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THORACIC DUCT DRAINAGE BEFORE AND AFTER CADAVERIC KIDNEY TRANSPLANTATION

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In a recent evaluation of thoracic duct drainage for renal transplantation, we suggested that the optimal use of the lymphoid depletion should include pretreatment for intervals influenced by the absence, presence or kinds of antibodies in the serums of the recipients (28). These recommendations which were then speculative have since been tested in 27 consecutive cadaveric renal transplantations. During follow-up periods of one to six months, only six of the 27 patients have had a rejection, which in five instances was reversed. The virtual elimination of early graft loss has made cadaveric renal transplantation a more predictable venture at our institution than at any time in the past. The clinical and serologic observations herein reported suggest the possibility of further improvements by small adjustments in the duration of preoperative thoracic duct drainage.

METHODS

The patients were ten to 61 years old (Table I) and included three who had diabetes, several who had ischemic heart disease and past myocardial infarctions and three who were undergoing retransplantation. The causes of the renal failure were variable, as in our past experience, with chronic glomerulonephritis being the most common. All of the recipients had been receiving chronic dialysis.

Antigens of the HLA-A, B and DR loci were determined for the recipients and their cadaveric donors (30). Since the typing results were not used in an attempt to obtain tissue compatible recipients for the donors, the random matches were poor (Table I).

Antibody analysis

Cytotoxic antibodies in the serums of the recipients were determined before starting thoracic duct drainage and every one to three weeks thereafter. The antibodies were detected by cross matching the serums against the lymphocytes of 30 healthy donors (30). If antibodies were present, they were further analyzed and categorized as anti-T and anti-B lymphocyte antibodies under warm and cold testing conditions (30).

At transplantation, standard direct cross matches were done between the recipient serums and donor lymphocytes (30). All 27 patients were given kidneys from cross match negative donors.

Timing of thoracic duct drainage

Previously recommended management scheme is summarized in Table II. Patients whose serums possessed no antibodies or only cold antibodies against the panel were scheduled for preoperative lymph drainage for three weeks; those with warm antibodies were pretreated for at least 30 days.

In this series, recipients usually were avoided who possessed broadly reacting warm anti-T antibodies. Because of their propensity to hyperacutely reject kidney grafts, such patients should be placed in a separate category if new immunosuppressive techniques are to be evaluated (28). Nevertheless, Patients 1, 2 and 27 had warm anti-T antibodies against 11, 47 and 75 per cent, respectively, of the screening panel (Table I).

Thoracic duct drainage was established in the neck as described before (12,25,28). As the series of 27 patients was compiled, no other recipients had attempts at thoracic duct drainage which failed. The vitally important details of operative and postoperative management have been thoroughly outlined elsewhere, including lymph collection, lymphocyte removal by centrifugation and lymph return intravenously.

Other management

To achieve reasonable conformity with the timing depicted in Table II, unusual reliance for the cadaveric organs was placed on regional and national organ procurement networks. In five of the grafts, function was delayed for three to 15 days, necessitating one to five dialyses postoperatively.

Azathioprine and prednisone were begun on the day of transplantation. Nine of the 27 recipients also had courses of antithymocyte globulin for at least five days. The daily azathioprine dosage was designed to avoid leukopenia. The prednisone dose was 200 milligrams on the first day. Thereafter, daily reductions by 10 milligrams were made if rejection did not supervene, until a dose of 40 milligrams was reached in 16 days. Further reductions were individualized, usually with monthly decrements of 5 milligrams.

Evaluation of rejection

Rejection was defined as a secondary rise of creatinine of more than 25 per cent above base line, along with the other biochemical findings of renal failure. The characteristic physical signs of rejection were looked for. Radionuclide scanning was routinely obtained and was particularly valuable in assessing the course of patients in whom the grafts initially had acute tubular necrosis, as described by Stables and associates (23).

