



Norursodeoxycholic acid as a candidate pharmacological therapy for nonalcoholic fatty liver disease

Masato Yoneda, Atsushi Nakajima

Department of Gastroenterology and Hepatology, Yokohama City University Hospital, Kanazawa-ku, Yokohama, Japan

Correspondence to: Masato Yoneda, MD, PhD. Department of Gastroenterology and Hepatology, Yokohama City University Hospital, 3-9 Fuku-ura, Kanazawa-ku, Yokohama, Japan. Email: yoneda-ycu@umin.ac.jp.

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Nonalcoholic fatty liver disease (NAFLD) has become one of the most frequent causes of chronic liver disease in the past 2 decades. Almost 25% of the adult population presently suffers from NAFLD worldwide (1,2). Especially, patients with nonalcoholic steatohepatitis (NASH), which is a more severe type of NAFLD, can progress to liver cirrhosis over time and associated with a high risk of hepatic failure and hepatocellular carcinoma (HCC). As mentioned previously, NAFLD/NASH is rapidly becoming the foremost cause of liver-related morbidity (e.g., end-stage liver disease, HCC, and liver transplantation) as well as cardiovascular disease (1,3).

Improvement of lifestyle, such as low-calorie diet and exercise (aerobic and resistance), are currently the first-line therapy for NAFLD/NASH, but can be difficult to succeed and continue good condition, emphasizing the urgent issue for pharmacotherapy. Nevertheless, no established pharmacological therapies and no Federal Drug Administration (FDA)-approved drugs or European Medicines Agency (EMA)-approved drugs are available for the treatment of NASH despite numerous clinical trials to date. Ursodeoxycholic acid (UDCA), a secondary bile acid, has historically been one of the most general-purpose therapies for chronic hepatitis, however it has no histological benefit over a placebo in NAFLD/NASH patients (4). Therefore, UDCA is not recommended as a therapeutic medication for NAFLD/NASH (5).

In recent years, several innovative medicines have been developed in the drug pipeline for the treatment of NAFLD/NASH. Among them, obeticholic acid, a selective

farnesoid X receptor (FXR) agonist, have entered phase 3 trials for NASH treatment and are thought to have potential for the treatment of NASH (6).

To overcome this background and these limitations, the medical need for an effective pharmacological treatment for NAFLD/NASH must be met. In their report on this issue, Traussnigg *et al.* showed a dose-dependent reduction in serum ALT in patients treated with norursodeoxycholic acid (norUDCA), a synthetic side chain-shortened C23 homologue of UDCA (7), versus a placebo in a phase 2, multicenter, double-blind, clinical trial (8). Although it is also well known that the serum ALT values may not always be well-correlated with the severity of liver disease (9), they also demonstrated a decrease in the hepatic fat fraction as measured using MRI or MRS in a group of receiving 1,500 mg of norUDCA, even if the number of patients in whom MRI/MRS was performed was too small to allow a definitive conclusion. NorUDCA is known not to activate FXR, but was reported to be relatively resistant to conjugation reaction with glycine or taurine, compared with UDCA. Furthermore, norUDCA goes through cholehepatic shunting, causing ductular targeting, bicarbonate-rich hypercholerisis, and cholangiocyte protection (10).

NAFLD with Advanced fibrosis is associated with an increased all-cause mortality and liver-related mortality (11,12), and several trials evaluating anti-fibrotic agents have been withdrawn because of insufficient efficacies over a placebo. Hopefully, the anti-fibrotic effect of norUDCA will be evaluated by liver biopsy or recent MRI-based technologies or US-based elastography.

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