20% killing; and −, less than 10% killing.

ly if renal function was adequate. One-gram boluses of hydrocortisone or methylprednisolone were given if rejection supervened, and a 3- to 7-day course of 5 or 10 mg/d of OKT3[19] was given intravenously if rejection persisted. Performance of a kidney biopsy in 17 of 36 patients reflected dissatisfaction with the clinical course and uncertainty about the diagnosis.

RESULTS

Mortality

Follow-up of surviving patients is 4 to 13 months. There were two deaths. A 31-year-old nondiabetic woman died of cardiac arrest 60 hours after receiving en bloc kidneys from a 6-month-old donor. At autopsy, the lungs and other tissues were congested, and there was left ventricular hypertrophy. The left main, left arterior descending, and circumflex coronary arteries had greater than 90% occlusion.

The triple-organ recipient of a cardiac retransplant, liver, and kidney (patient 29) had rapid recurrence of the hepatitis that had destroyed her native liver. She died after 4 months of liver failure; because there was no response to interferon alfa therapy, a family, physician, and patient decision was made not to attempt liver retransplantation.

Graft Losses

Three grafts given to the nine recipients with cytotoxic antigraft antibodies had irreversible humoral rejection within 1 week (patients 2, 12, and 16). In addition, patient 25, who was an earlier liver recipient and who had a positive cytotoxic crossmatch with his subsequent kidney donor, had a life-threatening hemorrhage and developed two large intrarenal arteriovenous fistulas after a kidney biopsy. His serum creatinine level was 350 μmol/L. The bleeding was controlled and the fistulas were closed by radiologically controlled embolization but with resulting infarction of two thirds of the renal graft and return to dialysis.

Five graft losses in 27 patients with negative crossmatches were caused by death (2 patients, cited earlier), a ruptured mycotic aneurysm (*Candida albicans*) of the renal artery suture line (1 patient), rejection (1 patient), and rejection plus recurrent sickle-cell disease (1 patient).

Graft Function

The result in each case is given in Table 5. After 4 to 13 months, 27 (75%) of 36 patients are dialysis free. Serum creatinine levels are less than 177 μmol/L in 17, between 177 and 221 μmol/L in 8, and more than 221 μmol/L in 2 (Table 5). Although graft survival is 5 (56%) of 9 when the cytotoxic crossmatches were equivocally or definitely positive, one of these kidneys was from the same donor whose liver was placed in the patient (case 31) a few hours earlier. This strategy is known to shield the kidney from antibody injury.[20] Two of the other 4 surviving renal grafts (cases 22 and 28) have imperfect function.

Immunosuppression End Points

Fourteen patients had a clinical rejection at some time in their course, usually early, and 6 with biopsy-documented rejection were given OKT3. The daily maintenance doses of FK 506 and plasma FK 506 levels 2 months after transplantation are shown in Table 5 for the 27 patients who have functioning grafts. Twenty of these 27 patients are taking 5 mg/d or less of prednisone, and in 16, steroid therapy has been stopped.

Infections

The recipient of a liver, second heart (first heart received 4 years earlier), and kidney had staphylococcal septicemia 5 days postoperatively and recrudescence of preexisting pancreatitis. Her pancreas, spleen, duodenum, and right colon were removed on the 20th posttransplantation day, and all had patchy necrosis. She recovered from this procedure but died of the same non-A non-B hepatitis in her hepatic graft that destroyed her native liver.