RESULTS

The details in individual patients are shown in Table I, including the duration of thoracic duct drainage, amount of lymph drainage and numbers of cells removed. In each of the 27 patients,

the numbers of lymphocytes obtained daily markedly diminished during the pretreatment period. Most of the thoracic duct fistulas were discontinued within a month after transplantation. The inability to obtain cadaveric kidneys exactly when needed introduced a variability into the pretreatment time upon which a division of patients was made for analysis.

Pretreatment of 26 to 58 days

These 14 patients included four who had preformed warm antibodies and who had prolonged lymph drainage for that reason. The other ten had more pre-treatment than planned because donors did not become available on schedule. Patient 3 had an abortive initial attempt at transplantation which was abandoned because of traction injuries of both donor renal arteries. Definitive transplantation was carried out a few days later.

There was one minor rejection during the follow-up periods of one to six months. All of the 12 surviving patients have normal kidney function (Table I). Their maintenance steroid dosages are variable, according to the duration of follow-up study (Table I).

In the first 14 consecutive patients, antibodies against the lymphocyte panel were restudied two weeks after transplantation. Twelve of the 14 patients then had warm anti-B antibodies (Table III) but these reacted against more than half of the donor panel in only one instance. Included were Patients 1, 2, 24 and 25 who had broadly reacting warm anti-B or anti-T antibodies (Table I) before 58, 55, 43 and 33 days, respectively, of thoracic duct drainage. As reported before (28), the antibodies were diminished during pretreatment but usually not eliminated. These four recipients had negative standard cross matches with their donors. By two weeks after transplantation, three of the four patients had a return of warm anti-B as well as anti-T antibodies. However, the resurgent antibodies were broadly reacting in only one instance. At two weeks, cold anti-B antibodies were found in the serums of four of the 14 patients (Table III) compared with an equal incidence of four in 14 before transplantation.

There were two deaths (Table I), a mortality of 13 per cent. Patient 5 was a 57 year old woman with known coronary artery disease who had been discharged after transplantation with normal renal function. A few weeks later, she died in an outlying hospital, immediately after she unfortunately was administered 2 grams of lidocaine intravenously during the treatment of a cardiac arrhythmia. An autopsy was denied.

Patient 13 died from a systemic viral infection, including diffuse pneumonitis two months after transplantation, despite prolonged ventilatory support and drastic reduction of steroid therapy. The kidney did not show evidence of rejection.

Pretreatment of 17 to 23 days

All but one of these 13 patients were free of warm antibodies preoperatively. Five of the 13 had rejection develop from eight to 30 days after transplantation, necessitating secondary increases of steroid therapy. The rejections were reversed without the necessity for dialysis, with one exception. The latter patient underwent retransplantation.

The 12 surviving patients have renal function which is normal in those who escaped rejection but variable in the five who did not (Table I). The penalty for rejection in the latter five recipients has been a higher maintenance dosage of prednisone (Table I).

By two weeks after transplantation, 11 of the 13 patients had warm anti-B antibodies develop, which in seven of the recipients were reactive against more than half of the lymphocyte panel (Table III). All five of the rejections were in the latter group of seven patients. The ability of patients with short pretreatment to form broadly reactive warm antibodies was significantly

greater than that of recipients pretreated for longer periods (Table III). In addition, cold antibodies were more frequently observed after the shorter preparation (Table III).

One of the 13 patients died of acute pancreatitis, one month after transplantation. An autopsy was denied.

DISCUSSION

The 27 cadaveric kidney recipients in this series had more effective immunosuppression than did similar patients treated by us at any time in the past. Only one of the organs was lost to rejection during follow-up study of one to six months. The influence of thoracic duct drainage was so obvious that it is hard to explain the neglect by surgeons of this potent immunosuppressive measure, which was first used in human renal transplantation by Franksson (4) and Newton (18) more than 15 years ago. Subsequent clinical trials with variable results were reported by Franksson (5,6), Tilney (31), Murray (17), Fish (3), Sarles (21), Archimbaud (1), Traeger (32), Martelli (14), Ianhez (7) and Sonoda (22) and their associates. The procedure was not accepted by transplantation surgeons, including those who had tried it, and it was generally abandoned. Further inquiry into the use of thoracic duct drainage has been done mainly by Walker (33), Johnson (10) and Niblack (19) and their associates, by Kaplan (11) and by us (25,28).

