

## Management of Intestinal Transplantation in Humans

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**W**E report here the clinical experience and management guidelines for the nine consecutive cases who received either an isolated small intestinal graft (n = 1) or an intestine liver combination at the University of Pittsburgh, with FK 506 being the basic immunosuppressive drug therapy.

### MATERIALS AND METHODS

The pretransplant clinical features and patient characteristics are fully described elsewhere in this issue.<sup>1</sup> In brief, three of the recipients were young adults and six were children. The donors were ABO-identical and HLA-histoincompatible, and cytotoxic crossmatches were positive in two cases. Donor and recipient were of the opposite sex in four of the cases. Attempts were made at selective decontamination of the donors with no efforts to alter the graft lymphoreticular tissue with antilymphocyte preparations or other modalities.

The principles of the donor operations and the techniques for both isolated intestinal transplantation and a composite intestine-liver graft are described elsewhere.<sup>2,3</sup> Continuity of the gastrointestinal tract was restored in stages. Eight to 16 weeks later, the vent-chimneys were excised at a second operation.

The basic immunosuppressive therapy was FK 506. The drug was given intravenously (IV) at first with 0.1 to 0.15 mg/kg per day and enterally later at a starting dose of 0.3 mg/kg per day in two divided doses as described elsewhere.<sup>4</sup> Dose adjustments were made based upon the quality of liver function, evidence of graft rejection, development of renal dysfunction, and daily FK 506 trough plasma levels. Prednisone was given at the outset in all but one pediatric case. Prophylactic steroid recycle was given to one adult recipient with a strong positive cytotoxic crossmatch. A low dose of azathioprine (1 to 2 mg/kg per day) was added in combination with FK 506 in one adult and one pediatric case.

Assessment of graft function and detection of graft rejection was based primarily upon clinical, biochemical, histopathologic, endoscopic, radiologic, and metabolic parameters. These included thorough clinical evaluation, serial graft biopsies, periodic GI series, frequent anthropometric measures, serial serum protein and fatty acid analyses, FK 506 oral kinetics, D-xylose, and vitamin E absorption tests.

Frequent blood and quantitative stool cultures were also obtained, and the results compared for similarity and dissimilarity of the intestinal flora. Selective decontamination was used for 4 to 6 weeks after transplantation and during rejection episodes.<sup>5</sup>

### RESULTS

The clinical course and total outcome of the nine patients are fully described in the current symposium by Tzakis et al.<sup>1</sup> Eight patients are currently alive and one pediatric recipient died of graft-versus-host disease (GVHD) 23 days after a combined liver-intestine transplantation.

The convalescence of all of our patients, particularly the isolated small bowel recipient, was difficult, requiring

protracted hospitalization. Consequently, the achievement of alimentionation was a slow process requiring 6 weeks to 9 months after transplantation.

The adopted histological criteria for the diagnosis of acute intestinal graft rejection included significant cellular infiltration, cryptitis, villous edema with abrasion, and even sloughing of the cell surface epithelium. Six of the nine grafts experienced one to eight episodes of rejection. The frequency and severity of hepatic graft rejection in these patients was similar to that in simple liver graft recipients. Interestingly, the most serious and persistent graft rejections were in the isolated small bowel and positive cytotoxic crossmatch recipients. The histological changes suggestive of chronic graft rejection were not evident in any of the endoscopic mucosal biopsies.

In most of the rejection episodes, the clinical, endoscopic, and radiologic pictures correlated with the concomitant histological findings. Clinically, most of the rejection episodes were presented with fever, high stomal output/diarrhea, dusky mucosa and graft ileus. A septic shock-like syndrome was also a concomitant finding in patients with severe rejection crisis.

The attacks of graft rejection were successfully treated with FK 506 dose augmentation and, less frequently, by steroid bolus and recycle. OKT3 was required only in the patient with isolated intestinal graft. Recovery of the intestinal mucosal changes was complete in all patients.

