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# Donor Bone Marrow Infusion in Liver Recipients: Effect on the Occurrence of Acute Cellular Rejection

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NUMEROUS recent studies have suggested that induction of donor-specific tolerance (DST) is an active process that requires the engagement of donor antigen-presenting cells with the recipient's alloreactive T cells.[1] Under appropriate conditions, this interaction results in antigen-dependent, activation-induced apoptosis of reactive T cells with their eventual deletion. Thus, the basic premise of this argument is that immune activation is a required event in the progressive induction of DST and that episodes of acute cellular rejection (ACR) are essentially a corollary of this process. Since 1992, our center has been involved in a clinical trial mandating adjuvant donor bone marrow (BM) infusion to induce DST in orthotopic liver transplant (OLT) recipients.[2] This study was designed to ascertain the incidence and the severity of ACR in BM-augmented and control OLT recipients and to correlate these findings with patient and graft survival in these two cohorts.

## PATIENTS AND METHODS

Since the initiation of this study, 77 adult unconditioned primary OLT recipients have received a single or multiple perioperative infusions of unmodified donor BM cells (3 to 6 $\times$ $10^8$/kg). In addition, for purposes of this analysis, patients who consented ($n$ = 50) and those receiving primary OLT prior to and immediately after the accrued study subjects ($n$ = 154) without BM infusion served as controls. Donor gender and age were additional parameters that were used to match the "artificial" controls to patients in the study cohort. The number of patients with evidence of biopsy-proven rejection as well as the total number of rejection episodes were analyzed. To estimate the occurrence of biopsy-proven rejection, person–time analysis with ACR incidence rate (IR) and incidence rate ratio (IRR) was employed; an approximate Poisson method was used to build a 95% confidence interval (CI) for IRR analysis. A one-way analysis of variance (ANOVA) model was used to compare the IR means estimated at various timepoints post-transplantation between groups. For determination of time between transplantation and the first episode of ACR, the product-limit estimator was used. $P < .05$ or, alternatively, the 95% CI, which did not include unity within the bounds, were considered statistically significant.

## RESULTS AND DISCUSSION

No significant difference ($P > .56$) was observed in the IR in patients in the study (.239) and the two control (.206) cohorts during the course of their follow-up; the time to first ACR was also comparable. Compared with controls, the IRR with the 95% CI in study patients was 1.16 [0.83, 1.82]. There was, however, a tendency for a slightly higher incidence of rejection in BM-augmented patients during the first 24 months posttransplantation—a trend that reversed during the subsequent period of follow-up. At 6 years posttransplantation, patient and graft survival was 81% and 74%, and 77% and 70% in the control patients, respectively.

Taken together these data suggest that, despite a slightly higher incidence of ACR in BM-infused liver recipients during the first 2 years post-Tx, patient and graft survivals were superior in the study patients as compared with controls. These findings are similar to those in rodents suggesting that "active" Ag presentation may be a more robust mechanism for eventual donor-specific immune modulation.

## REFERENCES

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