1490

Monitoring and Treatment of Intestinal Allograft Rejection in Humans

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OVER a period of 25 months, 23 small bowel transplants have been performed at the University of Pittsburgh since the advent of FK 506. Twelve patients were adults and 11 were children. Nine patients received an intestine alone, 12 received an intestine in continuity with the liver, and two received a full multivisceral graft. 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 lymphoreticular tissue with antilymphocyte preparations or other modalities. One of the isolated small bowel recipients required retransplantation after 22.5 months because of chronic rejection. Nineteen of the 23 patients are currently alive with a median follow-up of 231 days (range 67 to 754). The surgical techniques, details of patient and graft survival, as well as quality of graft function are fully described elsewhere in this issue.[1,2]

IMMUNOSUPPRESSION

FK 506 was the primary immunosuppressive agent. The drug was given intravenously as a continuous infusion initially at a dose of 0.15 mg/kg/d. Enteral administration of FK 506 was initiated 1 to 2 weeks after transplantation at a dose of 0.3 mg/kg/d in two divided doses as described elsewhere.[3] Gradual withdrawal of IV FK 506 doses was adopted in all cases with several days of overlap with oral therapy. The trough plasma levels of FK 506 (target range 1 to 3 ng/mL) were measured daily for the first 6 weeks, twice a week for the following 6 weeks and at longer intervals thereafter.

Methylprednisolone was started intraoperatively with 1-g bolus followed by a steroid taper for 5 days and a maintenance dose of 20 mg/d thereafter. Steroid therapy was scaled down for children. In the last 15 patients, Prostaglandin-E_1 was begun intraoperatively at a dose of 0.6 μg/kg/h and continued for 7 to 14 days. A low dose of azathioprine (1 to 2 mg/kg/d) was added in six patients.

MONITORING OF GRAFT REJECTION

All patients were monitored for the development of intestinal allograft rejection using a combination of clinical, endoscopic, histological, radiological, bacteriologic, and metabolic evaluations. Graft endoscopy with multiple mucosal biopsies was accomplished weekly for the first 3 months and whenever it was thereafter clinically indicated.

ACUTE REJECTION

Acute intestinal allograft rejection was always presented with fever, abdominal pain, vomiting, watery diarrhea and/or an increase in stomal output. In addition, graft ileus, intestinal bleeding, septic shock, and an ARDS-like picture developed in patients with severe rejection episodes. The endoscopic examination during each acute rejection episode documented an ischemic or dusky mucosa with focal ulcerations and reduced or even complete loss of peristalsis. Grafts with severe rejection showed either a nodular mucosa or a diffuse ulceration with bleeding. The adopted histological criteria for the diagnosis of acute intestinal allograft rejection included mononuclear cell infiltrate, villous blunting, and cryptitis. Complete sloughing of the intestinal mucosa with crypt destruction was seen in patients with severe rejection episodes.

Twenty-one of the 24 small bowel grafts experienced at least one episode of rejection with an overall incidence of 87.5%. There was little difference between patients with either a solitary or composite intestinal graft in terms of the incidence of graft rejection. The risk for rejection was greatest during the first 30 postoperative days (75%) and gradually declined to 17% during the third postoperative month. The intestine was more vulnerable to rejection than was the liver in patients with a combined liver and small bowel graft. The incidence of liver graft rejection in these patients was similar to that experienced by a control group of recipients receiving only a liver.[4]

Acute rejection of the small bowel graft once identified was treated. In addition to an increase in the basal FK 506 dose, patients were treated with a steroid bolus and, less frequently, with a steroid recycle depending upon the severity of the rejection episode. OKT3 was used in two cases. Recovery was complete in all but one graft.

CHRONIC REJECTION

Chronic rejection was documented in only one patient who received an isolated small bowel graft. His postoperative course was stormy with multiple episodes of graft rejection associated with drug noncompliance. Chronic graft dys-

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function was manifested as intractable diarrhea, abdominal pain, intermittent episodes of sepsis, progressive weight loss, and intermittent intestinal bleeding. Periodic endoscopic examinations revealed pseudomembrane formation, thickened mucosal folds, and chronic ulcers in a tubular intestine.

Serial intestinal biopsies showed apoptoses of crypt cells with a sparse inflammatory cell infiltrate. The angiographic study demonstrated segmental narrowing of the mesenteric arterial arcade which dictated graft enterectomy. The resected graft showed mucosal ulceration, abscesses, and obliterative arteriopathy.

GRAFT-VERSUS-HOST DISEASE (GVHD)

Using standard histological and in situ hybridization techniques, GVHD was unequivocally diagnosed in only one combined liver-intestine pediatric recipient. Light immunosuppression was attempted early in the postoperative course because of *Pneumocystis carinii* pneumonia and an intestinal anastomotic leak. The skin lesions appeared 10 days after transplant. The overall clinical picture simulated life-threatening sepsis. The immunosuppression was reduced significantly, and 13 days later the patient succumbed to multiple organ failure.

CONCLUSIONS

The current results of the present series demonstrate the efficacy of our current management scheme for intestinal allograft recipients. They also emphasize the utility of isolated intestinal transplantation in patients not requiring a simultaneous liver graft.

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