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Comparison of Short-Term Immunosuppressive Therapy with Cyclosporine and FK 506 in Small-Bowel Transplantation

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Since small-bowel transplantation was first described. experimentally in the late 1950s, control of graft rejection has been recognized as the primary obstacle to its successful Clinical implementation. Early experimental and clinical studies demonstrated that immunosuppressive regimens based upon azathioprine, antilymphocyte globulin, and corticosteroids were not sufficient to ensure long-term recipient and graft survival. More recently long-term functional survival of intestinal allografts has been achieved with cyclosporine in. a variety of experimental animal models and has led to renewed attempts at clinical small-bowel transplantation. Although long-term survival has been achieved in some instances, prevention of graft rejection remains a major problem.

The neutral macrolide FK 506 has been shown on a molar basis to be a more potent inhibitor of in vivo and in vitro assays of immune function than cyclosporine.[1] It has also been shown to significantly delay rejection of kidney,[2] heart,[3] and liver[4] allografts in a number of different experimental models. A rat model was therefore used to study the effectiveness of FK 506 in prolonging the survival of intestinal allografts and to compare its effectiveness with that observed for cyclosporine.

MATERIALS AND METHODS

One-stage orthotopic small-bowel transplantation utilizing systemic venous outflow was performed in the fully allogeneic Brown Norway (BN, RTln) to Lewis (LEW, RTll) rat strain combination using standard microsurgical techniques. Animals were allowed water ad libitum and were restarted on normal laboratory diets on the second postoperative day. The general health, appearance, and behavior of the animals was closely monitored. Body weight was measured at frequent regular intervals, and routine biochemical studies were periodically performed on serum samples. With long-term surviving graft recipients, graft inspection and biopsy were performed via laparotomy. Autopsies and histopathologic studies were performed on animals undergoing rejection.

Four experimental groups were prepared. In group I ($N = 6$), transplantation was performed without immunosuppressive therapy. In group II ($N = 11$), graft recipients received cyclosporine (15 mg/kg dissolved in 10% Intralipid) on days 0 to 4 administered via intramuscular injection. In group III ($N = 17$), cyclosporine was administered in the identical dose on days 0 to 6 and then every other day until day 28. In group IV ($N = 8$), recipients received FK 506 (2 mg/kg dissolved in normal saline) on days 0 to 4 administered via intramuscular injection.

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RESULTS

Rats undergoing allogeneic transplantation without immunosuppressive therapy (group I) all developed acute rejection with a mean survival of 10.8 ± 1.4 days. Grafts showed signs of acute rejection, which included distention and thinning of the bowel wall and inflammation of the graft mesentery. Histologic examination revealed acute mucosal destruction and a heavy cellular infiltrate. Group II rats receiving short courses of cyclosporine therapy began losing weight on approximately day 18 and had slightly prolonged mean survival (24.3 ± 3.9 days). These grafts showed evidence of less acute rejection, with filmy encapsulation of the grafts, less prominent cellular infiltration of the grafts, and fibrous thickening of the bowel wall.

All rats in groups III and IV receiving either FK 506 or extended courses of cyclosporine have remained alive for more than 180 days and free of signs of graft rejection. In both groups weight gain has been comparable to that observed in normal age-matched LEW rats; behavior and bowel function have appeared clinically normal. At laparotomy 6 months after transplantation, allografts in groups III and IV grossly appeared normal. Histologic examination of full-thickness graft biopsies appears normal with no signs of rejection; neither the liver nor the spleen show evidence of ongoing or prior graft-versus-host disease. Nutritional state as reflected by total protein, albumin, cholesterol, and triglyceride levels is normal in both groups. No evidence of cyclosporine- or FK 506-related toxicity has been observed.

DISCUSSION

The present study demonstrates that long-term recipient and graft survival can be achieved in this model of orthotopic small-bowel transplantation when very short courses of FK 506 are given. Similar long-term graft and recipient survival can be achieved with extended courses of cyclosporine (group III), confirming an earlier report,[5] but when the same dosage of cyclosporine is given for only five doses, long-term survival does not ensue as it does with PK 506.

These results demonstrate that FK 506 is a potent immunosuppressive agent that may be more effective than cyclosporine in preventing rejection of small-bowel allografts. Although the effectiveness of FK 506 as single-agent immunosuppressive therapy for clinical small-bowel transplantation must be established by additional studies, it is likely that combination of FK 506 with other established immunosuppressive agents such as cyclosporine will permit reduction of the dosage of these agents necessary to prevent graft rejection and thereby decrease the incidence of drug-related toxicity.

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