

1081

The Effect of FK 506 on Small Intestine Allotransplantation in the Rat

A.L. Hoffman, L. Makowka, X. Cai, B. Banner, D.V. Cramer, A. Pascualone, S. Todo, and T.E. Starzl

DESPITE a potent armamentarium of immunosuppressive agents, graft rejection remains the major barrier in the development of successful small intestine allotransplantation. FK 506 has extremely potent immunosuppressive properties, as demonstrated by in vivo and in vitro testing. Renal, hepatic, and cardiac allografts survive for prolonged periods under FK 506 immunosuppression alone or with CyA and steroids.¹⁻³ In vitro FK 506 inhibits lymphokine release and proliferation of lymphocytes in response to alloantigens at much lower concentrations than CyA.⁴ This study compares FK 506 and CyA for their ability to prevent graft rejection and graft-versus-host disease (GVHD) in a rat small intestine allotransplantation model.

MATERIALS AND METHODS

Adult male Lewis (LEW) and ACI rats and (ACI × LEW) F1 progeny allowed for separate examination of graft rejection (F1 → LEW), GVHD (LEW → F1), or their combined effects (ACI → LEW). Heterotopic transplantation was performed using a complete jejunoileal segment with mesocaval outflow and a Thiry-Vella loop. Acute rejection was defined as progressive stomal discoloration (ischemia) and death of the host. Chronic rejection resulted in a firm abdominal mass occurring more than 30 days following transplantation. A diagnosis of GVHD was made if four or more of the following signs were present: diffuse erythema, hyperkeratosis of the foot pads, generalized dermatitis, unkempt appearance, weight loss, or diarrhea.⁵ Specimens of donor and host small intestine, skin, and tongue were processed for routine light microscopy. Kaplan-Meier survival curves were plotted for each group, assessed by Mantel-Cox statistical analysis, and reported relative to untreated controls. Statistical comparisons of the incidence of acute rejection or GVHD between experimental and control groups were performed using chi-square (Yates') analysis.

RESULTS

In the "rejection only" trial (F1 → LEW), intramuscular FK 506 (2 mg/kg/d, days 0-6; then 1 mg/kg four times per day, days 8-30) allowed for significantly prolonged survival (83.0 ± 82.6 days, $P < 0.0022$) as well as a lower incidence (3 of 10, $P < .05$) and a histologically milder form of acute rejection than untreated controls (9.0 ± 2.0 days; 8 of 8). In the ACI → LEW trial, FK 506-treated animals demonstrated prolonged survival (50.6 ± 46.5 days, $P < 0.0001$) relative to the control group (7.3 ± 1.0 days), but rejection was never demonstrated (0 of 10, $P < 0.05$) following treatment, and all untreated controls (11 of 11) died of severe acute rejection. High-dose intramuscular CyA (40 mg/kg/d, days -2-7) was associated with prolonged survival (34.3 ± 35.2 days, $P < 0.0007$), but rejection was

common (4 of 9, $P = \text{NS}$) and severe, as demonstrated in histologic preparations. The cessation of FK 506 was associated with chronic rejection and, ultimately, death of the animal. In the "GVHD only" trials (LEW → F1), following FK 506 treatment, only a single case of GVHD was noted, and this process resolved within 2 weeks of its onset. This animal and 6 others in this group (7 of 8, $P < 0.05$) never developed clinical evidence of GVHD and became tolerant to their graft (188.0 ± 72.1 days, $P < 0.0002$). CyA (20 mg/kg/d, days -2-14) was not associated with tolerance induction (38.3 ± 38.6 days, $P < 0.1035$) and fatal acute GVHD was noted in at least 2 of 6 cases ($P = \text{NS}$). Six of 14 control animals developed GVHD, and 4 others had 3 signs of GVHD at death (13.9 ± 6.1 days).

