Annals of Hepatology
The Official Journal of the Mexican Association of Hepatology, the Latin-American Association for Study of the Liver and the Canadian Association for the Study of the Liver

LIVER NEWS ELSEWHERE

May-June, Vol. 15 No. 3, 2016: 453-454

Bile acids and the risk for hepatocellular carcinoma in primary biliary cholangitis

Alejandra Altamirano-Barrera,* Misael Uribe,* Frank Lammert,** Nahum Méndez-Sánchez*

* Liver Research Unit, Medica Sur Clinic & Foundation. Mexico City, Mexico.
** Klinik für Innere Medizin II. Universitätsklinikum des Saarlandes, Homburg, Germany.

Article commented:

Trivedi PJ, Lammers WJ, van Buuren HR, Parés A, Floreani A, Janssen HL, Invernizzi P, *et al.;* Global PBC Study Group. Stratification of hepatocellular carcinoma risk in primary biliary cirrhosis: a multicentre international study. *Gut* 2016; 65: 321-9.

Comment:

Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world and the third most common cause of cancer death, and accounts for 5.6% of all cancers. Nearly 82% of the approximately 550,000 liver cancer deaths each year occur in Asia. In some regions, cancer-related death from HCC is second only to lung cancer.[1] The most frequent risk factors include chronic viral hepatitis (types B and C), alcohol intake and aflatoxin exposure. However, it has been reported that HCC occurs in 1-6% of patients with primary biliary cholangitis (PBC) per year. In addition HCC surveillance with abdominal imaging and α-fetoprotein is recommended every 6-12 months for patients. Furthermore, some studies suggested that risk factors for the development of HCC in patients with PBC include older age, male sex, presence of portal hypertension, advanced histological stage, and poor response to ursodeoxycholic acid (UDCA).[2,3]

We read with a great interest the article by Trivedi, *et al.*[4] on the stratification of HCC risk in PBC. The risk for HCC in patients with PBC has been reported in previous publications and it has also been demonstrated by Liang, *et al.*[5] in a systematic review and meta-analysis, suggesting that PBC is significantly associated with an increased risk for HCC. Two major risk factors have been suggested to predispose patients with PBC to develop HCC. The first one is gender and the second the biochemical non-response to UDCA. In the present study the univariate analysis showed that male sex (unadjusted HR 2.91, $p < 0.0001$) is one the factors at PBC diagnosis associated with future HCC development.[4] The reason for increased hepatocarcinogenesis in men compared to women remains yet to be defined, but a role of estrogen-related differences in inflammatory cytokine production has been suggested.[6]

Here we would like to suggest a hypothesis to explain in part the increased risk in men with PBC for HCC. Both risk factors gender and non-response to treatment may be related to each other and increase HCC susceptibility. PBC is more frequent in women than men. However, men are more prone to the development of HCC. Currently the gold standard for treatment of PBC is UDCA.[7] This bile acid constitutes < 5% of the bile acid pool under physiological conditions. After oral administration of UDCA an enrichment of bile with this hydrophilic bile acid occurs, which represents the requirement for treatment response in patients with chronic cholangiopathies. The mechanism of action of UDCA is multifactorial[8] and involves replacement of endogenous cytotoxic bile acids [chenodeoxycholic (CDCA) and deoxycholic (DCA) acid] by the non-cytotoxic bile acid UDCA; one of the mechanisms is likely to be competition for active ileal transport.

Interestingly, it has been suggested that gender has a major effect on fasting plasma concentrations of individual bile acids in healthy individuals. In fact, Xiang, *et al.*[9] reported that fasting plasma concentrations of individual bile acids are 111% higher in men than in women. Consequently, the mean concentration of total bile acids is about 50% higher in men than in women. These differences were also observed in the 70's by Bennion, *et al.*[10] in healthy male subjects whose chenodeoxycholic acid pool sizes were larger than in women. In addition, Diger, *et al.*[11] reported that PBC patients differ from healthy individuals

Manuscript received: March 26, 2016. **Manuscript accepted:** March 26, 2016.