Table 5.—Data on 27 Patients With Functioning Renal Grafts

No.	Date of Operation	Rejection	Creatinine Level, μmol/L	Serum Urea Nitrogen Level, mmol/L	No. of Drugs for Hypertension	Prednisone, mg/d	FK 506 Level in Plasma, ng/mL	FK 506, mg/kg/d§
1*	3/27/89	Yes	115	9.6	0	15	0.6	0.15 BID
2†	4/14/89	Yes	...	...	...	...	...	...
3*	5/21/89	No	...	...	...	...	...	...
4*	8/17/89	No	106	7.1	0	0	0.7	0.16 qd
5	9/14/89	No	176	8.6	1	5	0.5	0.15 qd
6*	10/16/89	No	71	4.6	0	0	0.2	0.3
7†	10/20/89	Yes	133	22.5	0	15	0.6	0.17 qd
8	10/21/89	Yes	220	13.6	1	15	0.3	0.08 BID
9	10/22/89	Yes	203	11.1	0	5	0.7	0.19 BID
10	10/25/89	Yes	336	20.0	0	10	1.1	0.17 BID
11	10/25/89	No	194	12.9	1	0	0.4	0.17 qd
12†	10/25/89	Yes	...	...	...	...	...	...
13	10/26/89	No	150	7.5	2	0	0.6	0.14 BID
14*‡	11/2/89	No	106	7.9	0	0	0.2	0.20 qd
15	11/2/89	No	80	6.4	0	0	0.7	0.15 BID
16†	11/2/89	Yes	...	...	...	...	...	...
17	11/9/89	No	150	10.4	0	0	0.6	0.10 BID
18	11/9/89	Yes	212	9.6	2	10	1.7	0.21 BID
19	11/10/89	Yes	...	...	...	...	...	...
20	11/10/89	Yes	...	...	...	...	...	...
21†	11/19/89	No	124	9.6	0	0	0.4	0.13 BID
22†	11/19/89	Yes	292	25.0	2	10	0.5	0.18 BID
23	11/19/89	No	80	9.3	1	0	0.1	0.12 BID
24	11/19/89	No	221	10.4	1	0	1.0	0.10 BID
25*†	11/26/89	Yes	...	...	...	...	...	...
26	11/26/89	No	150	11.4	0	0	0.4	0.10 BID
27	11/28/89	No	80	6.4	1	0	0.8	0.15 BID
28*†	11/28/89	Yes	194	7.1	1	20	0.2	0.11 BID
29*	12/2/89	No	Dead	...	...	...	...	...
30	12/2/89	No	Dead	...	...	...	...	...
31*†	12/10/89	No	80	6.8	0	5	0.8	0.12 qd
32	12/14/89	No	115	5.0	0	5	0.8	0.07 qd
33	12/14/89	No	221	11.8	0	0	0.5	0.14 BID
34*	12/16/89	No	194	10.7	2	0	0.5	0.08 BID
35	12/16/89	No	133	9.6	0	0	1.2	0.13 BID
36‡	1/2/90	No	133	7.9	0	0	1.5	0.09 BID

*Also had other organs transplanted (see Table 1).
†Positive cytotoxic crossmatch with current or historical sera.
‡Patient 14 was son to mother; patient 36 was father to daughter. All other donors were cadavers.
§BID indicates twice daily; qd, every day.

Two bacterial wound infections (drained) and two urinary tract infections were treated easily. The *C albicans* infection that caused a renal artery mycotic aneurysm and graft loss in patient 3 came from the cadaver donor since the recipient of the other kidney taking cyclosporine-azathioprine-steroid therapy had the same complication, with a fatal outcome. Patient 4, a three-organ recipient, had the pancreatic graft removed because of an adjacent *Candida* abscess.

Four patients with fever had cytomegalovirus infection diagnosed by buffy coat examination or gastrointestinal tract endoscopic biopsy. These four patients (patients 3, 8, 18, and 22), who were among the six who were treated with OKT3, responded to ganciclovir (DHPG) therapy. No Epstein-Barr virus or adenovirus infections were seen.

Potential Adverse Reactions

The adverse reactions of FK 506 therapy, which are worse with the intravenous route, resembled those of cyclosporine[21-24] and included nausea, vomiting, and headaches.[22] Gastrointestinal tract complaints were solicited in detail because of reports of lethal emaciation in dogs.[25] Patient 24 was found to have a chronic duodenal ulcer 10 days after transplantation. Prednisone treatment was stopped, with ulcer healing. Other than in the triple-organ recipient (patient 29), who had pancreatitis before transplantation, this complication was not seen. Liver dysfunction was not observed except in patients who also had liver transplantation.