Postoperative weight gain for all groups transplanted with FK 506 began at approximately 9 days and, by 3 months, the hosts had gained 25%-50% of their pretransplantation weight. Rejection and GVHD were commonly associated with severe weight loss.

DISCUSSION

Small intestine allotransplantation has been unsuccessful primarily due to the inability to prevent graft rejection.⁶ Immunocompetent intestinal lymphocytes induce a graft-versus-host response, which may complicate the treatment of rejection.^{7,8} CyA has curtailed graft rejection in hepatic, renal, and cardiac models, resulting in enhanced survival in a variety of species. However, CyA has provided only a minor breakthrough in small intestine allotransplantation^{9,10} relative to other organ systems. Traditional immunosuppressive agents such as azathioprine and corticosteroids were virtually ineffective.¹¹ Despite CyA, rejection is not uncommon¹² and high-yield, long-term survival is the exception,¹³ not the rule. Furthermore, CyA does not prevent GVHD, especially after cessation of the drug.^{14,15} These findings associated with CyA have been verified in this study. The potency of FK 506 makes this drug an intriguing antidote for the ills of small intestine allotransplantation. FK 506 inhibited rejection when GVHD was genetically restricted and prevented the fatal effects of acute GVHD in a model unopposed by graft

From the Department of Surgery, University Health Center of Pittsburgh, University of Pittsburgh; and the Veterans Administration Medical Center, Pittsburgh, PA.

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

Address reprint requests to T.E. Starzl, MD, PhD, Department of Surgery, 3601 Fifth Avenue, Falk Clinic 5C, Pittsburgh, PA 15213.

© 1990 by Appleton & Lange
0041-1345/90/\$3.00/+0

rejection. In the most clinically relevant system, ACI → LEW, FK 506 prevented rejection during administration of the drug and for up to 2.5 months thereafter, but chronic rejection was invariably demonstrated in surviving hosts on cessation of the drug. Furthermore, histologic sections of donor intestine revealed that rejection was more severe in the control and CyA-treated rats than in the FK 506-treated animals. No histologic evidence of drug toxicity was noted, and weight gain occurred in all FK 506-treated groups.

CONCLUSIONS

Equivalent doses of FK 506 may prevent acute rejection of the small intestine allograft and may abrogate fatal GVHD, despite a significant major histocompatibility complex (MHC)/non-MHC mismatch. FK 506 may represent a major breakthrough in immunosuppressive therapy, although further testing is required to enhance its efficacy and safety.

REFERENCES

1. Todo S, Demetris AJ, Ueda Y, et al: *Transplant Proc* 19:57, 1987
2. Todo S, Podesta L, Chapchap P, et al: *Transplant Proc* 19:64, 1987
3. Murase N, Todo S, Lee PH, et al: *Transplant Proc* 19:71, 1987
4. Kino T, Inamura N, Sakai F, et al: *Transplant Proc* 19:40, 1987
5. Oaks MK, Cramer DV: *Transplantation* 39:69, 1985
6. Fujiwara H, Grogan JB, Raju S, et al: *Transplantation* 44:469, 1987
7. Diffo T, Maki T, Balogh K, et al: *Transplantation* 47:7, 1989
8. Grant D, Zhong R, Gunn H: *Transplant Proc* 20:1279, 1988
9. Hatcher PA, Deaton DH, Bollinger RR: *Transplantation* 43:478, 1987
10. Grant P, Duff J, Zhong R, et al: *Transplantation* 45:279, 1988
11. Taylor RMR, Watson JW, Walker FC, et al: *Br J Surg* 53:134, 1966
12. Kimura K, LaRosa G, Money SR, et al: *J Surg Res* 45:349, 1988
13. Lee KKW, Schraut WH: *Am J Surg* 151:55, 1986
14. Deeg HJ, Storb R, Weiden PL, et al: *Transplantation* 34:30, 1982
15. Powles RL, Clink HM, Spence D, et al: *Lancet* 1:327, 1980