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Successful Orthotopic Small Bowel Transplantation With Short-Term FK 506 Immunosuppressive Therapy

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ALTHOUGH small bowel transplantation is the physiologic treatment of the short bowel syndrome, its clinical implementation awaits development of immunosuppressive regimens that ensure satisfactory control of graft rejection. Agents such as CyA and corticosteroids are useful for transplantation of most other vascularized organ allografts. However, rejection of the transplanted small intestine has been found more difficult to prevent, probably because the large lymphoid content of the intestine renders it more immunogenic and because the barrier function of the intestine magnifies defects in immunosuppression that would otherwise be inconsequential in transplantation of other organs. Prolonged and, in some instances, indefinite survival of small bowel allografts using CyA has been demonstrated in several large and small animal models. However, in clinical small bowel transplantation, <25% long-term functional graft survival has been achieved when CyA has been used as the primary immunosuppressive agent (Grant D, personal communication, October 1989), demonstrating the need for other more effective immunosuppressive agents.

The macrolide FK 506 has been shown to have potent *in vitro* and *in vivo* immunosuppressive activity and to delay rejection of kidney,¹ heart,² and liver³ allografts in a number of experimental animal models. The effectiveness of FK 506 has also recently been reported in clinical liver and kidney transplantation.⁴ To determine whether FK 506 can effectively prevent the rejection of small bowel allografts, studies were undertaken in a rat model of small bowel transplantation.

MATERIALS AND METHODS

One-stage orthotopic small bowel transplantation was performed in the fully allogeneic Brown Norway (RT1n) to Lewis (RT1l) rat strain combination using male rats weighing between 180 and 240 g. Animals in group 1 (n = 6) received no immunosuppressive therapy. Animals in group 2 (n = 9) received FK 506 at a dosage of 2 mg/kg intramuscularly on postoperative days 0 through 4. For comparison, animals in group 3 (n = 11) received CyA at a dosage of 15 mg/kg intramuscularly on postoperative days 0 through 4; this dosage has previously been shown in the same strain combination to result in significantly prolonged graft and recipient survival and occasional (30%) indefinite survival when administered on days 0 through 7, and to result uniformly in indefinite survival when further continued every other day until postoperative day 28.⁵ Syngeneic (Lewis to Lewis) transplantation was performed in six animals.

Transplantation was performed using standard microsurgical techniques as previously described. After revascularization of the graft, the recipient's own small bowel was resected and the transplanted bowel was anastomosed into intestinal continuity,

thereby rendering the recipient nutritionally dependent on the transplanted small bowel. Immunosuppression was begun immediately postoperatively.

RESULTS

In the absence of immunosuppressive therapy (group 1), all graft recipients developed acute graft rejection characterized by the development of severe diarrhea and weight loss and culminating in a moribund state requiring death of the recipient; mean survival was 10.8 ± 1.4 days. Gross and microscopic examination of the intestinal allografts showed changes consistent with acute fulminant rejection, with necrosis or perforation of the bowel wall associated with extensive mucosal destruction and marked cellular infiltration of the graft.

With short courses of CyA therapy (group 3), graft rejection was delayed and recipient survival prolonged (mean survival, 24.3 ± 3.9 days); however, long-term survival, as seen with more prolonged courses of CyA, was not observed. After initially appearing healthy and gaining weight, these graft recipients developed progressively worsening diarrhea, leading to profound inanition and death. Findings at autopsy were consistent with less fulminant rejection. Filmy encapsulation of the grafts was evident, and perforation and necrosis of the grafts were infrequently seen. Histologic examination of the grafts demonstrated fibrosis and thickening of the bowel wall.

