Does Ursodeoxycholic Acid Exert a Protective Effect on Liver Grafts in Orthotopic Liver Transplantation?

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Biliary lesions remain a frequent problem after liver transplantation. In addition to ischemic and immunologic factors, toxic bile acids may cause severe bile tract injury [1]. A high bile-acid/phospholipid ratio and intrhepatic bile retention has been suggested to contribute to hepatobiliary injury early after orthotopic liver transplantation (OLT) [2]. Indeed, during the past 40 years, hepatic retention of bile acids has been postulated to significantly contribute to progressive liver damage in cholestatic liver disease. In 1962, Blomquist and Holsti [3] were able to show that hydrophobic lithocholic acid and taurolithocholic acid induce cholestasis and subsequently cirrhosis. Hydrophobic, endogenous bile acids are potent hepatobiliary cytotoxins with detrimental effects ranging from the disruption of cellular membrane integrity to the induction of apoptosis. Hepatocellular cell death is induced mainly via ligand-independent death receptor pathways as the Fas receptor [4]. Indeed, bile acids trigger death receptor aggregation and activation, recruitment of adaptor proteins and consecutively the activation of caspases and cleavage of downstream apoptosis molecules, which induce mitochondrial dysfunction and, thus, cellular damage, resulting in cell death and cast formation.

The cytotoxicity of hydrophobic bile acids is naturally inhibited by formation of micelles with phospholipids and can be influenced by biliary enrichment with hydrophilic bile acids like ursodeoxycholic acid (UDCA).

UDCA renders bile acid composition more hydrophilic, shifts the bile-acid/phospholipid ratio towards less toxic effects and, thus, might protect against hepatobiliary injury by hydrophobic bile acids. UDCA is a constituent of human bile in a low concentration of 3% of total bile acids. It is the major bile acid of the bile of black bears and has been used for centuries in traditional Chinese medicine as a remedy for liver disease [5]. First reports of beneficial effects on serum liver tests in cholestatic disorders appeared in the 1980s in the Western literature, but similar observations were also made in Japan. In the meantime the potential molecular mechanisms of the cytoprotective effects of UDCA have become apparent. Obviously, UDCA does not only antagonize toxic bile acids at a biophysical level. A series of observations revealed that UDCA blocks cell death by interfering with apoptotic pathways and stimulating survival signals which, in turn, stimulate the activation of the intracellular MAPK pathway through the activation of the epidermal growth factor receptor [6]. Moreover, UDCA has been shown to modulate intracellular calcium levels and cellular trafficking [7].

These effects of UDCA have been recognized to be therapeutically useful and exploited for the treatment of a variety of chronic cholestatic liver diseases. It is the only drug approved by the United Stated Food and Drug Administration for the treatment of primary biliary cirrho-
sis [8]. In primary sclerosing cholangitis, UDCA has been shown to improve serum liver tests as well as bilirubin levels and is therefore also in use for the treatment of this disease. Furthermore, UDCA is used for intrahepatic cholestasis of pregnancy [9], liver affection in cystic fibrosis [10] and progressive familial intrahepatic cholestasis [11] as well as chronic graft-versus-host disease [12] and drug-induced cholestasis [13].

In the setting of OLT, bile secretion is not normalized early after transplantation. A relatively high bile-acid/phospholipid ratio at that early stage results in increased toxicity of bile. A high bile-acid/phospholipid ratio may cause injury of bile duct epithelium and may act synergistically with preservation injury in liver grafts.

Although UDCA is also used frequently in liver transplanted patients, a beneficial effect of UDCA administration after OLT has not been determined until now. In fact, there are presently no studies investigating and defining a benefit for this indication so far.

Wang et al. [14] address this issue, postulating that altered bile acid composition by UDCA early after OLT might protect against hepatobiliary injury due to hydrophobic bile acids. More than 100 patients after OLT received UDCA or placebo for 4 weeks after OLT. Liver enzymes as well as bile acids were analyzed and in addition, biliary complications as well as patient and graft survival were analyzed not only early postoperatively, but also up to 5 years after transplantation. As the authors state, overall outcome as determined by graft and patient survival after 5 years was not affected by UDCA treatment. However, not only liver enzymes but also the incidence of biliary sludge and casts was significantly diminished after administration of UDCA. This, in conclusion, may result not only in a gain in quality of live for the patient but also in a reduction of costs as less endoscopic interventions would be necessary. Another interesting point that has not yet been made by this study was the incidence of cholangitis with or without UDCA. One might speculate that bacterial and fungal infections of the bile ducts, which can take a severe course under immune suppression, might be considerably reduced if bile flow is improved and cast development is reduced.

In conclusion, the diligent study of Wang et al. [14] is a first step towards an evidence-based use of UDCA after OLT. Nevertheless, further studies are needed evaluating a longer administration of UDCA that might be even more beneficial as well as the effect of new substances coming up, as for example 24-norursodeoxycholic acid (norUDCA).

References