TAURINE-CONJUGATION CRITICALLY DETERMINES
THE THERAPEUTIC EFFECTIVENESS OF 24-NOR-
URSOODEXYCHOLIC ACID (NORUDCA) IN THE
TREATMENT OF SCLEROSING CHOLANGITIS IN MDR2
(ABC34) KNOCKOUT MICE


Background and Aims: We recently demonstrated that norUDCA reverses sclerosing cholangitis and biliary fibrosis in Mdr2−/− mice (Fickert et al., Gastroenterology 2006) and hypothesized that its therapeutic efficacy may be critically related to its relative resistance against taurine- and glycin-conjugation resulting in cholehepatic shunting and bicarbonate-rich hypercholerasis (Hofmann et al., Hepatology, 2005). Therefore we aimed to compare the therapeutic mechanisms and effects of norUDCA and its taurine conjugate (ThrUDCA) in the Mdr2−/− model for sclerosing cholangitis.

Methods: Adult Mdr2−/− mice were fed a diet containing norUDCA or ThrUDCA (0.5% w/w) for 4 weeks, controls received standard chow. Liver histopathology was assessed semi-quantitatively using a modified scoring system (Nieuwkierk et al., Gastroenterology, 1996) considering mitotic activity, apoptosis, portal inflammation, ductular proliferation and fibrosis. Effects on bile flow and composition, serum liver enzymes, markers of hepatic fibrosis (α-smooth muscle actin, αSMA) and ductular proliferation (cytokeratin 19, CK19) as well as mRNA expression of key detoxification enzymes and transport systems were compared.

Results: norUDCA resulted in stronger reductions of serum ALT and AP levels, hepatic αSMA expression and improvement of liver histology than ThrUDCA. Moreover, norUDCA reduced CK19 protein levels (30% of untreated controls, p < 0.05), while ThrUDCA only tended to reduce ductular proliferation. Likewise, norUDCA stimulated the expression of alternative basolateral bile acid efflux systems such as Mrp4 (3-fold, p < 0.05), while induction by ThrUDCA was less pronounced (1.5-fold, p < 0.05). A significant induction of mRNA expression of biotransformation enzymes (Cyp2b10, 10-fold, p < 0.05; Sult2a1, 31-fold versus ThrUDCA) was observed only with norUDCA. Both, norUDCA and ThrUDCA stimulated bile flow as well as biliary output of bicarbonate, bile acids and glutathione compared with untreated controls. However, biliary bicarbonate-output was 2-fold higher in norUDCA than ThrUDCA-treated animals (p < 0.05).

Conclusion: norUDCA is superior to ThrUDCA in the reduction of liver injury, periductal fibrosis and ductular proliferation in Mdr2−/− mice suggesting that its relative resistance to taurine-conjugation critically determines the therapeutic efficacy.