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LETTER TO THE EDITOR

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A trial of high-dose ursodeoxycholic acid therapy in a liver transplant recipient

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Sir: Long-term administration of ursodeoxycholic acid (UDCA) to patients with primary biliary cirrhosis (PBC) [9] and chronic active hepatitis [11] improves both clinical and biochemical parameters. Recently, suppressive effects of UDCA on the production of inflammatory cytokines [2, 12] and immunoglobulin [12], and aberrant expression of major histocompatibility complex (MHC) class I on hepatocytes [1] have been reported, suggesting that the beneficial effect of UDCA therapy might be mediated in part by an immune mechanism. We previously reported that UDCA at a dose of 10 mg/kg per day was safe and effective for normalizing serum liver enzymes in chronic hepatitis due to hepatitis C virus (HCV) in liver transplant recipients [6].

We recently tried high-dose (15–20 mg/kg per day) UDCA therapy in a liver transplant recipient. A 58-year-old man suffering from cryptogenic cirrhosis received a liver transplant in 1989 and his condition remained stable until 1991. HCV reinfection was revealed shortly afterwards. A liver biopsy performed in June 1993 revealed chronic hepatitis, type C, with low-grade activity. However, serum alkaline phosphatase (ALP) and γ-glutamyltranspeptidase (GGT) remained at consistently high levels (> 400 IU/l), and the serum alanine aminotransferase (ALT) level frequently fluctuated.

Since two cases of acute vanishing bile duct syndrome after interferon (IFN) therapy for recurrent hepatitis have been described [3], UDCA therapy (10 mg/kg per day, orally) was initiated in May 1994. One month later, the patient's serum ALP and ALT levels had normalized, but the serum GGT level still remained around 150 IU/l. Therefore, with informed consent, high-dose (15–20 mg/kg per day) UDCA therapy was attempted to decrease the GGT level. After this therapy, the serum GGT level decreased to around 80 IU/l (Fig. 1). His serum HCV RNA, determined by competitive reverse transcription-polymerase chain reaction (CRT-PCR) [5], showed as many as $10^{5.5}$–$10^{6.5}$ copies/50 µl, suggesting no virological elimination. During UDCA administration, the liver was exposed to a lower level of endogenous bile acids and to an increased concentration of UDCA. Poupon et al. [10] reported that serum total bile acid and UDCA concentrations in patients with PBC who had received UDCA (13–15 mg/kg per day) for 2 years were 31 µM and 16 µM (52 % of total bile acids) on average, whereas the corresponding values for a placebo group were 26 µM and 3 µM (12 % of total bile acids), respectively. In our patient, recently determined serum total bile acid and UDCA concentrations have been as high as 115 µM and 88 µM (77 % of total bile acids), respectively. Recently, Mohler et al. [7] also reported that UDCA (500 mg/day) had no impact on titers of HCV RNA, while a 3-month UDCA treatment significantly improved transaminases and cholestatic enzymes in chronic HCV patients. Thus, the major improvement in liver enzymes in patients with chronic HCV is not induced by a significant change in HCV replication. Taken together, the beneficial effect of UDCA in this patient might have been induced by other UDCA effects, such as choleresis or some immunosuppressive effect.

It is still controversial whether adjuvant UDCA administration can reduce the incidence of acute cellular rejection after liver transplantation [4, 8]. However, we feel that long-term administration of UDCA at a dose of 10–20 mg/kg per day might have some beneficial effect on liver allografts, which are always the target of the recipient's humoral and cellular immune response and recurrent viral hepatitis.

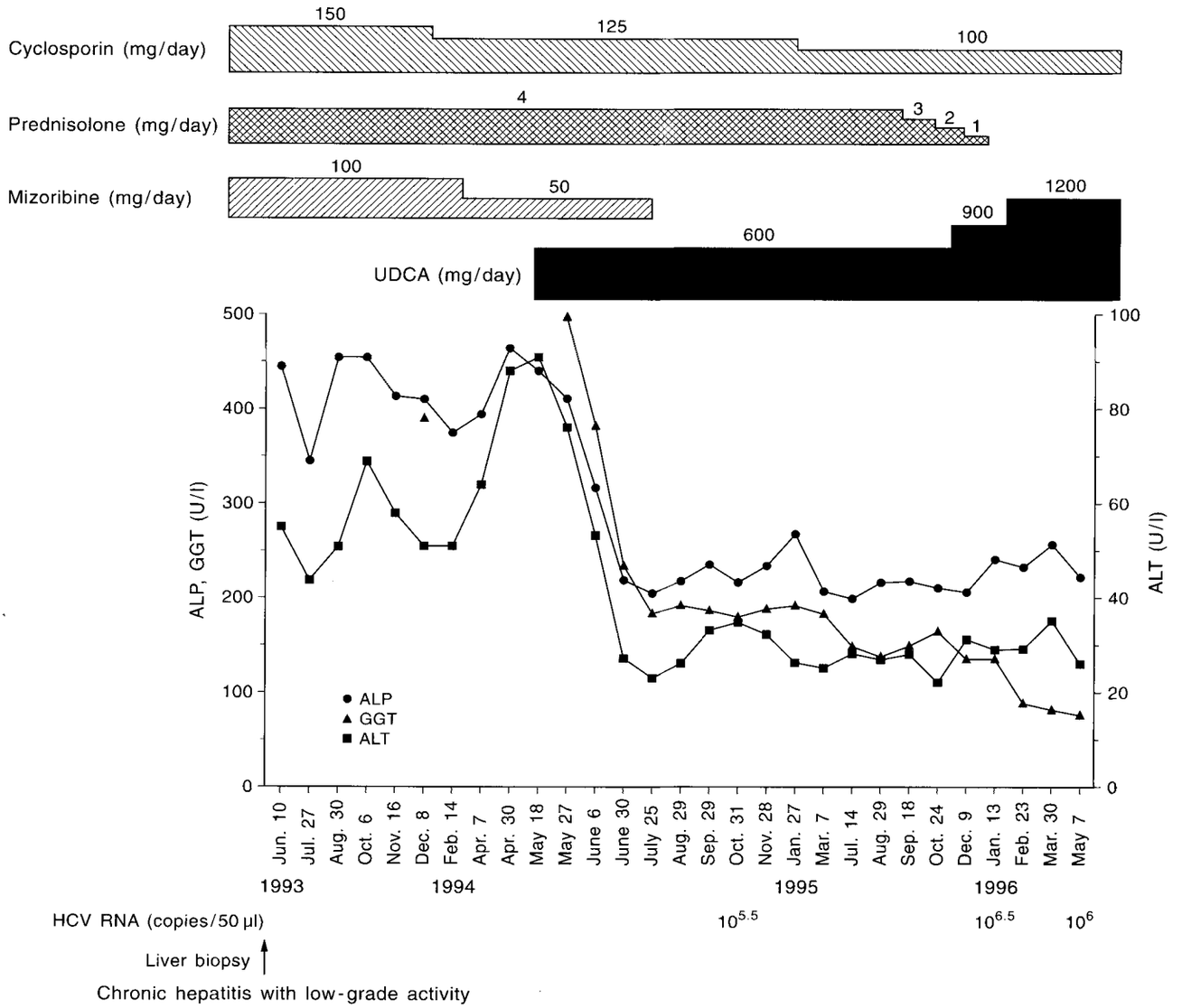

Fig. 1 Changes in laboratory data before and after the course of UDCA therapy

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