Non-alcoholic fatty liver disease (NAFLD) and the quest for effective treatments

Kessarin Thanapirom[1,2] , Emmanuel A. Tsochatzis[1]

1. UCL Institute for Liver and Digestive Health, Royal Free Hospital and UCL, London, UK

2. Division of Gastroenterology, Department of Medicine, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, The Thai Red Cross Society, Bangkok, Thailand.

Correspondence: Emmanuel A. Tsochatzis, Sheila Sherlock Liver Unit and UCL Institute for Liver and Digestive Health, Royal Free Hospital and UCL, Pond Street, NW3 2QG, London, UK, Phone: (0044)2077940500 ext. 31142, Fax: (0044)2074726226, email: e.tsochatzis@ucl.ac.uk

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease worldwide, affecting 24% of the population, and is impacting on global public health care with a considerable financial burden (1). NAFLD encompasses a wide disease spectrum ranging from simple steatosis to non-alcoholic steatohepatitis (NASH), fibrosis and cirrhosis. Patients with simple steatosis typically do not develop liver-related complications, whereas patients with NASH are at increased risk of hepatic and extra-hepatic mortality. Furthermore, NAFLD is associated with an increased risk of type 2 diabetes, cardiovascular disease and cancer (2). In addition, NASH is the second leading cause of cirrhosis in adult patients on the liver transplant waiting list in the United States (3,4).

In the past decade, there has been immense progress in the understanding of the pathogenesis of NAFLD, which led to an exponential increase in clinical trials of pharmacotherapies targeting identified pathways. Despite this progress, there is still no approved medication for treating NASH. The recent article by Friedman *et al*. extensively reviews current evidence on risk factors, pathogenesis and treatment of NAFLD, with an emphasis in preclinical models and ongoing phase II and III pharmacological clinical trials (5). As the authors point out, the traditional two-hit hypothesis for the pathogenesis of NASH is now outdated. A multi-hit theory has been proposed, that reflects the diverse potential pathways for the

development and progression of NAFLD. Interplay among multiple insults, including insulin resistance, adipokines and inflammatory cytokines secreted from the adipose tissue, intestinal microbiota, genetic and epigenetic factors, oxidative stress, environmental and dietary factors lead to the development of NAFLD and to the progression to NASH and fibrosis (6). Different mechanisms of injury might prevail in individuals, which if true will complicate the therapeutic landscape, as future treatments might not be effective for all patients. A better understanding of such pathways will open the opportunity to develop novel non-invasive diagnostic tests and targeted pharmacological treatments.

Multiple agents are currently being investigated and have been summarized by the authors in their article (7-10). Novel drugs, such as obeticholic acid, selonsertib, elafibranor and cenicriviroc have shown encouraging results in phase II and are currently in phase III trials, with expected results within the next 1-4 years. The primary endpoints of phase IIb and III trials are focused on NASH resolution without worsening of liver fibrosis or improvement/regression in fibrosis without worsening of NASH. Commenting on the trial endpoints is beyond the scope of this editorial, however NAS score is a problematic surrogate treatment endpoint because of its high inter- and intra-observer variability and its lack of association with clinical events. Even though the results of these trials were so far promising in phase II, unfortunately only 10-30% of treated patients show a net

benefit compared to placebo. Additionally, none of the agents have a proven advantage on long-term outcomes. The issue is further complicated by the long natural history of NAFLD. Combination therapies might have greater response, however this will need to be proven in future studies. There is therefore an urgent need to improve the efficacy of treatment strategies for NASH.

The review did not comment on the current mainstay strategy for NASH treatment, which is weight reduction through lifestyle interventions. These include a combination of increase in exercise/physical activity and caloric restriction and should be individually tailored. Weight loss of ≥7% of total body weight is associated with improvement in histologic features of NASH, while a weight loss of ≥10% is associated with fibrosis regression regardless of the method used (11). Previous randomized controlled trials in NASH reported a histological improvement in the placebo arm that ranges between 10-30%. Although it is difficult to fully explain this, it is probable that a significant proportion of these patients improved due to the successful implementation of lifestyle changes. Unhealthy lifestyle habits, such as smoking might be associated with more severe liver fibrosis and increased incidence of cardiovascular outcomes (12). However, this approach is difficult to sustain, as most patients have low compliance to weight loss maintenance in the long term. To improve the efficacy and sustainability of this strategy, a multidisciplinary team approach is needed that

includes primary care physicians, hepatologists, dietitians, physical trainers and psychologists. Bariatric surgery is a promising option for reducing weight and metabolic complications. Although it is not yet an established therapy for NASH and more data are required to support its use for the liver disease component, some experts suggest considering bariatric surgery in morbidly obese non-cirrhotic patients who failed lifestyle modifications (13).

In conclusion, the growing burden of NAFLD worldwide is an emerging concern. NASH is classified as a medical condition of an immediate unmet therapeutic need. Therefore continuous research is required in order to better understand its pathogenesis, develop of non-invasive markers of severity and identify new therapeutic targets.

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