The missed opportunities with thoracic duct drainage in the past were caused by gaps in knowledge which have since been filled and by technical problems which have since been solved. The timing of the immune depression caused by thoracic duct drainage in human beings was not well defined until Machleder and Paulus (13) showed that nearly three weeks were required for major immunologic changes and that these changes continued to deepen for an additional ten or 15 days. The sequence was far longer than had been observed in rats by MacGregor and Gowans (15,16). Moreover, although MacGregor and Gowans (15,16) had demonstrated suppression in rats of both humoral and cell mediated immunity, this dual effect in humans was not unequivocally established until the reports by Machleder and Paulus (13) and by us (25,28). Finally, the exploitation of this information depended upon increasing the reliability of chronic lymph drainage. This was achieved by Koep and associates (12) using improved operative and management techniques.

The precision with which thoracic duct drainage could be applied was further increased by developments in transplantation serology. The cytotoxic antibodies that may be found in recipient serums before or after transplantation were recently characterized on the basis of their reactivity against homologous T-lymphocytes and B-lymphocytes at warm and cold temperatures (2,8,30). Subsequent reports about the significance of these antibodies have been so conflicting that it is difficult to summarize this confusing literature. Our own experience has been that warm anti-T antibodies cause hyperacute rejection if present preoperatively (2, 8,30), that pre-existing warm anti-B antibodies diminish the chances of long term function (8,9) and that the development of either warm anti-T or anti-B antibodies after transplantation jeopardizes the prognosis (8). The so-called cold antibodies have been thought to be innocuous or possibly even enhancing (2,8,30). The variable duration of pretreatment with thoracic duct drainage (Table II) was designed to reduce pre-existing warm antibodies and to curb the fresh development of these antibodies in response to transplantation. More sophisticated and discriminating tests could have been used for immune assessment and monitoring, but the antibody analysis had the merit of simplicity.

The validity of this approach was supported by the experience herein reported. It was evident that many of the patients were pretreated for too short a time. Grafts placed into recipients conditioned by approximately three weeks of thoracic duct drainage still could provoke strong

antibody responses in recipients who were previously antibody-free. These organs were jeopardized by a 38 per cent incidence of significant, although usually reversible, rejection. In contrast, antibody responses were blunted, and early rejection was almost eliminated when thoracic duct drainage was in effect for four weeks or longer. Thus, we have modified our previous recommendations (Table II) in the direction of more protracted pretreatment (Table IV).

With pretreatment for four or more weeks, early rejection was almost totally prevented. It would be surprising if the same objective could not be achieved by preoperative lymphoid depletion with other means for a period of several weeks. An obvious possibility is mechanical removal of lymphocytes from the peripheral blood, a procedure for which instrumentation is already commercially available. The technique of total lymphoid irradiation, described by Strober and associates (29) is a variation of the same theme, so would be pretransplantation conditioning with powerful antilymphocyte serums and globulins, an approach that has been made impractical in patients by immune reactions to the heterologous protein (27). With any of these methods, treatment in the pretransplantation period will be essential for maximum benefit. Even with as potent a lymphoid depleting tool as thoracic duct drainage, much of the value is lost if treatment is begun contemporaneous with transplantation, as was shown with our own systematic trial (25,28) in which the results were distinctly inferior to those herein reported.

