MedicalXpress

Crucial protective role observed for farnesoid-X receptor in cholestatic liver injury

January 29 2015

The farnesoid-X receptor (FXR), also known as the chief regulator of bile acid metabolism, is thought to play a role in some hepatobiliary and gastrointestinal disorders. In a study published in the *American Journal of Pathology*, researchers demonstrated dysfunctional intestinal FXR-signaling in a rat model of cholestatic liver injury, accompanied by intestinal bacterial translocation (BTL) and increased permeability and inflammation. Notably, a highly potent, selective FXR agonist obeticholic acid (INT-747) counteracted these effects, suggesting a potential new therapeutic avenue for liver disease.

The FXR has been recognized as a key transcription-regulator in hepatic and intestinal bile metabolism. "In experimental cholestasis, FXR-agonism improves ileal barrier function by attenuating intestinal inflammation leading to reduced bacterial translocation, demonstrating a crucial protective role for FXR in the gut-liver axis," said lead investigator Len Verbeke, MD, PhD, of the Division of Liver and Biliopancreatic Disorders at University Hospitals Leuven, KU Leuven-University of Leuven, Belgium.

The model used generated cholestatic liver injury in rats (cholestasis refers to a condition in which the flow of bile is blocked). In one experiment, 51 rats underwent ligation of the common bile duct (BDL) and were then treated with vehicle, 5 mg/kg ursodeoxycholic acid (UDCA), or 5 mg/kg of the FXR agonist INT-747 by gavage every two days for 10 days after surgery. UDCA is a bile acid similar in molecular structure to INT-747, which lacks FXR-agonizing properties. INT-747 is

a semisynthetic bile acid derivative that is a first-in-class FXR agonist.

In vehicle-treated rats, chronic cholestatic liver injury resulted in FXR pathway deficiency, as indicated by reduced expression of the FXR downstream target receptor small heterodimer partner (SHP). This deficiency was accompanied by increased intestinal permeability, as shown by decreased transepithelial electrical resistance (TEER) in the jejunum and ileum. "This, in turn, was related to a disproportional up-regulation of the pore-forming tight-junction protein claudin-2 throughout the small bowel," explained Dr. Verbeke. The expression of counter-balancing pore-closing claudin-1 was unchanged in vehicle-treated animals.

Oral administration of INT-747 resulted in the re-activation of the FXR pathway (as measured by SHP levels) in the ileum, not the jejunum, of the BDL rats. FXR agonist treatment also selectively restored intestinal permeability, as measured by TEER, although the effects were confined to the ileum. Claudin-1 levels were significantly elevated in the ileum of INT-747-treated animals (P ?0.02).

INT-747 treatment also improved survival. All 19 INT-747-treated rats survived, compared with 11 of 16 vehicle control rats (P =0.01).

Another encouraging finding was the effect of INT-747 on intestinal BTL. Intestinal BTL is defined "as the migration of viable micro-organisms from the gut lumen toward the mesenteric lymph nodes and extra-intestinal sites such as the peritoneal cavity," explained Dr. Verbeke. Because BTL may be a harbinger of hepatic decompensation or worsening of liver impairment, leading to multi-organ failure and death, minimizing or preventing BTL may be pivotal in reversing the cascade of events associated with serious liver injury. In this study, the median number of translocated bacterial strains decreased from 4 to 2 in the mesenteric lymph nodes of BDL rats after treatment with INT-747

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