1386

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LIVER TRANSPLANTATION IN POSITIVE CYTOTOXIC CROSSMATCH CASES USING FK506, HIGH-DOSE STEROIDS, AND PROSTAGLANDIN E_1[1]

Although the liver is resistant to antibody-mediated rejection (*1*), a significant adverse effect has been reported of its transplantation into recipients with preformed cytotoxic antibodies (*2*). We report here a strategy that appears to convert the prognosis in such potentially disadvantaged patients to essentially the same if not better than that in conventionally treated crossmatch-negative recipients.

The crossmatch status was determined with recipient sera treated with dithiothreitol (DTT) (*3*). Four cohorts of adult liver recipients were studied. In all, intravenous FK506 was started with doses of 0.075 to 0.15 mg/kg/day, and converted to oral dosing after resumption of diet. Treatment was guided by plasma FK506 levels (target approximately 1 ng/ml), toxicity (primarily renal), the clinical status of the patient, and the quality of postoperative liver function (*4*). The 4 study groups (Table 1) differed in the cytotoxic crossmatch state (negative in group 1 only), the use of prostaglandin E_1 (group 4 only), and the prophylactic use of methylprednisolone (MP). Low-dose MP was with 20 mg/day starting on the day of transplantation (most of group 1 and all of group 2). High-dose MP was with 1 g i.v. during operation, followed by a "burst" with 200 mg the first day and daily decreases of 40 mg until 20 mg/day was reached on the 6th day if the course was uneventful (groups 3 and 4). In group 4, i.v. PGE_1 (Prostin VR) was started after completion of the operation with 0.2 μg/kg/hr and gradually increased to 0.6 μg/kg/hr if tolerated without cardiovascular instability. One of the 14 patients in group 4 had transient hypotension. There were no other side effects of PGE_1, which was stopped without weaning when the patients resumed diet after 5–7 days.

The crossmatch positive cases in groups 2–4 were consecutive, with no omissions. The incidences of hepatic malignancy, high UNOS urgency scores (50–78% III or IV), and cytotoxic titers >1:8 were similar in the cytotoxic groups 2–4. Females were disproportionately represented in all of the crossmatch-positive groups compared with crossmatch-negative controls. In the crossmatch-positive cases, the outcome was remarkably different according to treatment (Table 1). With high-dose steroid therapy (group 3), the unacceptably high early and delayed graft loss seen with low-dose steroid therapy (group 2) was reduced by two-thirds. Graft loss was reduced further if PGE_1 was added to the high-dose steroid regimen (group 4). The only death in the 14 patients of group 4 was caused by a biliary leak and subhepatic infection in a patient whose native gall bladder had empyema. The favorable course of the group 4 recipients relative even to group 3 and especially group 2 patients was reflected by an improvement in the perioperative renal function (Fig. 1), and superior postoperative liver function (Fig. 2).

The superior renal function in the liver recipients of group 4 was noteworthy. It is possible the PGE_1 specifically protects the kidneys from FK506 nephrotoxicity by a mechanism similar to that described by Makowka et al. (*5*) for cyclosporine. However, protection of the liver graft from antibody-mediated rejection and consequent avoidance of prerenal complications may have been a significant or even more important factor.

The pathogenesis of hyperacute rejection of kidney grafts,

TABLE 1. T lymphocytotoxic crossmatch state

Group	1 (n=216)	2 (n=28)	3 (n=12)	4 (n=14)
Crossmatch	Negative	Positive	Positive	Positive
Methyl prednisolone	Variable	Low	High	High
PGE_1	No	No	No	Yes
Hepatic malignancy	7.4%	3.6%	7.1%	8.3%
Male/female	130/86	12/16	0/12	3/11
High-titer (>1:8)	—	14	9	9
Survival (6 months)[a]				
Patient	90.5%	71.4%[b]	92.3%	92.9%
Graft	84.8%	60.7%[c]	83.3%	92.9%
Median follow-up[d]	454[d]	446[d]	320[d]	240[d]

[a] Actual survival.
[b] Group 1 vs. 2, P=0.0006.
[c] Group 2 vs. 3, P=0.125; group 2 vs. 4, P=0.03.
[d] Follow-up of 6 to 25 months.

