EBioMedicine 42 (2019) 32–33

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

EBioMedicine
Published by THE LANCET

Commentary

Nitro-oleic acid as a new drug candidate for non-alcoholic steatohepatitis

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With the global epidemics of obesity and metabolic syndrome, non-alcoholic fatty liver disease (NAFLD) is emerging as the most common chronic liver disease in the world [1]. Non-alcoholic steatohepatitis (NASH) is the severe form of NAFLD that may progress to liver cirrhosis and hepatocellular carcinoma. The risk of liver-related mortality is increased only in NASH patients especially with advanced fibrosis [1]. Furthermore, NAFLD is also associated with increased incidence of type 2 diabetes, cardiovascular disease (CVD) and chronic kidney disease (CKD), and the leading cause of death in patients with NAFLD is CVD [1]. However, current treatment strategies of NASH have only focused on lifestyle intervention and pharmacological treatments for cardiometabolic risk factors [2]. There is an urgent unmet need to develop effective drugs for NASH and liver fibrosis, and to find imaging-based biomarkers for non-invasive prognostication and selection of patients for treatment and monitoring.

Dysregulated redox mechanisms under oxidative and nitrative stress condition play a pivotal role in the development of chronic metabolic and inflammatory disorders, including NASH and CVD [2–5]. Nitro-fatty acids are reactive signaling mediators that are formed when unsaturated fatty acids react with nitric oxide or nitric oxide-derived species [3]. Nitro-oleic acid (OA-NO_2) is the most studied nitro-fatty acids with potent anti-inflammatory properties. Preclinical studies in a variety of animal models have indicated the potential diverse protective role of OA-NO_2 in obesity-related cardiovascular, renal and metabolic diseases and made it a new and promising drug candidate [3–5]. Currently, OA-NO_2 is undergoing phase 2 clinical trials in patients with obesity. However, the therapeutic potential of OA-NO_2 in NASH and related fibrosis has barely been explored.

In this article of *EbioMedicine*, Oren Rom and colleagues explored the effect and mechanism of OA-NO_2 on the development of fibrotic NASH both *in vivo* and *in vitro* [6]. In an established NASH mouse model, Rom *et al* demonstrated that long-term administration of OA-NO_2 improved the body composition and energy metabolism of mice chronically fed with high-cholesterol, high-fructose diet, and meanwhile alleviated the degree of hepatic steatosis, lobular inflammation and liver fibrosis along with normalization of serum alanine aminotransferase level. Authors continued to perform a serial of experiments *in vitro* to show that OA-NO_2 inhibited triglyceride biosynthesis and accumulation in hepatocytes and fibrogenesis in human stellate cells. Authors also found that OA-NO_2 suppressed NASH diet-induced transforming growth factor β (TGF-β) signaling and regulated expression of genes involved in lipogenesis and β-oxidation. Taken together, these results indicated that OA-NO_2 can be an effective therapeutic agent against several obesity-related diseases including NASH. However, the underlying mechanisms of OA-NO_2 against steatohepatitis and liver fibrosis were not deeply investigated. The results from the preclinical models *in vivo* warranted further evaluation of OA-NO_2 in clinical settings.

Liver biopsy remains the golden standard for the diagnosis of NASH and the evaluation of histological severities of hepatic steatosis, necroinflammation and fibrosis. Currently, liver biopsy is considered mandatory by regulatory authorities as a surrogate to assess drug efficacy in phase 3 clinical trials of NASH. However, repeated liver biopsy to assess histological changes for therapeutic response is usually impractical, as its invasive nature, poor patient acceptability and sampling variability [7]. Some imaging modalities are thus used in non-invasive evaluation of hepatic steatosis and liver fibrosis. Magnetic resonance spectroscopy (MRS) and magnetic resonance elastography (MRI) are regarded as the best non-invasive modality to quantify the alterations of hepatic steatosis and fibrosis, respectively. However, they are usually not readily available both in clinic and in experiment research [7]. Recently, two preclinical studies on phantoms and mouse model have suggested the capability of a new dual-modality photoacoustic/ultrasound system in the characterization of hepatic steatosis and liver fibrosis [8,9]. Photoacoustic physio-chemical analysis (PAPCA) could contribute to the diagnosis of many diseases involving diffusive patterns such as fatty liver [10]. In this study, photoacustic-ultrasound was successfully applied to mimic an ideal scenario for diagnosis of hepatic steatosis and fibrosis in an experimental mouse model of NASH before the treatment of OA-NO_2. However, the authors did not perform photoacustic-ultrasound measurements to evaluate the therapeutic efficacy of OA-NO_2.

In summary, the results published in this paper of *EBioMedicine* brought good news to NASH patients, especially the one co-existing with CVD and CKD, as the study provided strong preclinical evidence of the effectiveness of OA-NO_2 for prevention and treatment of obesity-related steatohepatitis and liver fibrosis. Furthermore, it suggested that photoacustic-ultrasound might be a novel non-invasive imaging approach for evaluation of hepatic steatosis and liver fibrosis with the potential for future clinical diagnosis and monitoring of NASH.

DOI of original article: https://doi.org/10.1016/j.ebiom.2019.02.019.

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https://doi.org/10.1016/j.ebiom.2019.03.059

Disclosure

The authors declared no conflicts of interest.

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