

24-nor-Ursodeoxycholic Acid — Substance for curing Sclerosing Cholangitis and Cholestatic Liver Disease

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BACKGROUND

Current medical treatment for human primary sclerosing cholangitis (PSC), a chronic cholestatic liver disease representing an important indication for liver transplantation and cause of liver-related death, is of limited efficacy. Multidrug resistance gene 2 (*Mdr2/Abcb 4*) knockout mice (*Mdr2*^{-/-}) represent a well characterized model for sclerosing cholangitis. We aimed to test the therapeutic effects of 24-nor-ursodeoxycholic acid (norUDCA), a side chain-modified UDCA derivative undergoing cholehepatic shunting) in *Mdr2*^{-/-}.

METHODS

2-months-old *Mdr2*^{-/-} received standard chow (controls) or 0.5% norUDCA-supplemented diet or 0.5% UDCA-supplemented diet for 4 weeks. Effects on serum liver tests, liver histology, markers of inflammation and fibrosis, and bile acid transporters and detoxification enzymes were compared.

RESULTS

norUDCA significantly improved serum liver tests (ALT 165±23 vs. 405±187 IU in controls; p<0.05; AP 235±55 vs. 162±25; p<0.05) and liver histology, reduced hydroxyproline content (124±16 vs. 229±94 mg/g liver; p<0.05), infiltrating neutrophils (2±1 vs. 20±5/portal field; p<0.05) and proliferating Ki-67-positive hepatocytes (0.7±0.9 vs. 39±15/high power field; p<0.05), stimulated biliary bicarbonate excretion (99±14 vs. 61±8 nmol/g liver weight/min; p<0.05) and resulted in coordinated induction of sulfotransferase *Sult2a1* and bile acid sulfate efflux pump *Mrp4* together with urinary bile acid sulfate excretion. UDCA significantly increased ALT and AP levels, had no significant effects on hydroxyproline content and bicarbonate excretion, and weaker effects on biliary transporters and enzymes.

CONCLUSIONS

norUDCA cures sclerosing cholangitis in *Mdr2*^{-/-}. Its therapeutic mechanisms likely involve (i) flushing of injured bile ducts by bicarbonate-induced choleresis, (ii) induction of alternative detoxification and elimination routes for bile acids and (iii) antiinflammatory as well as (vi) antifibrotic properties.

SUMMARY

Nor-UDCA > reduces liver injury >reduces fibrosis >Reduces inflammation
> reduces TIMP1 expression >induces bicarbonate secretion > induces adaptive transporter and metabolic response
Nor-UDCA cures sclerosing cholangitis in *Mdr2*^{-/-}-mice
Nor-UDCA may represent a novel treatment option for PSC and PBC.

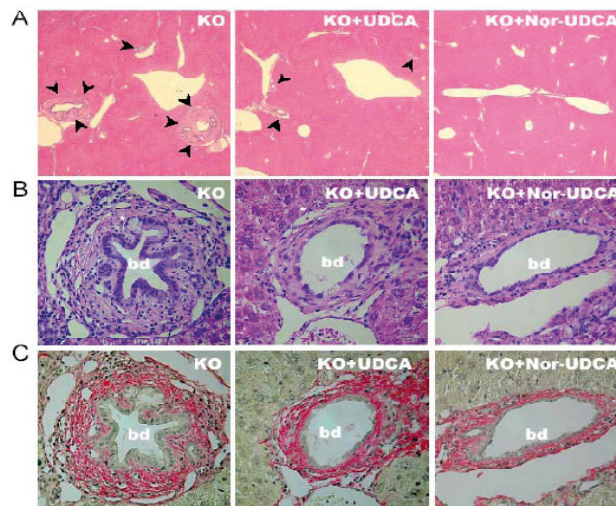


Figure 1: norUDCA cures sclerosing cholangitis in *Mdr2*^{-/-} mice. (A) Liver histology (H&E staining) in control diet-fed *Mdr2*^{-/-} mice (KO), UDCA-fed *Mdr2*^{-/-} mice (KO+UDCA), and norUDCA-fed *Mdr2*^{-/-} mice (KO+norUDCA) (Magnification x 10). Pronounced large bile duct disease in KO (arrow heads) which is significantly reduced in KO+UDCA (arrow heads) and absent in KO+norUDCA. (B) Sclerosing cholangitis in KO with periductal fibrosis, altered bile duct epithelial cells and mixed inflammatory infiltrate. This features are ameliorated in KO+ UDCA and absent in KO+norUDCA (Magnification x 40). (C) Sirius red staining showing significant fibrosis with periductal collagen fibers (red) in KO. Moderate reduction of fibrosis in KO+UDCA and even more pronounced reduction in KO+norUDCA (Magnification for b, c x 40); bd, bile duct.

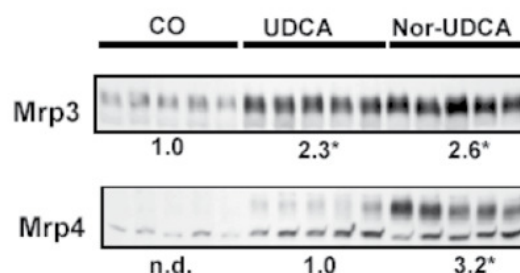


Figure 2: Suggested therapeutic mechanisms of norUDCA in *Mdr2*^{-/-} mice: norUDCA is taken up by hepatocytes and secreted into canalliculi and bile ducts where it is taken up by cholangiocytes leading to ductular bicarbonate secretion. norUDCA is secreted back into the peribiliary plexus and shunted back to the hepatocytes (cholehepatic shunting). NorUDCA induces expression of *Sult2a1* etc. and *Mrp3* and *Mrp4* which detoxifies bile salts and makes them amenable for renal elimination.

CONTACT

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COLLABORATION DETAILS

- Collaboration can be in the form of a license agreement or a technical research cooperation for clinical development of NorUDCA in USA.

POSSIBLE PARTNERS

- Pharma

DEVELOPMENT STATUS

- preclinical studies
- patent pending