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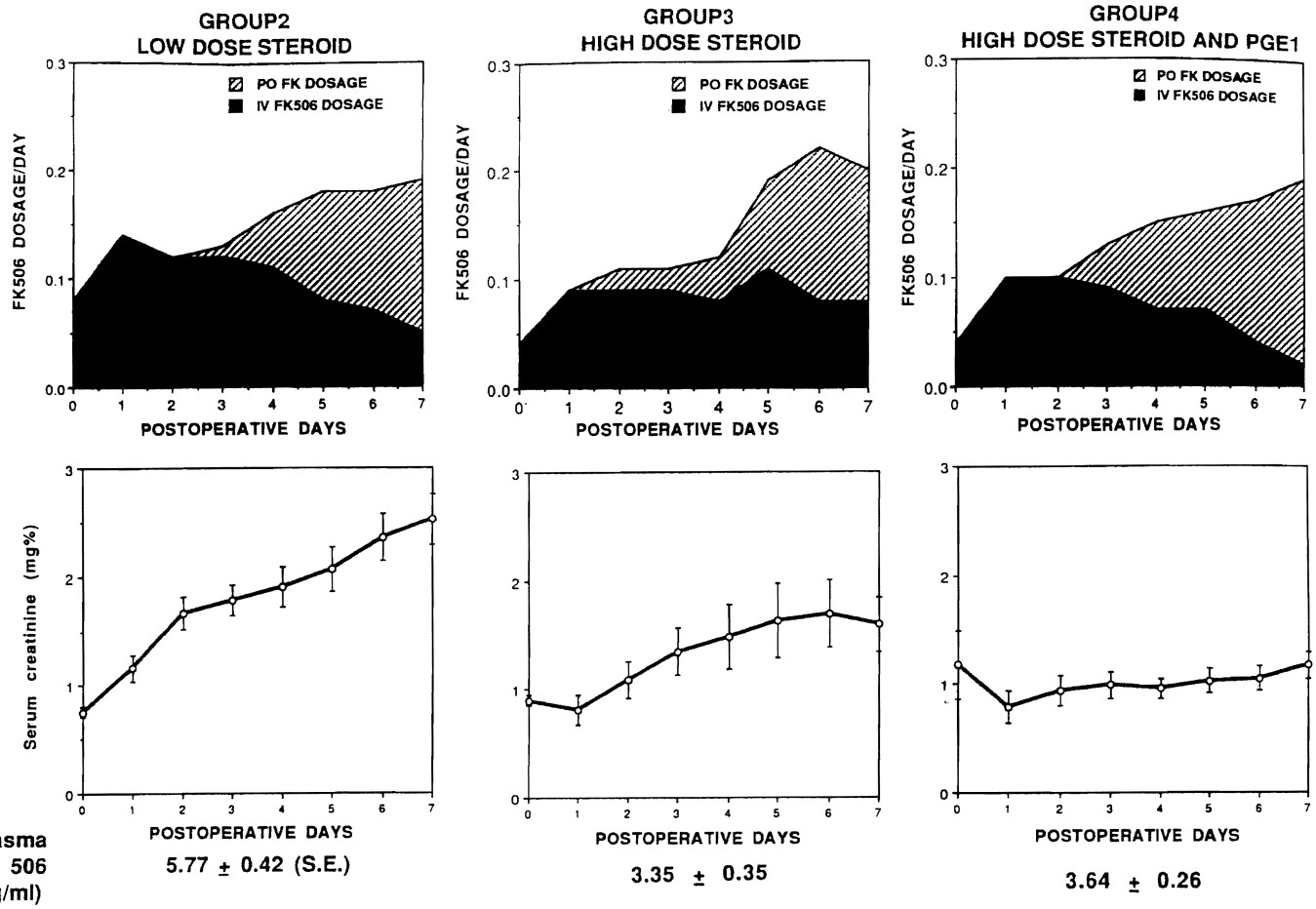

FIGURE 1. First-week FK506 doses and plasma concentrations and serum creatinine (Cr) in crossmatch-positive liver recipients (groups 2, 3, 4). (Cr)—group 2 vs. 3 $P<0.0001$, 2 vs. 4 $P<0.0001$, 3 vs. 4 = P = 0.007. FK506 dose—2 vs. 3 $P<0.0001$, 2 vs. 4 $P<0.0004$, 3 vs. 4 = P = 0.2. The average plasma FK506 value in group 2 was significantly higher than in groups 3 and 4 ($P = 0.0004$). Wilcoxon rank-sum test.

and the much slower manifestations of antibody-mediated rejection seen in liver grafts are not fully understood (*6*). Whatever the mechanisms, it has been known since the earliest work of Dempster (*7*) that intense vasoconstriction occurs of the graft microvasculature (*8*). PGE_1 treatment added to FK506 and high doses of steroids could have ameliorated this consequence, aside from its inherent immunosuppressive (*9*) and cytoprotective (*10*) qualities. Amelioration by PGE_1 of humoral rejection has not been reported clinically, but there have been clues of its potential value in xenograft transplant models that have heterospecific antibody barriers, including cat-to-dog (*11*), hamster-to-rat (*12*), and pig-to-dog (*13*).

High-dose prednisone in conjunction with FK506 but without PGE_1 also was effective. The steroid mitigation of humoral rejection presumably was by different pathways although both glucocorticoids and PGE suppress cytokines (*14*, *15*). Accurate delineation of these drug actions and interactions will be of the greatest interest in providing clues for other therapeutic improvements.

At a practical level, the experience reported herein indicates not only the feasibility but also the surprising ease with which the liver can be transplanted to sensitized recipients. If optimum therapy is given, a policy of excluding patients with widely reacting cytotoxic antibodies from candidacy for liver transplantation would seem unwarranted. The results in the high-dose steroid–PGE_1 group 4 were at least as good as in the cases with negative crossmatches. Whether all liver transplantations, including those with crossmatch-negative donors should be given this treatment deserves consideration. PGE_1 already has been used in this way in cyclosporine-based drug cocktails for crossmatch-negative kidney transplantation (*16*).

