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Prolonged Survival of Islet Allografts Following Combined Therapy With Tacrolimus and Leflunomide

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DE NOVO diabetes mellitus is encountered in approximately 10% of patients treated with either Tacrolimus (FK506) or cyclosporin (CSA) within the first year posttransplantation.[1,2] This outcome is largely attributed to the direct inhibitory effects of these primary immunosuppressants on pancreatic islet cell function and on their ability to release insulin. While this altered glucoregulatory function can be reversed in the majority of patients by dose reduction, it nevertheless has an adverse influence on long-term patient and graft survival. The latter finding has fomented interest in the discovery of novel immunosuppressive agents, which in addition to preventing rejection, would also be innocuous to β cells, thus allowing widespread clinical use of islet cell transplantation (Tx) for the treatment of insulin-dependent type I diabetes mellitus (IDDM). Leflunomide (LEF) is a powerful immunosuppressive agent, which when used in rats, prevented kidney and skin allograft rejection.[3] Interestingly, when used in combination with subtherapeutic doses of CyA, it also enhanced islet allograft survival in preclinical models of diabetes.[4] However, the efficacy of LEF used in combination with subtherapeutic, nondiabetogenic doses of FK506 to prevent islet cell rejection, has as yet not been ascertained; this study was therefore designed to address this latter issue.

MATERIALS AND METHODS

Animals and Islet Cell Transplantation

Male MHC-disparate ACI ($RT1^a$) and LEW ($RT1^l$) rats were used as donors and recipients respectively of islet cell Tx. Recipients were rendered hyperglycemic by streptozotocin administration (60 mg/kg; IV; day −4) followed by implantation of isolated islets (approximately 1.3×10^3 per animal) under the left kidney capsule; their blood glucose levels and body weight were serially measured thereafter. Based on the regimen used, the animals were divided into nine groups (Table 1).

Table 1. Graft Survival Following Islet Cell Transplantation Across ACI → LEW Rat Strain Combination

Groups[1]	Treatment (mg/kg/d)[2] LEF[3] (gavage)	Treatment (mg/kg/d)[2] FK506 (IM)	Graft Survival (days) (mean ± SD)
I	—	—	9 ± 1
II	0.2	—	19 ± 2
III	0.5	—	21 ± 4
IV	—	5	30 ± 3
V	—	10	30 ± 2
VI	0.2	5	41 ± 3
VII	0.2	10	39 ± 6
VIII	0.5	5	39 ± 3
IX	0.5	10	40 ± 5

[1] n = 4/group.
[2] Administered daily from day 0–14 post-Tx.
[3] Obtained as a generous gift from CINKATE Corporation, Oak Park, IL.

RESULTS AND DISCUSSION

Untreated recipients (Group I) rejected their grafts within 10 days post-Tx, whereas; modest prolongation was achieved in animals treated with two different doses of LEF alone (Table 1; Groups II and III). Interestingly, when used alone, subtherapeutic doses of FK506 also resulted in moderate prolongation of islet allograft survival with maintenance of euglycemia for up to 30 days post-Tx (Table 1). However, islet allograft survival was further augmented when both LEF and FK506 were administered simultaneously (Table 1; Groups VI to IX). It is noteworthy that allograft survival was comparable in animals treated contemporaneously with either low or high doses of LEF (Table 1; Groups VI and VII) and FK506 (Table 1; Groups VIII and IX), suggesting that this drug combination could be used at relatively lower doses to achieve the desired outcome. In addition to being relatively innocuous to transplanted islets, LEF and FK506, when used either alone or in combination, had little or no effect on recipient's body weight, which continued to increase during the course of this analysis. From these observations, we conclude that LEF, when used alone, prolongs islet allograft survival, an effect further potentiated by its combined use with subtherapeutic nondiabetogenic doses of FK506. It is therefore, rational to suggest that this drug combination could

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serve as an ideal immunosuppressive regimen for successful clinical islet cell Tx.

REFERENCES

1. Sumrani NB, Delaney V, Ding Z, et al: Transplantation 51:343, 1991

2. Fung JJ, Alessiani M, Abu-Elmagd K, et al: Transplant Proc 23:3105, 1991

3. Kuchle CA, Thoenes GH, Langer KH, et al: Transplant Proc 23:1083, 1991

4. Guo Z, Chong AS, Shen J, et al: Transplantation 63:716, 1997