A New FGF21 Analog for the Treatment of Fatty Liver Disease

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Nonalcoholic fatty liver disease (NAFLD) describes a non–alcohol-induced cluster of conditions related to excessive fat stored in the liver. Defined as 5% or more hepatic fat content, NAFLD is prevalent, affecting ∼25% of the general population (1). Approximately 20% of individuals with NAFLD have a more aggressive form of the disease, termed nonalcoholic steatohepatitis (NASH), which is in addition characterized by liver inflammation and extensive scarring (cirrhosis) (1,2). NASH is a growing cause of liver cancer and a leading indication for liver transplantation (2). In addition, NAFLD and NASH are risk factors for chronic kidney disease (3), type 2 diabetes (4), and cardiovascular disease (5).

Despite being serious afflictions, NAFLD and in particular NASH face two major headwinds. One, they are difficult to diagnose because they require liver biopsies for conclusive diagnosis. Two, there are currently no approved medications for treatment. Lifestyle intervention to reduce body weight is the primary strategy to manage the disease. However, while reducing caloric intake and increasing physical activity are obvious remedies, such lifestyle modification has very limited efficacy in the long run, with typically no more than 3–4% of weight loss after 4 years (6). With a quickly growing population of patients with NAFLD/NASH (2) and no approved therapies, there is an unmet yet steadily increasing medical need for safe and effective pharmacotherapy. Unfortunately, resembling the quest for the Holy Grail, the development of such a therapy seemed, as of today, a mission impossible. In this issue of *Diabetes*, Cui et al. (7) make a significant step forward in developing a pharmacotherapy to treat NAFLD and NASH. The authors developed a chemical derivate of fibroblast growth factor 21 (FGF21) that showed remarkable effects in melting away hepatic fat in mice and monkeys.

FGF21 is an endocrine hormone that signals via a receptor complex consisting of FGF1 receptor and coreceptor βKlotho. FGF21 is expressed in multiple peripheral tissues, including liver, skeletal muscle, pancreas, and white and brown adipose tissue (8). Interest in FGF21 exploded with the discovery that pharmacological administration of FGF21 to diabetic rodents and primates increased insulin sensitivity, energy expenditure, and weight loss (6). Moreover, administration of an FGF21 analog to humans with obesity significantly lowered body weight and decreased LDL cholesterol and triglycerides while increasing HDL cholesterol (9). These studies have spurred a number of drug development programs designed to enhance FGF21 activity (10). Several preclinical animal studies have also demonstrated that FGF21 could improve NAFLD/NASH by reversing hepatic steatosis, counteracting obesity and alleviating insulin resistance (11). The short half-life of native FGF21 (∼1–2 h) (12), however, has hampered a successful translation of these FGF21 benefits into the clinic.

In this issue of *Diabetes*, Cui et al. assess the efficacy of a novel polyethylene glycolylated (PEGylated) and genetically modified long-acting FGF21 analog, called B1344, with a half-life of ≥50 h, in improving NAFLD/NASH in obese nonhuman primates and in lean mice. In one study, diet-induced obese (DIO) male cynomolgus monkeys, with more than 10% hepatic fat content, were injected twice weekly with 0.5, 1.0, or 2.0 $mg \cdot kg^{-1}$ of B1344 for 11 weeks. An additional group was injected only once a week with the high dose of B1344. All doses of B1344 reduced body weight by ∼5% relative to vehicle-treated controls. Most importantly, liver-specific end points, assessed by magnetic resonance imaging and liver biopsies, demonstrated that B1344 reduced hepatic fat content by 40%, decreased scarring, and lowered markers of hepatic inflammation (Fig. 1*A*).