The frequency and severity of arterial hypertension were judged by the need for antihypertensive medications (Table 5). Sixteen of 27 patients with functioning kidney grafts are not receiving such drugs, 7 more are taking one agent, and 4 patients are undergoing double drug therapy.

Neurotoxicity was limited to tremors, an increased sensitivity to light, burning or tingling sensations that usually affected the palms of the hands or soles of the feet, headaches, insomnia, nightmares, a mood change (some better, some worse), tinnitus (two patients), and a sensation of "racing" were described by variable numbers of patients when questions were asked from a checklist. Most of the foregoing symptoms were viewed by the patients as minor annoyances and were not reported spontaneously.

Seven of 36 patients were insulin-dependent diabetics before transplantation, and an 8th was taking oral hypoglycemic agents. This last patient

(HLA-DR types 2 and 4) required insulin after operation. With the institution of prednisone therapy, patient 7, who did not have the class II HLA-DR types 3 and 4 antigen phenotypes that are associated with diabetes mellitus,[26,27] became insulin dependent. Patient 17, whose DR antigens are 3 and 6, had minor elevations of blood sugar levels before transplantation and since then has been treated with oral hypoglycemic agents.

Serum cholesterol concentrations of 27 patients with functioning kidneys were determined from 1 to 10 months after transplantation. The results were 4.6 ± 1.1 (SD) mmol/L (range, 2.8 to 7.4 mmol/L; normal range, 3.4 to 6.2 mmol/L, depending on age). At the same time, serum uric acid levels were 416 ± 137 (SD) μmol/L, with a range of 202 to 749 μmol/L (normal, <506 μmol/L for males and <416 μmol/L for females).

Hirsutism and gingival hyperplasia were not seen. Patients who previously received cyclosporine reported hair loss.

COMMENT

These first trials of FK 506 therapy for renal transplantation were in difficult patients, with a number of recipients of other organs, an unusual representation of older patients and those undergoing retransplantation, and the presence of several original kidney diseases that impose an increased risk for transplantation. One fourth of the patients were presensitized with broadly reacting cytotoxic antibodies, and 9 had donor-specific cytotoxic antibodies detectable in their current or stored sera. HLA matching was uniformly poor. Finally, 14 donors were above or below the usual age range of acceptability for organ donation.

The effectiveness and safety of FK 506 under these circumstances was impressive. The mortality was 5.6% after a mean follow-up of 170 days. Three fourths of the kidneys are functioning after 4 to 13 months, for the most part well. This was accomplished with administration of low doses of steroids. The only kidney lost to cellular rejection was in a patient who also had reactivation of sickle-cell disease.

In contrast, humoral rejection destroyed four grafts, three of these in the group of nine patients whose historical or current sera contained antidonor cytotoxic antibodies. The loss of one third of the grafts to humoral rejection in this subgroup as well as the suboptimal function of several of the remaining six grafts (inluding one lost from a renal biopsy accident) suggests that FK 506 will not permit relaxation of classical crossmatch criteria.

The ability to reduce prednisone therapy to a minimum or to eliminate steroid use altogether in more than half of the patients within a few postoperative weeks suggests that more prednisone than was necessary may have been given. Reserving secondary therapy for agents such as OKT3 and for the specific indication of rejection might be preferable. It was not known at the outset if OKT3 would be as compatible with FK 506 as has proved to be the case in both our liver and kidney recipients.

The optimal dose of FK 506 for kidney recipients has not yet been determined accurately. In liver recipients, a starting maintenance oral dose of 0.15 mg/kg twice daily has been enough to prevent rejection in the majority of patients. Because oral FK 506 presumably is presented to the liver preferentially via the portal vein and is largely metabolized there,[28] larger doses might be indicated when organs exposed only to systemic blood are transplanted. Consistent with, but not proving this hypothesis, is the fact that the incidence of rejection in the kidney patients herein reported was greater than that in our liver recipients.

