NEWS RELEASE
FOR IMMEDIATE RELEASE

Contacts:
Eileen Leahy
Elsevier
Tel: 732-238-3628
ajpmedia@elsevier.com

Dr. Chhavi Chauhan
Scientific Editor
The American Journal of Pathology
Tel: 301-634-7953
cchauhan@asip.org

Crucial Protective Role Observed for Farnesoid-X Receptor in Cholestatic Liver Injury

The Oral FXR-Agonist INT-747 Normalizes Dysfunctional Intestinal FXR-Signaling and Changes in Intestinal Permeability, Inflammation, and Bacterial Translocation, According to Study Published in The American Journal of Pathology

Philadelphia, PA, 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 ($P \leq 0.02$).

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 ($P <0.01$).

Other findings suggest that INT-747 exerts anti-inflammatory effects. Consistently, INT-747–treated rats showed lower average spleen weights, with significantly fewer white blood cells and natural killer cells in the spleen and mesenteric lymph nodes. Rats in the control group showed a significant increase in the expression of interferon-$\gamma$, a cytokine produced by natural killer cells and known to drive intestinal permeability; this increase was suppressed in INT-747–treated rats.

“The available clinical approach toward the prevention and treatment of bacterial translocation is currently limited to intestinal decontamination by means of antibiotics. The increasing rate of treatment failures due to the numerous infections with gram-positive and multiresistant microorganisms in these patients has encouraged the need for novel therapies in the treatment/prevention of BTL and spontaneous bacterial peritonitis, the most common infection in patients with cirrhosis,” concluded Dr. Verbeke. The results of this study support the hypothesis that FXR dysfunction is a part of the molecular pathogenesis of serious liver injury, and FXR-agonists should be investigated further as potential alternative therapeutic options.

Notes for Editors


This work received support from the Fund for Scientific Research – Flanders (FWO Vlaanderen) and the Deutsche Forschungsgemeinschaft (SFB TRR57 project 18).

Full text of this study is available to credentialed journalists upon request; contact Eileen Leahy at 732-238-3628 or ajpmedia@elsevier.com. Journalists wishing to interview the authors are welcome to contact the lead investigator Dr. Len Verbeke at +32 476217945 or Len.verbeke@med.kuleuven.be.

About The American Journal of Pathology

The American Journal of Pathology (http://ajp.amjpathol.org), official journal of the American Society for Investigative Pathology, seeks to publish high-quality, original papers on the cellular and molecular biology of disease. The editors accept manuscripts that advance basic and translational knowledge of
the pathogenesis, classification, diagnosis, and mechanisms of disease, without preference for a specific analytic method. High priority is given to studies on human disease and relevant experimental models using cellular, molecular, animal, biological, chemical, and immunological approaches in conjunction with morphology.

The leading global forum for reporting quality original research on cellular and molecular mechanisms of disease, The American Journal of Pathology is the most highly cited journal in Pathology – over 39,000 cites in 2013 – with an Impact Factor of 4.602 and Eigenfactor of 0.07076 according to the 2013 Journal Citation Reports®, Thomson Reuters, and an h-index of 206 according to the 2013 SCImago Journal and Country Rank.

ABOUT ELSEVIER
Elsevier is a world-leading provider of information solutions that enhance the performance of science, health, and technology professionals, empowering them to make better decisions, deliver better care, and sometimes make groundbreaking discoveries that advance the boundaries of knowledge and human progress. Elsevier provides web-based, digital solutions — among them ScienceDirect (www.sciencedirect.com), Scopus (www.scopus.com), Elsevier Research Intelligence (www.elsevier.com/research-intelligence) and ClinicalKey (www.clinicalkey.com) — and publishes nearly 2,200 journals, including The Lancet (www.thelancet.com) and Cell (www.cell.com), and over 25,000 book titles, including a number of iconic reference works.

The company is part of Reed Elsevier Group PLC (www.reedelsevier.com), a world-leading provider of professional information solutions in the Science, Medical, Legal and Risk and Business sectors, which is jointly owned by Reed Elsevier PLC and Reed Elsevier NV. The ticker symbols are REN (Euronext Amsterdam), REL (London Stock Exchange), RUK and ENL (New York Stock Exchange).