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Prolonged Small Bowel Graft Survival Using Photochemotherapy and Low-Dose FK 506

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WHILE immunosuppressive therapy for organ transplantation improved greatly, rejection remains a major obstacle to successful small bowel transplantation (SBTx).[1] Photochemotherapy (PCT), the combination of ultraviolet A (UVA) irradiation and the photosensitizing agent, 8-methoxypsoralen (8-MOP), has been reported to be effective in inhibiting in vitro and in vivo responses to alloantigens.[2] When added to conventional immunosuppressive therapy, PCT has been shown to reduce the number of acute or recurrent rejection episodes in heart transplant patients.[3] This study investigated the efficacy of PCT in preventing allograft rejection after SBTx.

MATERIALS AND METHODS

Inbred male ACI ($RT1^a$) and LEW ($RT1^l$) rats weighing 200 to 300 g were used as donors and recipients, respectively. Orthotopic SBT with portocaval drainage was performed as previously described.[4] The recipients were divided into five groups: group 1 (n = 6) were untreated controls; group 2 (n = 6) received 100×10^6 PCT-treated splenocytes on day 3; group 3 (n = 17) received low-dose intramuscular (IM) FK 506 (0.5 mg/kg/d) for 2 postoperative weeks; group 4 (n = 13) received 100×10^6 PCT-untreated splenocytes on day 3 plus the 2-week course of low-dose FK 506; group 5 (n = 24) received 100×10^6 PCT-treated splenocytes on day 3 and the 2-week course of low-dose FK 506. Splenocytes transfused into the recipients in groups 2, 4, and 5 were obtained by killing other low-dose FK 506-treated LEW recipients of ACI small bowel grafts 3 days after transplantation. Splenocytes in groups 2 and 5 were treated by 8-MOP (100 ng/mL) for 20 minutes and exposed to UVA (1 J/cm^2, Therakos, Inc, West Chester, Pa).

RESULTS

Untreated recipients (group 1) died in 7 days (Fig 1). Infusion of PCT-treated splenocytes into SBTx recipients was not effective by itself, with a median survival of 8 days (group 2). Low-dose FK 506 treatment slightly improved graft survival to 17 days without splenocyte infusion (group 3; $P < .05$ vs group 1, Mann-Whitney U test) and 15 days with PCT-untreated splenocytes (group 4; $P < .01$). Small bowel graft survival was significantly improved to 86 days in group 5, when recipients were treated with low-dose FK 506 and PCT-treated splenocytes ($P < .005$). Seven of 24

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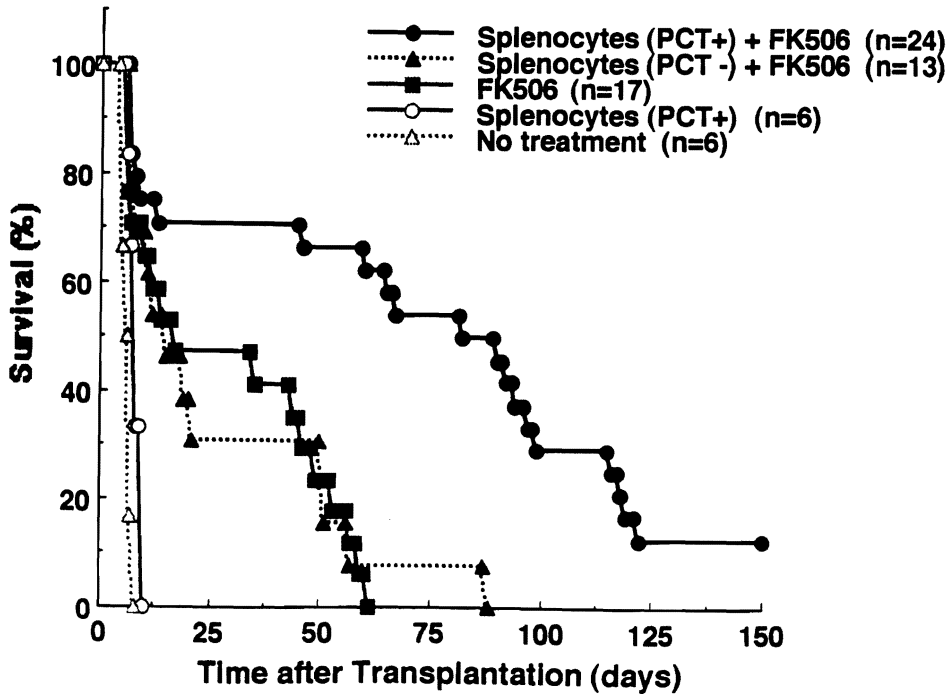

Fig 1. Survival of LEW recipients after allogeneic SBT (ACI-LEW).

animals in this group survived for more than 100 days. Histopathologic examination of these long-surviving small bowel grafts revealed chronic rejection.

DISCUSSION

This study shows that the combination of PCT with a subtherapeutic dose of FK 506 is effective in prolonging graft survival after SBTx. PCT has been successfully used for the treatment of autoimmune diseases and cutaneous T-cell lymphoma. However, application of this treatment in the field of transplantation is still preliminary.

The mechanism involved in this treatment is not clearly defined. The splenocytes we used for PCT treatment contained 2.7 ± 0.3% donor phenotype cells with a slightly lower CD4/CD8 ratio (1.8), compared to LEW-LEW isograft recipients (2.2). These splenocytes proliferated strongly in mixed lymphocyte reaction (MLR) to donor and third-party (PVG) lymphocytes and showed vigorous spontaneous proliferation in medium. These preliminary observations may suggest that activated allogeneic cells play an important role in PCT treatment of allograft recipients. Further studies to clarify the mechanism of this treatment are needed.

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