Even without clarification of this important matter, a randomized trial in more conventional kidney recipients is planned at the University of Pittsburgh. The high success rate that can be anticipated with either cyclosporine or FK 506 therapy may make comparisons difficult in terms solely of short-term patient or graft survival. Comparisons will then hinge on morbidity and chronic risk factors, of which most are identifiable already. These include nephrotoxicity, alterations of carbohydrate metabolism, hypertension, hypercholesterolemia, and neurotoxicity, which are recognized complications of cyclosporine use[10] as well as FK 506 therapy. From what has been learned so far, such side effects will not vitiate the value of FK 506.

In animals[29] and humans,[21] nephrotoxicity of FK 506 is less than that of cyclosporine. When used by itself in liver recipients, renal function abnormalities in patients treated with FK 506 usually are relatively minor, and as in the kidney recipients in this report, there has been a notable freedom from hypertension. If, in a randomized trial of renal transplantation, a crossover is attempted from cyclosporine to FK 506 therapy or vice versa, extreme caution will be required since FK 506 enhances the nephrotoxicity of cylcosporine.[1,21] It originally was planned to use these two drugs together because of their immunosuppressive synergism in vitro[8,9] and in animals.[30] The plan was abandoned after only a few clinical cases because of the alarming renal deterioration that followed.[1,21]

Both cyclosporine and FK 506 influence carbohydrate metabolism by inhibiting insulin secretion and by increasing peripheral insulin resistance. The changes with cyclosporine use have been documented extensively,[10,31-34] but far less is known about FK 506. The insulin secretion of rat and human pancreatic islets in culture is reduced when either cyclosporine or FK 506 is added to the medium,[35,36] but the effect of FK 506 is weaker and more quickly reversible.[36] In healthy rats undergoing long-term FK 506 therapy, there is a 10% increase in fasting blood sugar levels without obvious histopathologic changes in the pancreas.[37] New-onset diabetes has been common after renal transplantation and azathioprine therapy and has been ascribed to the concomitant use of steroids.[38,39] Our belief is that both cyclosporine and FK 506 have diabetogenic qualities independent of steroids. The ability to use FK 506 with no or low-dose steroids may reduce the actual incidence of posttransplantation diabetes. Testing this hypothesis requires randomized trials.

Major neurotoxicity has not been a serious problem with FK 506 use, but the exact delineation of minor complaints could be especially important for discriminating management. With other commonly used immunosuppressive agents, toxic reactions to drug use promptly can be detected by characteristic changes in laboratory test results. Well-known examples are leukopenia with azathioprine therapy and deterioration of renal function test results with cyclosporine therapy. In the absence of such overt system-specific toxic effects with FK 506, a "litmus test" or complaint profile is needed to warn against overdose. This can be obtained by asking specific questions that the patient might otherwise consider trivial about headaches, sleep patterns, motor skills, muscle cramps, mood, and paresthesias.

Because it is known that cyclosporine use causes hypercholesterolemia[40] and elevations in uric acid level,[41] the unusually low serum cholesterol levels and normal uric acid levels in our FK 506–trated patients are noteworthy. The cyclosporine-associated cosmetic side effects of hirsutism, gingival hyperplasia, and coursening of facial features[10] have not been seen in our liver, kidney, or thoracic organ recipients, who now total more than 300.

In the 1980s, the greatly improved immunosuppression made possible with

cyclosporine revolutionized the field of transplantation.[10] FK 506 should be the means for further improvement and also for application to autoimmune diseases, including those affecting the kidney. Remissions of steroid-resistant nephrotic syndrome from focal glomerulosclerosis[42] and hemolytic uremic syndrome[11] already have been reported with FK 506 treatment. To the extent that such observations are verified, the ultimate need for kidney transplantation could be reduced.

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