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The effect of ursodeoxycholic acid in cystic cholangiopathies

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Article commented:

D'Agnolo HM, Kievit W, Takkenberg RB, Riaño I, Bujanda L, Neijenhuis MK, Brunenberg EJ, *et al*. Ursodeoxycholic acid in advanced polycystic liver disease: A phase 2 multicenter randomized controlled trial. *J Hepatol* 2016; 65: 601-7.

Comment:

We have read with great interest the publication from Hedwig D'Agnolo, *et al.*[1] on the effect of ursodeoxycholic acid (UDCA) in advanced polycystic liver disease due to autosomal-dominant polycystic kidney and/or liver diseases (ADPKD/ADPLD). The Dutch group of investigators reported interesting results on UDCA administration for 24 weeks. They reported a reduction of liver cyst volume growth but did not observe a reduction of total liver volume.

Polycystic liver diseases (PCLD) are genetic diseases characterized by bile duct dilation and/or the development of cysts derived from the bile duct epithelial cells (cholangiocytes). Hence, PCLD are considered as cholangiopathies, which are progressive disorders that lead to end-stage liver disease owing to a lack of effective medical therapies.[2]

UDCA has been used for long time to treat cholangiopathies, including primary biliary cholangitits, primary sclerosing cholangitis, cystic fibrosis-associated liver disease and PCLD with variable clinical, biochemical and histopathological outcomes. At this line, we would like to point out two observations: Firstly, both experimental and clinical studies suggest the beneficial effect of UDCA in PCLD. In an experimental study, Munoz-Garrido P, *et al*.[3] found that chronic UDCA treatment in a rodent polcystic kidney and liver disease model inhibits hepatic cystogenesis and fibrosis, and improves their motor behavior. As compared to wild-type animals, PCK rats show increased hepatic bile acid (BA) contents, similar hepatic *Cyp7a1* steady-state mRNA levels, and diminished BA concentrations in bile.

In humans, Iijima, *et al*.[4] reported in a series of PCLD cases where UDCA was effective for reducing serum liver enzyme activities and inhibiting the growth of liver cysts. The study from D'Agnolo, *et al.* is the first randomized clinical controlled trial that shows some beneficial effects of UDCA in patients with PCLD. In addition, a recent publication in patients with other cholangiopathies such as cystic fibrosis suggests that UDCA might prevent the progression of liver fibrosis as reflected by reduced liver stiffness in patients with mild cystic fibrosis-associated liver disease.[5]

The second comment is on the potential mechanisms of UDCA. It is known that this hydrophilic bile acid has several mechanisms of action, since it protects hepatocytes against bile acid-induced apoptosis, protects cholangiocytes against toxic cytokines produced in response to bile acids, and stimulates bile secretion.[6] Interestingly, in an experimental study in ATP-binding cassette transporter B4 (ABCB4/MDR2) deficient mice, a well characterized model for sclerosing cholangitis, Peter Fickert, *et al.* showed that norUDCA ameliorates sclerosing cholangitis within four weeks of administration and was superior to UDCA. Those investigators concluded that norUDCA is more effective than UDCA in this model and suggested that the mechanisms contributing to the therapeutic effects of norUDCA include (1) increased hydrophilicity of the bile acid pool, (2) induction of hydrophilic choleresis, (3) anti-inflammatory and anti-fibrotic mechanisms, and possibly (4) induced hepatocellular bile acid detoxification and export systems.

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How can we explain the results both from experimental and clinical studies? Obviously there are important differences. Probably one of them is the transport of UDCA conjugates with glycine and taurine across the hepatocanalicular membrane in humans and rats. In favor of this, one experimental study compared the transport between the human and rat bile salt export pump (BSEP/ABCB11). The investigators found that both human and rat ABCB11 transport taurine-conjugated better than glycine-conjugated bile salts, but human ABCB11 transports glycine conjugates to a greater extent as compared to the murine transporter.[8]

Also it is important to mention that in the rat before canalicular secretion, UDCA is commonly conjugated with taurine. Interestingly, Miriam Úriz, *et al*.[9] have observed *in vivo* and *in vitro* that secretin-stimulated hydrocholeresis in normal rats infused with UDCA involves, at least partially, taurine-conjugation and tauro-UDCA-secretion interaction in cholangiocytes, with subsequent activation of PKCa, PI3K, MEK and PKA pathways. In addition, they observed that the bicarbonate extruder AE2 is also involved in the choleretic effect. Taken these findings together, we suggest that norUDCA and/or taurine-conjugated norUDCA might represent a complement or alternative to UDCA therapy for patients with symptomatic PCLD.

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