DOI:10.5604/16652681.1198826.

with respect to the bile acid conjugation pattern. The investigators observed that PBC patients showed higher rates of taurine conjugation in bile. Taurine conjugation as compared to glycine conjugation reduces the hepatotoxicity of hydrophobic bile acids.[11]

Taken together this information we speculate that PBC patients who do not respond to UDCA therapy might have high plasma concentrations of bile acids, in particular CDCA, because there is incomplete replacement by UDCA, or UDCA is not completely conjugated with taurine. This in turn could also contribute to both the null response and the induction of carcinogenesis via intrahepatic accumulation of bile acids. In favor of this hypothesis it has been shown that farnesoid X receptor (FXR), which represents the bile salt sensor in liver and intestine and is activated by CDCA, plays an important role in protecting against HCC.[12] In conclusion we believe that in patients with PBC the bile acid metabolism is changed and this in turn results in extensive remodeling of expression/activity of bile acid-activated receptors in the liver and intestine. However, more studies focusing on those alterations in patients with PBC are needed, especially in those at high risk for HCC.

REFERENCES

1. Méndez-Sánchez N, Ridruejo E, Alves de Mattos A, Chávez-Tapia NC, Zapata R, Paraná R, Mastai R, et al. Latin American Association for the Study of the Liver (LAASL) Clinical Practice Guidelines: management of hepatocellular carcinoma. *Ann Hepatol* 2014; 13(Suppl. 1): S4-S40.
2. Lammers WJ, Kowdley KV, van Buuren HR. Predicting outcome in primary biliary cirrhosis. *Ann Hepatol* 2014;13:316-26.
3. Imam MH, Silveira MG, Sinakos E, Gossard AA, Jorgensen R, Keach J, DeCook AC, et al. Long-term outcomes of patients with primary biliary cirrhosis and hepatocellular carcinoma. *Clin Gastroenterol Hepatol* 2012; 10: 182-5.
4. Trivedi PJ, Lammers WJ, van Buuren HR, Parés A, Floreani A, Janssen HL, Invernizzi P, et al. Stratification of hepatocellular carcinoma risk in primary biliary cirrhosis: a multicentre international study. *Gut* 2016; 65: 321-9.
5. Liang Y, Yang Z, Zhong R. Primary biliary cirrhosis and cancer risk: a systematic review and meta-analysis. *Hepatology* 2012; 56: 1409: 17-27.
6. Naugler WE, Sakurai T, Kim S, Maeda S, Kim K, Elsharkawy AM, Karin M. Gender disparity in liver cancer due to sex differences in MyD88-dependent IL-6 production. *Science* 2007; 317: 121-4.
7. Carey EJ, Ali AH, Lindor KD. Primary biliary cirrhosis. *Lancet* 2015; 386 (10003): 1565-75.
8. Beuers U. Drug insight: Mechanisms and sites of action of ursodeoxycholic acid in cholestasis. *Nat Clin Pract Gastroenterol Hepatol* 2006; 3: 318-28.
9. Xiang X, Backman JT, Neuvonen PJ, Niemi M. Gender, but not CYP7A1 or SLCO1B1 polymorphism, affects the fasting plasma concentrations of bile acids in human beings. *Basic Clin Pharmacol Toxicol* 2012; 110: 245-52.
10. Bennion LJ, Drobny E, Knowler WC, Ginsberg RL, Garnick MB, Adler RD, Duane WC. Sex differences in the size of bile acid pools. *Metabolism* 1978; 27: 961-9.
11. Dilger K, Hohenester S, Winkler-Budenhofer U, Bastiaansen BA, Schaap FG, Rust C, Beuers U. Effect of ursodeoxycholic acid on bile acid profiles and intestinal detoxification machinery in primary biliary cirrhosis and health. *J Hepatol* 2012; 57: 133-40.
12. Fiorucci S, Distrutti E, Ricci P, Giuliano V, Donini A, Baldelli F. Targeting FXR in cholestasis: hype or hope. *Expert Opin Ther Targets* 2014; 18: 1449-59.

Correspondence and reprint request:
Prof. Nahum Méndez-Sánchez, MD, MSc, PhD.
Liver Research Unit. Medica Sur Clinic & Foundation
Puente de Piedra, Núm. 150, Col. Toriello Guerra,
C.P. 14050. Mexico City, Mexico.
Tel.: (+5255) 5424-7200. Ext. 4215
Fax: (+5255) 5666-4031
E-mail: nmendez@medicasur.org.mx