GVHD was unequivocally diagnosed in a combined liver-intestine pediatric recipient using the standard histological and in situ hybridization techniques. Because the donor and recipient were opposite sexes, karyotyping provided a definitive cross-check of the other techniques. Light immunosuppression was attempted early in the course because of disruption of the upper enteric anastomosis and consequent soilage. In this patient, the skin lesions started to appear 10 days after transplant, and the clinical picture simulated that of life-threatening sepsis. Therefore, immunosuppression was significantly reduced

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Supported by research grants from the Veterans Administration and Project Grant No. DK 29961 from the National Institutes of Health, Bethesda, Maryland.

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0041-1345/92/\$3.00/+0

and 13 days later the patient succumbed to multiple-organ failure.

Serial evaluation of the anthropometric parameters (weight, upper-arm measurement of fat and muscle), the need for IV nutrition, and the conduction of different absorption and metabolic studies were used for the assessment of graft function. The intermittent reinstatement of partial or complete IV nutrition was primarily due to either prominent intestinal graft rejection or severe systemic/enteric infection. Interestingly, complete oral administration of the standard FK 506 dose was able to maintain a therapeutic plasma level in all patients within the first 4 postoperative weeks. D-Xylose was adequately absorbed by the intestinal graft in most of the studied patients (n = 7). However, vitamin E absorption was slightly depressed in most cases. Posttransplant serum IgA levels were within the normal range for both the pediatric and adult recipients.

Recovery of the intestinal graft motility was clinically, radiologically, and endoscopically documented 1 to 2 weeks after transplantation. Temporary dysfunction of the gastrointestinal motility in the form of gastric atony (n = 1), pylorospasm (n = 2), and gastroesophageal reflux (n = 3) were observed during the first 3 postoperative months.

Five episodes of translocation (4 bacterial, 1 fungal) developed in a total of three patients. Severe rejection of the intestinal graft was concomitant on only one occasion. Treatment was successful in all cases with the specific systemic antibiotics and proper intestinal decontamination.

## DISCUSSION

Our experience suggests that small bowel transplantation in humans could become more practical with the clinical use of FK 506. However, development of allograft rejection was still a major potential barrier to successful clinical small intestinal transplantation. In the current study, the clinical, endoscopic, histologic, radiologic, and metabolic parameters were effective in detecting acute graft rejection early enough to be successfully treated with complete healing of the intestinal mucosa. Simultaneous evaluation of the circulating lymphokines, the brush-border enzymatic activities, and the expression of the major histocompatibility complex (MHC) class II antigen on the enterocytes may make possible an even earlier immunohistochemical diagnosis. Augmented FK 506 and steroid therapy was effective in reversing most of the rejection episodes.

The infectious implications of rejection have been pre-

viously demonstrated with liver transplantation.<sup>6,7</sup> The paradoxical therapeutic philosophy of treating infection (related to rejection) with increased immunosuppression is designed to stop or prevent bacterial translocation. The concept is even more applicable with the intestine than with the liver, because a disrupted mucosal barrier quickly creates a lethal environment for the total body. Proper adjustment of the immunosuppressive therapy combined with efficient antibiotic treatment was successful in all of our morbid cases except in the child who died of GVHD.

GVHD may complicate the early and late postoperative course of intestinal transplant recipients, particularly those with inadequate immunosuppressive therapy. Such morbidity is better understood in view of the striking phenomenon of cell migration and repopulation which was recently described.<sup>3,8,9</sup> Early diagnosis of GVHD and prompt adjustment of the immunosuppressive treatment should be effective in such cases, as has been described recently with FK 506 after experimental bone marrow transplantation.<sup>10</sup>

The anthropometric measures, oral FK 506 kinetic studies, serum protein and fatty acid analyses, and D-xylose tolerance test seem to be reliable indices for the assessment of the quality of graft function. Monitoring of the gastrointestinal motility of both the grafted and recipient intestinal segments with thorough evaluation of the graft neuroendocrine functions are currently under evaluation.

In conclusion, the current results underscore the possible clinical utility of intestinal transplantation, particularly in continuity with the liver, but emphasize equally the complexity and difficulty of management in these cases.

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