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Adjuvant treatment with ursodeoxycholic acid reduces acute rejection after liver transplantation

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Abstract. Acute rejection, occurring with a reported frequency of 50–70%, is still a dominating problem after liver transplantation. Medication with ursodeoxycholic acid (UDCA) has beneficial effects in different cholestatic conditions and has also been shown to reduce HLA class I antigen expression on hepatocytes in patients with PBC. Since August 1989 we have consecutively treated all patients with primary graft function with UDCA ($n = 41$). Patients transplanted in the first half of 1989 served as a control group ($n = 8$). All patients in this study were given sequential quadruple drug immunosuppression. The treatment group were given oral UDCA 10 mg/kg per day. During the first postoperative month, 17% of the UDCA-treated patients had an episode of acute rejection compared with 75% of the control patients ($P < 0.01$). Liver biochemistry tests 1 month postoperatively were significantly better in patients treated with UDCA. The results suggest that adjuvant treatment with UDCA reduces acute liver graft rejection.

Key words: Ursodeoxycholic acid – Liver – Liver transplantation – Rejection – Immunosuppression

Acute rejection is reported to occur in 50–70% of patients receiving liver transplants. Although this is no longer the most frequent cause of death, acute rejection is still a major problem in liver transplant surgery [3, 9, 10, 21]. Ursodeoxycholic acid (UDCA) has been used in the medical treatment of cholesterol gallstone disease, and beneficial effects of treatment with UDCA in different cholestatic liver diseases such as primary biliary cirrhosis, sclerosing cholangitis, chronic hepatitis and biliary atresia have recently been reported [6, 12, 15–18, 22]. The rationale for using UDCA treatment after liver transplantation was to substitute for more toxic bile acids and alter the bile acid pool to a more atoxic composition, as liver transplantation can be associated with problems due to a number of reasons such as graft dysfunction and drug toxicity.

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Materials and methods

Patients

All patients with primary graft function transplanted between August 1989 and June 1991 ($n = 41$) were treated with ursodeoxycholic acid. The mean age was 47 ± 2 years and the distribution of preoperative diagnosis is listed in Table 1. Patients transplanted during the first half of 1989 ($n = 8$) served as a control group. The mean age of the control group was 42 ± 2 years. During this period three patients were lost during or immediately after surgery. These patients did not receive bile acid treatment and are not included in this report.

Operative procedure

All donor livers were harvested in a similar manner using UW solution. No venovenous bypass was used. The median anhepatic time in the control group was 55 min (range 45–75 min) and in the UDCA group, 40 min (range 31–65 min). Perioperative blood loss was comparable, with a median transfusion of 10 units (400 ml) of blood (range 5–80 units) in the control group and a median of 9 units (range 1–41 units) in the UDCA group.

Immunosuppression

Four out of 41 (10%) of the UDCA-treated patients and one out of eight (13%) of the control patients had a positive T-cell cross-match. All patients received blood-group-compatible grafts, eight patients in the UDCA group (19%) received non-blood-group-identical grafts compared with two patients in the control group (25%). All patients received sequential quadruple drug immunosuppression with anti-thymocyte globulin (Mérieux), azathioprine (Imurel, Wellcome) and steroids. Cyclosporine (Sandimmun, Sandoz) was given orally only and was started when the renal function was stable, usually on the 5th to the 7th postoperative day.

UDCA treatment

UDCA treatment was started as soon as possible, usually on the first or second postoperative day and in all cases within the first 5 days. The patients received UDCA (URSOFALK, Falk Co, FRG) orally

Table 1. Preoperative diagnosis in the liver transplanted patients

Diagnosis	Control ($n=8$)	UDCA ($n=41$)
Advanced chronic liver disease	5	30
Metabolic liver disease		2
Tumour	2	4
Acute fulminant hepatic failure	1	5

at a dose of 10 mg/kg per day. In most cases UDCA was dissolved and given through the patients' nasogastric tube the first postoperative days.

The rejection diagnosis was based on the clinical course and biochemistry in combination with histopathological examination of biopsies in all cases given antirejection treatment.