The potential value of pretreatment is not necessarily limited to the foregoing specific lymphoid depleting techniques. In the early days of our program, almost all human kidney recipients were given azathioprine for eight to ten days before transplantation. The practice was based upon analogous canine experiments in which average homograft survival was thereby doubled over that obtained when the drug was begun on the day of operation (24). Gradual abandonment of the policy of preoperative treatment of the patients in our series with azathioprine and often with steroids may have been a systematic error, inasmuch as other immunosuppressive adjuncts to condition the recipients were not being substituted. Wilson and Kirkpatrick (34) and Opelz and colleagues (20) were among the first to appreciate the role of intrinsic immunologic reactivity in determining the early postoperative course. If the patients were immunologically reactive, pretreatment with any effective immunosuppressive agent would reduce this adverse factor, apart from coincidentally ameliorating undetected presensitization states by erasure of immunologic memory.

Unfulfilled promises have been so common in renal transplantation that cautionary notations are automatic and, particularly so, if long follow-up study periods are not available. In the patients in our series, it remains to be seen if a delayed immunologic rebound will cause major kidney losses long after discontinuance of thoracic duct drainage. However, Walker (33) and Johnson (10) and their associates have not seen a catch-up deterioration of grafts in patients observed for two to five years after preoperative and postoperative thoracic duct drainage. It seems likely that the poorly understood change in host-graft relationship (26) which has made clinical transplantation practical will be expedited rather than hindered by properly timed thoracic duct drainage. If so, improvements in early graft survival should be translated into better long term results.

SUMMARY

Twenty-seven consecutive recipients of cadaveric kidneys, including five with pre-existing warm cytotoxic antibodies, were treated with thoracic duct drainage before and after transplantation. Fourteen patients who had lymph drainage for 26 to 58 days before transplantation had minor cytotoxic antibody responses after grafting, even if the antibodies had been present before therapy. Only one of the 14 recipients had any rejection during the

follow-up periods of one to six months. There were two deaths. The 13 patients pretreated for 17 to 23 days exhibited stronger cytotoxic antibody responsiveness, and five of these recipients had significant rejections of which four were reversible. One of the latter 13 patients died. These clinical and immunologic studies have established the value and have defined the appropriate timing of preoperative thoracic duct drainage in kidney transplantation. They have also directed attention to the rationale and the probable value of using other immunosuppressive methods for preparatory host conditioning instead of beginning such therapy at the time of transplantation.

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TABLE I
CADAVER KIDNEY RECIPIENTS TREATED WITH THORACIC DUCT DRAINAGE BEFORE AND AFTER TRANSPLANTATION

Patient No.	Age, yrs.	Days lymph drainage		Total lymph drainage, L.	Total lymphocytes removed, $\times 10^9$	Mismatches			Performed antibodies, per cent of panel of 30			Highest creatinine during rejection, mgm. per cent	Present creatinine, mgm. per cent	Post-transplant follow-up, mos.	Present prednisone dose, mgm./day	
		Preop.	Postop.			A and B	DR	T warm	B warm	B cold						
1 ^f	47	58	40	644	197	3	Not done	11	43	8	—	<2	6	20		
2 ^f	47	55	30	295	107	2	Not done	47	0	6	—	<2	5	30		
3	21	40	24	426	295	3	1	0	0	0	—	<2	4	30		
4	18	31	16	292	142	3	0	0	0	0	—	<2	4	25		
5	57	30	24	350	114	2	0	0	3	0	—	Dead	Died 2 mos.	30		
6	34	37	17	156	112	3	Not done	0	0	0	—	<2	3½	30		
12	58	29	23	156	104	2	0	0	0	0	—	<2	2½	30		
13	40	26	38	403	183	3	0	0	0	6	—	Dead	Died 7 wks.	30		
15	39	28	26	152	160	1	1	0	0	0	—	<2	2½	30		
23	34*	27	23	165	129	2	1	0	0	0	2.5 (41 days)	<2	2	50		
24 ^f	52	43	26	593	266	3	2	0	70	0	—	<2	1½	40		
25	10	33	23	222	119	3	1	75	17	0	—	<2	1½	30		
26	35	28	27	310	145	3	1	0	0	6	—	<2	1½	35		
27	61	40	28	313	168	2	0	0	0	0	—	<2	1	35		
PRETREATMENT FOR 26 TO 58 DAYS																
7	27	20	27	425	247	3	1	0	32	68	—	<2	3½	35		
8	15	18	25	149	84	3	0	0	0	0	—	<2	3	30		
9	23	19	18	194	161	3	1	0	0	8	—	<2	3	30		
10	57	20	32	465	131	2	1	0	0	25	—	<2	3	30		
11	46*	20	60	546	211	3	1	0	0	8	4.1 (30 days)	2.4	3	50		
14	35	23	27	236	158	1	2	0	0	0	—	Dead	Died 1 mo.	35		
16	19	18	37	366	184	2	1	0	0	0	—	<2	2½	30		
17	23	17	29	203	106	4	0	0	0	0	—	<2	2½	30		
18	41	17	29	158	132	3	1	0	0	0	4.4 (18 days)	<2	2½	40		
19	27	20	43	219	112	2	0	0	0	0	3.8 (12 days)	<2	2	40		
20	38	18	30	170	147	3	0	0	0	0	—	<2	2	30		