In contrast, long-term (>180 days) functional graft survival has been achieved in all rats receiving five doses of FK 506, with the exception of one rat dying from pneumonia on postoperative day 120 who had no gross or microscopic evidence of graft rejection or graft-versus-host disease. Among the long-term surviving rats, no clinical signs of graft rejection or graft-versus-host disease have been observed. When examined at laparotomy 6 months after transplantation, the intestinal allografts appeared grossly normal. Full-thickness allograft biopsies demonstrated normal architecture with no evidence of rejection (Fig 1). Biopsies of the liver and spleen were also histologically normal, with no findings of periportal infiltration

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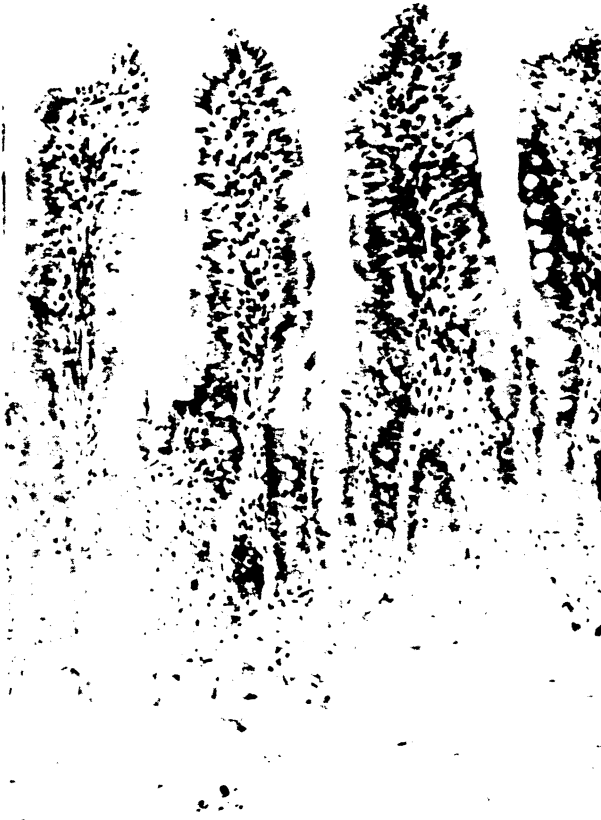


Fig 1. A biopsy of an intestinal allograft in a recipient treated with FK 506 on postoperative days 0-4 shows a normal histologic appearance 6 months after transplantation. Villi are well-preserved and there is no evidence of rejection.

or disruption of splenic architecture suggestive of ongoing or prior graft-versus-host disease.

Function of the allografts has been clinically normal. Recipient weight gain has been comparable to age-

matched normal rats and syngeneic controls. Maltose absorption from the transplanted bowel, an indicator of the integrity of the mucosal brush border enzymes, has not differed significantly from controls. Measurements of serum total protein, albumin, triglyceride, and cholesterol levels, indicative of the recipient's nutritional state, have not differed significantly from the control groups. Measurements of serum glucose, blood urea nitrogen, creatinine, and liver enzymes also have not differed significantly from the control groups.

DISCUSSION

Satisfactory prevention of graft rejection remains the primary problem in small bowel transplantation. In this model of orthotopic small bowel transplantation, very short courses of FK 506 effectively controlled the rejection of intestinal allografts and prevented the development of clinical graft-versus-host disease, while preserving graft function sufficiently to permit normal recipient growth and to maintain a normal nutritional state. In contrast, equally short courses of CyA in a dosage previously found to result in long-term survival when given in extended courses were less effective. The results of this study demonstrate that FK 506 is a highly potent immunosuppressive agent which may be more effective than CyA and may be useful in small bowel transplantation. These findings suggest that improved success in clinical small bowel transplantation may be possible using FK 506 either alone or in combination with other established immunosuppressive agents.

REFERENCES

1. Ochiai T, Nagata M, Nakajima K, et al: *Transplant Proc* 19:53, 1987 (suppl 6)
2. Ochiai T, Nagata M, Nakajima K, et al: *Transplant Proc* 19:1284, 1987
3. Todo S, Podesta L, ChapChap P, et al: *Transplant Proc* 19:64, 1987 (suppl 6)
4. Starzl T, Todo S, Fung J, et al: *Lancet* 1000, 1989
5. Lee KKW, Schraut WH: *Am J Surg* 151:55, 1986