Results

In the group treated with UDCA, seven patients had a least one episode of acute rejection (17%). In the control group, six out of eight patients (75%) had at least one rejection episode needing treatment during the first postoperative month. The rejection incidence was significantly lower in the UDCA-treated group ($P<0.01$; Fisher's exact test) (Fig. 1). Biochemistry 1 month after transplantation demonstrated significantly lower average values of aminotransferases and alkaline phosphatases ($P<0.05$, ANOVA) in patients treated with UDCA than in the control group (Table 2).

At the time of writing the observation time was a median of 12 months (range 4–24) in the treatment group and 24 months (range 3–30 months) in the control group.

In the control group one patient was lost after 9 months due to chronic graft dysfunction and one patient died after 3 months from graft rejection, CMV pneumonitis and fungal septicaemia. In the UDCA-treated group four patients were lost. One patient died after 1 year with infectious complications, one patient died after 5 months due to chronic rejection and one patient due to recurrent hepatocellular carcinoma. The fourth patient died following retransplantation for acute rejection. This patient was early in the series and UDCA treatment was not started until the 5th postoperative day and an acute rejection was diagnosed on the 6th postoperative day.

Discussion

In this study we report a reduced frequency of acute rejection in 41 consecutive liver transplant recipients treated with adjuvant UDCA compared with numbers given in

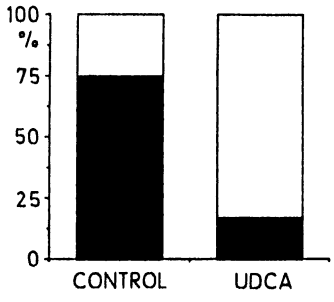

Fig. 1.

Table 2. Liver biochemistry 1 month following orthotopic liver transplantation

	AST (μkat/l)	ALT (μkat/l)	ALP (μkat/l)	Bilirubin (μmol/l)
Control ($n=8$)	1.3 ± 0.3	1.9 ± 0.4	12.7 ± 3.0	86 ± 34
UDCA ($n=41$)	0.7 ± 0.1**	0.9 ± 0.2*	6.1 ± 0.7**	40 ± 9

* $P<0.05$; ** $P<0.01$

AST, asparagine aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase

the literature and to a preceding group of eight liver transplant patients. The difference between our groups cannot be explained by improved surgical technique or by differences in immunosuppression protocol since these were not changed during 1989 or later.

UDCA was first discovered in the beginning of this century in bile from a polar bear. This bile acid normally appears in small amounts in the bile acid pool of man. UDCA was first synthesized in Japan in the 1950s and was there used for treatment of different cholestatic conditions, like chronic hepatitis [8]. This atoxic bile acid has also been used to dissolve cholesterol gallstones [14]. In recent years, reports of a beneficial effect of this bile acid on different cholestatic conditions have been frequent [6, 12, 15–18, 22]. UDCA has also been shown to have a direct protective effect on hepatocytes [5, 7]. The rationale for using UDCA after liver transplantation was to substitute for more toxic bile acids and alter the bile acid pool into a more atoxic composition. This would protect the hepatocytes from toxic effects of other bile acids in cases of cholestasis. It has previously been shown that with this treatment, UDCA becomes the dominant bile acid with a proportion of 40–60% [2, 13]. UDCA has also a high choleretic potency, which could be of importance especially during the first weeks postoperatively when bile acid treatment would initiate bile secretion [4, 20].

In a recent retrospective report, however, an Italian group did not see any effect on the rejection frequency following UDCA treatment, but they did not start treatment until the 5th to the 7th postoperative day and since acute rejection probably starts during the first postoperative week, it is important to start treatment on the first postoperative day [19]. This is further supported by treatment failure in one of our patients where treatment was started on the 5th postoperative day.

In a recent study Calmus et al. have shown that treatment with UDCA reduces HLA class I antigen expression on hepatocytes in patients with PBC [1]. Preliminary data from a German group also studying PBC patients confirm the immunomodulating capacity of this bile acid and they found a reduction of HLA class I/II antigen expression on bile duct cells [11]. The ability of this bile acid to alter this antigen expression in these patients may indicate that it also has the potency to alter antigen expression in liver-grafted patients. The reduced rejection frequency seen in the present series may be explained on these grounds. The findings warrant controlled clinical trials as well as studies to analyse the underlying mechanisms.

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