There were no obvious artifacts that would undermine these conclusions, such as the use in later cases of a different titer cutoff for a positive-crossmatch reading. About the same percentage of titers greater than 1:8 were in groups 2–4, but the highest positive titer was not measured systematically at the time of the case accrual. In 6 subsequent patients who were given the optimal recommended treatment and who had titers equal to or greater than 1:256, only 1 had a humoral rejection. This was a female patient with a titer of 1:1024 who required retransplantation 2 days after primary graft nonfunction, using a crossmatch-positive donor liver (titer 1:2) on the second occasion. She is well 4 months later.

The influence of titers, different sensitization schedules, and the nature of the antibody upon humoral rejection of the liver in rats has been described elsewhere.[4] These experimental studies, combined with our clinical experience herein reported,

[4] Furuya T, Murase N, Nakamura K, *et al.* Preformed lymphocytotoxic antibodies: the effects of Ig class, titer and specificity on liver versus heart allografts. (Submitted for publication.)

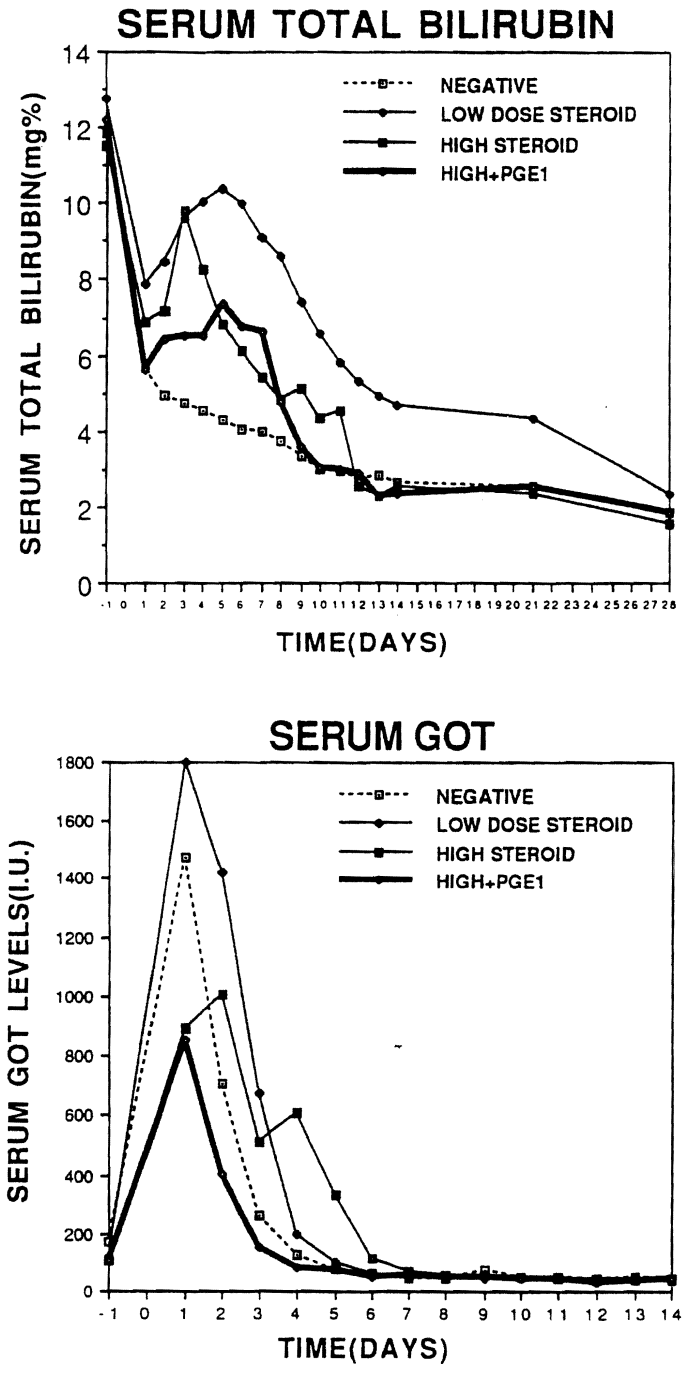

FIGURE 2. Serum total bilirubin (1st month) and serum GOT levels (2 weeks) in crossmatch-positive liver recipients. Bilirubin in first week—group 2 vs. 3 $P = 0.007$, 2 vs. 4 $P<0.01$, 3 vs. 4 $P=0.36$. SGOT in first week—group 2 vs. 3 $P=0.36$, 2 vs. 4 $P<0.02$, 3 vs. 4 $P=0.38$. Wilcoxon rank-sum test.

have led to our present policy of not delaying urgently needed liver transplantation in order to search for a more appropriately crossmatched donor.

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