1279

The Effect of Cyclosporine, Rapamycin and FK 506 the Survival Following Allogeneic Bone Marrow Transplantation

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WE have previously reported that treatment with FK 506 and cyclosporine (CyA) are effective in reversing established acute graft-versus-host disease (GVHD) in an allogeneic rat model.[1] In clinical bone marrow transplantation, however, recovery from GVHD has not necessarily been associated with prolongation of survival.[2,3] Therefore, we were interested in comparing the immunosuppressive agents, CyA, rapamycin (RPM), and FK 506, in respect to survival after allogeneic bone marrow and spleen cell transplantation (BMSPTX).

MATERIALS AND METHODS

Induction of Acute GVHD

A total of 60 × 10^6 bone marrow and 30 × 10^6 spleen cells from ACI donors were infused IV 2 hours after Lewis (LEW) recipients had been exposed to 1000 rad total body irradiation (TBI). Animals were assessed for clinical signs of GVHD on a daily basis. GVHD was diagnosed when at least three of the following signs were present: erythematous ear, hyperkeratosis of the footpad, dermatitis, weight loss, unkempt appearance, and diarrhea.

Immunosuppression

CyA was obtained from Sandoz Pharmaceuticals (Hanover, NJ) and dissolved in intralipid. Rapamycin was a gift from Wyeth-Ayerst Research Laboratories (Princeton, NJ) and prepared fresh daily by suspension in 0.2% carboxymethyl-cellulose and thoroughly homogenized before administration. FK 506, provided by Fujisawa Pharmaceutical Co (Osaka, Japan), was diluted (with carrier solvent HCO-60 and D-mannitol) in normal saline.

Survival was calculated by the life-table method. Comparisons of survival were analyzed using the Wilcoxon signed rank test with unequal variances. Two-tailed P values <.05 were considered statistically significant.

Study Design

Animals suffering from GVHD were treated with CyA, RAP, or FK 506 IM on days 12 to 25 post-BMSPTX. Group 1 was used as irradiation control and received 1000 rad TBI without bone marrow rescue. Group 2 received BMSPTX without immunosuppressive therapy. The remaining groups received BMSPTX and treatment on days 12 to 25 postreconstitution with CyA at 25/mg/kg per day (group 3), RAP at 1 mg/kg per day (group 4), and FK 506 at 1 mg/kg per day (group 5). The follow-up was 60 days post-BMSPTX. Each group consisted of 7 to 10 animals.

RESULTS

Recovery From GVHD

Acute GVHD was induced in recipients of allogeneic BMSPTX at a median day of 11 in the range of days 8 to 12. CyA, given at 25 mg/kg per day and days 12 to 25 (group 3), was able to reverse GVHD in 55% of treated animals. The remaining rats failed to recover from GVHD and died during or after therapy. All animals (100%) receiving FK 506 at 1 mg/kg per day on days 12 to 25 were rescued. In contrast, treatment with RPM was ineffective in reversing GVHD. All animals died displaying signs of GVHD.

Survival From GVHD

Survival during and after immunosuppressive therapy is presented in Table 1. Irradiation controls receiving only TBI died within 16 days. Survival of RPM-treated rats (MST = 21.6 ± 5.0) was similar to that of untreated controls (MST = 22.1 ± 4.0). Survival of CyA-treated animals (MST = 29.2 ± 12.4) was prolonged compared to untreated controls (not statistically significant, $P > .15$). Only the FK 506-treated group (MST = 56.3 ± 4.1)

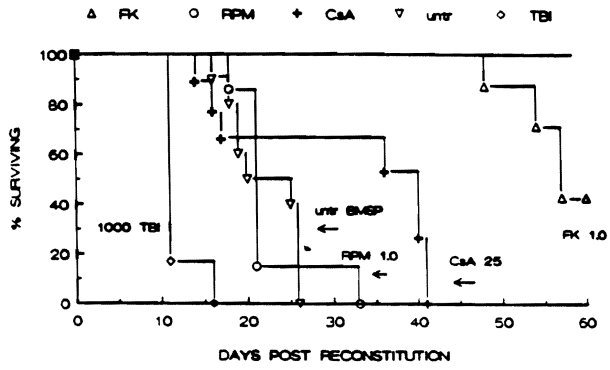

Fig 1. Survival from acute GVHD of allogeneic BMSP recipients treated with CyA, RPM, or FK 506. Animals received either CyA at 25 mg/kg per day (CyA 25), RPM at 1.0 mg/kg per day (RPM 1.0), or FK 506 at 1.0 mg/kg per day (FK 1.0) on days 12 to 25 post-BMSPTX. Included are untreated recipients of BMSP (untr BM) and irradiation controls (1000 TBI). Data represents survival for 7 to 10 animals in each group.

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showed significant prolongation of survival when compared to untreated controls ($P < .01$).

DISCUSSION

CyA and FK 506 have been shown to be effective in reversing acute GVHD in 55% and 100%, respectively, of treated rats following allogeneic BMSPTX. In CyA-treated rats, death during therapy was associated with the presence of clinical signs of GVHD. In contrast, RAP was ineffective in reversing GVHD and rats died maintaining GVHD. Recurrence of GVHD after cessation of immunosuppressive therapy was responsible for subsequent death of both CyA and FK 506-treated animals.

Both CyA and FK 506 have been reported to interfere with the activation of T cells. Both drugs suppress the release of IL-2 and the expression of the IL-receptor.[4,5] RPM has little or no effect on these events, but inhibits the response to IL-2.[6] Why CyA and, in particular, FK 506 and not RPM, are effective in this model long after immunologic activation starts, remains speculative and needs further investigation. Nevertheless, a similar effect of FK 506 has been shown in human organ transplantation where the drug was able to rescue patients experiencing rejection episodes of liver grafts despite prior treatment with CyA, OKT3, and corticosteroids.[7]

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