Patient No.	Age, yrs.	Days lymph drainage		Total lymph drainage, L.	Total lymphocytes removed, $\times 10^9$	Mismatches			Performed antibodies, per cent of panel of 30			Highest creatinine during rejection, mgm. per cent	Present creatinine, mgm. per cent	Post-transplant follow-up, mos.	Present prednisone dose, mgm./day
		Preop.	Postop.			A and B	DR	T warm	B warm	B cold	T warm				
21	47*	19	40	185	130	3	1	0	0	0	44	6.5 (8 days)	Retransplantation in 6 wks.	2	60
22	49	20	36	440	170	4	0	0	0	0	0	3 (15 days)	2.4	2	50

*Diabetic.
Retransplantation.

TABLE II
STEPS IN MANAGEMENT

STEP 1. Accurate assessment of antibodies against screening panel Possibilities are:

- A. Antibody-free
- B. Antibodies present*
 - 1. Anti-T, warm ... worst
 - 2. Anti-B, warm ... bad
 - 3. Anti-B, cold ... good?

STEP 2. Time or thoracic duct drainage pretreatment leading to transplantation from a cross match negative donor

- A. Patient antibody-free or with cold antibodies ... 21 days
- B. Patient with warm anti-T or warm anti-B antibodies ... ≥ 35 days

STEP 2 (alternative). Time or thoracic duct drainage pretreatment leading to transplantation from a cross match positive donor

- A. Patient with warm anti-B antibodies ... ≥ 35 days
 - B. Delay transplantation in patients with warm anti-T antibodies until titer is below 1:4
-

*Warm antibodies are IgG. Cold antibodies are IgM.

TABLE III
 ASSOCIATION BETWEEN THORACIC DUCT DRAINAGE AND PRODUCTION OF ANTI-B ANTIBODIES TO A PANEL
 TWO WEEKS AFTER TRANSPLANTATION

	No.	0-5 per cent*	6-15 per cent	16-50 per cent	>50 per cent
B Warm antibody					
TDD 18-23 days ..	13	2	2	2	7 ^{†‡}
TDD 26-58 days ..	14	2	7	4	1
B Cold antibodies					
TDD 18-23 days ..	13	4	7	2	0
TDD 26-58 days ..	14	10	1	3	0

TDD, Thoracic duct drainage.

* Considered to be negative.

[†] Four of the five patients with rejection were in this group.

[‡] The results were significant, $p < 0.05$, in comparison with those with pretreatment for 26-58 days.

TABLE IV
REVISED STEPS IN MANAGEMENT

STEP 1. Antibody assessment, same as Table II

STEP 2. Duration of pretreatment, cross match negative donor

- A. Antibody-free or cold antibodies ... ≥ 28 days
- B. Warm anti-T or anti-B antibodies ... ≥ 35 days

STEP 2 (alternative). Duration of pretreatment, cross match positive donor, same as Table II
