Side-chain-modification Critically Determines the Physiologic and Therapeutic Properties of 24-norUrsodeoxycholic Acid in the Treatment of Sclerosing Cholangitis in Mdr2 (Abcb4) Knockout Mice and in Isolated Bile Duct Units

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Background I: *nor*UDCA reverses sclerosing cholangitis in *Mdr2*-/- mice

**Control**

**norUDCA**

bd, bile duct

pv, portal vein

*Fickert et al., Gastroenterology 2006*
Background II: Proposed mechanisms of norUDCA action in Mdr2⁻⁻ mice

- Anti-inflammatory
- Anti-fibrotic
- Anti-proliferative
- Increased Hydrophilicity
- Flushing Ducts

Fickert et al., Gastroenterology 2006
Side-chain-modified analogues of UDCA

Ursodeoxycholic acid (UDCA)

24-norUrsodeoxycholic acid (norUDCA)

23,24-bis-norUrsodeoxycholic acid (bis-norUDCA)

Tauro-norUrsodeoxycholic acid (T-norUDCA)
Bicarbonate-rich hypercholeresis due to cholehepatic shunting

Modified from Yoon et al., Gastroenterology 1986
Hypotheses

Taurine conjugation of norUDCA impairs the therapeutic efficacy in $Mdr2^{-/-}$ mice

Bis-norUDCA ameliorates sclerosing cholangitis in $Mdr2^{-/-}$ mice
To compare the therapeutic efficacy and mechanisms of norUDCA and its analogues in Mdr2-/- mice
Experimental approach

• 8-weeks-old $Mdr2^{-/-}$ mice:
  – Untreated: control
  – NorUDCA (0.5% w/w)
  – T-norUDCA (0.5% w/w)
  – Bis-norUDCA (0.5% w/w)

• Read out:
  – Serum liver enzymes
  – Liver histology
  – Bile flow, bile acids, bicarbonate and glutathione output
  – Bile acid composition

• Isolated bile duct units (IBDUs)
Differential effects of nor-bile acids on bile flow and composition

Differences in Bicarbonate-rich Hypercholeresis

Cholehepatic Shunting

norUDCA

T-norUDCA

bis-norUDCA

Mdr2^-/-

HCO3^-

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• *Nor*UDCA is unique for treatment of sclerosing cholangitis in *Mdr2-/-* mice

• Beneficial effects of *nor*UDCA should be followed clinically