116 TAURINE-CONJUGATION CRITICALLY DETERMINES THE THERAPEUTIC EFFECTIVENESS OF 24-NOR-URSODEOXYCHOLIC ACID (NORUDCA) IN THE TREATMENT OF SCLEROSING CHOLANGITIS IN MDR2 (ABCB4) KNOCKOUT MICE

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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 hypercholeresis (Hofmann et al., Hepatology, 2005). Therefore we aimed to compare the therapeutic mechanisms and effects of norUDCA and its taurine conjugate (TnorUDCA) in the Mdr2$^{-/-}$ model for sclerosing cholangitis.

Methods: Adult Mdr2$^{-/-}$ mice were fed a diet containing norUDCA or TnorUDCA (0.5% wt/wt) 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 TnorUDCA. Moreover, norUDCA reduced CK19 protein levels (30% of untreated controls, $p < 0.05$), while TnorUDCA 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 TnorUDCA 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 TnorUDCA) was observed only with norUDCA. Both, norUDCA and TnorUDCA stimulated bile flow as well as biliary output of bicarbontate, bile acids and gluthatione compared with untreated controls. However, biliary bicarbonate-output was 2-fold higher in norUDCA than TnorUDCA-treated animals ($p < 0.05$).

Conclusion: norUDCA is superior to TnorUDCA 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.