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Rejection of Human Intestinal Allografts: Alone or in Combination With the Liver

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OVER a period of 3 years (May 2, 1990 to April 15, 1993), 43 consecutive patients were given 45 intestinal allografts at the University of Pittsburgh. The basic immunosuppressive therapy was FK 506. Twenty-one patients were adults and 22 were children. Fifteen received an intestine alone, 21 received an intestine in continuity with the liver, and 7 received a multivisceral graft that contained 4 or more organs (liver in 6). The ascending and right transverse colon were included with the small bowel in 13 recipients, almost evenly distributed between the three groups. The donors were all ABO-identical and HLA-histoincompatible. The lymphocytotoxic crossmatch was positive in two cases. No attempts were made to alter the graft immunologic tissue with antilymphocyte preparations or other modalities. One of the isolated intestinal and one of the combined liver-intestinal recipients required retransplantation after 667 and 47 days, respectively, because of chronic and acute rejection. After 6 to 40 months, 30 of the 43 patients are alive, 29 bearing grafts. Of these, 25 (86%) are supported nutritionally solely with their functioning grafts. The surgical techniques, details of patient and graft survival, as well as quality of graft functions are fully described elsewhere in this issue.[1-3]

METHODS

Immunosuppression

Intravenous FK 506, steroids, and prostaglandin E_1 (prostin) were begun intraoperatively as previously described.[4-6] Enteral administration of FK 506 was started 1 to 2 weeks after transplantation with several days of overlap with intravenous treatment. The target range of FK 506 trough plasma levels was between 3 to 1 ng/mL. During the study period, the FK 506 doses, plasma trough levels, and the prednisone doses were similar in the 3 kinds of allograft recipients. A low dose of azathioprine (1 to 2 mg/kg/d) was added in 22 patients.

Augmented immunosuppressive therapy was initiated during rejection episodes, based upon their severity. A steroid bolus was given and FK 506 dosage was increased when this was possible without drug toxicity. A steroid recycle for 5 days and/or a 7-day course of OKT3 were backup options.

Monitoring of Graft Rejection

Detection of graft rejection was based primarily on clinical observations, endoscopic findings, and histopathologic studies of endoscopic-guided mucosal biopsies. Graft endoscopy with random multiple mucosal biopsies (particularly of the ileum) was accomplished at least once per week for the first 3 months, monthly for the next 3 months, and every 3 to 6 months thereafter and whenever it was clinically indicated. The adopted criteria for the diagnosis of intestinal allograft rejection are described elsewhere.[7]

RESULTS

Acute Rejection

With a mean follow-up of 15 ± 10 months, only 2 patients (both with combined liver-intestine grafts) were spared clinical or histopathologic diagnosis of intestinal graft rejection. Although the clinical diagnosis of rejection was made in 95% of cases, this was confirmed histologically in only 31 patients (72%). The mean postoperative time to the first episode in all cases was 19 ± 28 days; 11 ± 6 for the isolated intestine, 22 ± 34 for the combined liver and intestine, and 15 ± 7 for the multivisceral allografts. Most of the rejections were mild to moderate, and the number of episodes per graft were similar for the 3 kinds of intestinal allografts with an average of 4.1. Beyond 3 months after transplantation, about 50% of the patients in each transplant group experienced rejection of the intestinal graft. This often was associated with attempts to reduce immunosuppression because of cytomegaloviral enteritis, post-transplant lymphoproliferative disease, or other opportunistic infections. Twenty-three (10 isolated intestine, 10 combined liver-intestine, and 3 multivisceral) of the 45 grafts required 1 or more steroid recycles for treatment of moderate rejection episodes. OKT3 was used to treat 8 severe rejection episodes among isolated intestinal (n = 5), combined liver-intestinal (n = 1), and multivisceral recipients (n = 2).

Twelve of the 28 composite visceral grafts (43%) that contained liver experienced histologically diagnosed and clinically treated liver allograft rejection. The number of episodes per graft was 0.6. On 88 occasions on which both liver and small bowel biopsies were taken simultaneously or closely together, 47 of the dual specimens (53%) had no signs of rejection in either organs, 12 (14%) had rejection in both, 15 (17%) had rejection only in the liver, and 14 (16%) had rejection in the intestine only.

Five of the 13 bowel grafts (38%) that included colon showed histologic evidence of colonic rejection at some time. None of the multivisceral grafts had histopathologically proven gastric rejection, but 1 developed 2 episodes

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0041-1345/94/$3.00/+0

of pancreatitis that responded to augmented immunosuppressive therapy.

Chronic Rejection

The histopathologic examination of full-thickness sections of 6 resected grafts (5 isolated intestine, 1 combined liver-intestine) showed chronic rejection in 2 of the isolated intestinal grafts. In addition, one combined liver-intestine recipient with strong positive cross-match developed chronic rejection of both organs. This patient died of hepatorenal failure with the graft in place.

Rejection and Graft Loss

Eight of the 16 (6 isolated intestine, 9 liver-intestine, and 1 multivisceral) implanted grafts that were lost either by patient's death (n = 10) or graft removal (n = 6) showed histologic evidence of either acute rejection (n = 5), chronic rejection (n = 2), or both (n = 1). Five were isolated intestine (4 recipients) and 3 were combined liver-intestine (2 recipients). Graft enterectomy (n = 5) rescued only one of the 4 isolated intestinal recipients, and the 2 combined liver-intestinal recipients died despite successful graft replacement in 1. Refractory rejection of the isolated intestinal grafts was precipitated by a significant reduction in immunosuppression in 4 and misdiagnosis of rejection in 1. The reduction or withdrawal of immunosuppression was due to either drug noncompliance, cytomegaloviral enteritis, respiratory syncytial viral pneumonia, or demyelination of the brain white matter. The three combined liver-intestinal grafts were rejected despite augmented immunosuppressive therapy.

Graft-Versus-Host Disease

Using standard histologic and in situ hybridization techniques, graft-versus-host disease was unequivocally diagnosed in only 1 combined liver-intestine pediatric recipient who had preexisting immunoglobulin (Ig)A deficiency. Light immunosuppression was attempted early in the postoperative course because of *Pneumocystis carinii* pneumonia and an intestinal anastomotic leak.

SUMMARY AND CONCLUSION

The current results of the present series demonstrate that intestinal allografts are more vulnerable to rejection and continue to be at a significantly higher risk long after transplantation compared with isolated liver allograft recipients. Unexpectedly, a combined liver allograft does not protect small bowel from rejection.

The necessarily continuous heavy immunosuppression for these unique recipients is potentially self-defeating. This is clearly demonstrated by their high susceptibility to early and late infectious complications after transplantation as reported in this issue.[8,9] With the minimal graft-versus-host disease threat in this clinical trial, our revised protocol for future intestinal transplantation is to maximize the passenger leukocyte traffic with supplementary bone marrow from the same intestinal donor in an attempt to augment the development of systemic chimerism and the gradual induction of donor-specific nonreactivity.[10]

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