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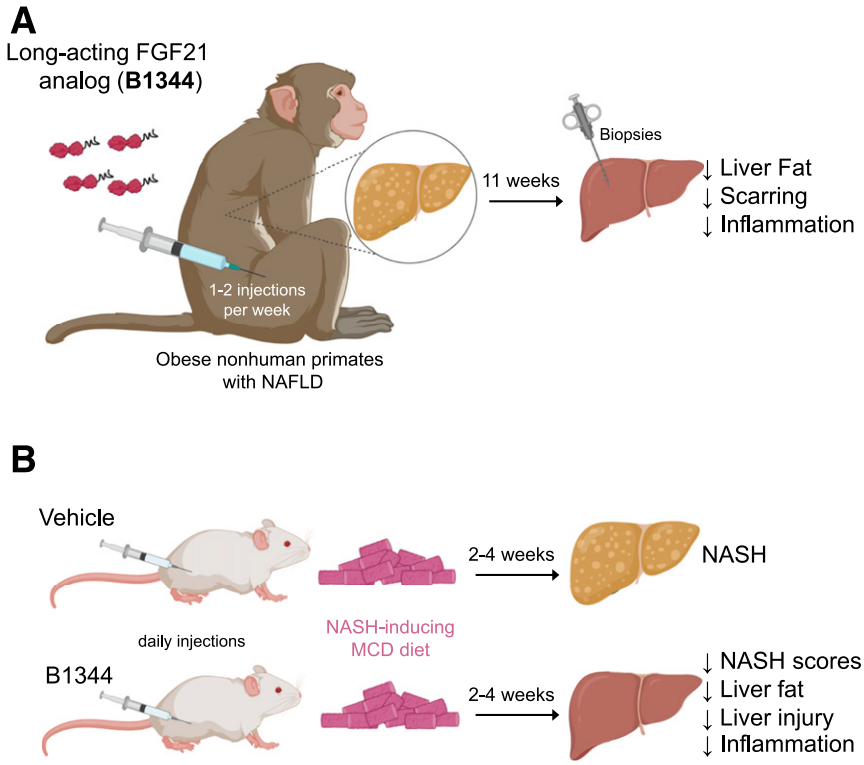

Figure 1—A new FGF21 analog improves NAFLD/NASH in nonhuman primates and mice. *A*: DIO male cynomolgus monkeys with >10% hepatic fat content were injected twice a week for 11 weeks with B1344, a novel PEGylated and genetically modified long-acting FGF21 analog. Magnetic resonance imaging and liver biopsies demonstrated that B1344 reduced hepatic fat content by 40%, decreased scarring, and lowered markers of hepatic inflammation. *B*: An MCD diet was used to induce NASH in lean mice. After 2 weeks on the MCD diet, mice were treated with daily injections of vehicle or B1344 for up to 4 weeks. While control mice developed patent NASH, B1344-treated mice had low histological NASH scores, low liver fat content, lower circulating levels of alanine aminotransferase and aspartate aminotransferase, which are markers of liver injury, and low expression of hepatic genes indicative of inflammation.

In the mouse study, a methionine- and choline-deficient (MCD) diet was used to induce NASH without obesity (13). After a lead-in period of 2 weeks on the MCD diet, two doses (0.125 and 2 $mg \cdot kg^{-1}$) of B1344 were tested by daily injections for up to 4 weeks. While control mice developed patent NASH, B1344-treated mice maintained low histological NASH scores, low liver fat content, markedly lower circulating levels alanine aminotransferase and aspartate aminotransferase, and low expression of hepatic genes indicative of inflammation (Fig. 1*B*). The data from these two animal studies suggest that B1344 can both partially reverse and prevent NAFLD/NASH.

The data obtained from the cynomolgus monkeys are the major strength of this work. The liver biopsies especially provide direct evidence that B1344 improves NASH. A minor limitation is that the DIO monkeys presented only mild NASH, evidenced by low immune cell infiltration. It is also unclear whether B1344 elicits hepatic benefit via direct actions in the liver or whether these effects are partially affected by weight loss and enhanced glycemic control. In addition to reducing weight, B1344 also improved fasting glucose, glycated hemoglobin, and glucose tolerance. A calorie-restricted control group to match the B1344-induced weight loss could have provided additional valuable information. Similarly, a head-to-head comparison with native FGF21 would have added value to fully appreciate the superior metabolic action of the long-acting FGF21 analog. The study in mice indicates that B1344 can prevent NASH in a non–body-weight-related manner. While these effects are promising, the MCD diet model has some limitations. For one, the MCD diet does not reflect any diet consumed by humans. In addition, already lean mice lost 40% of their body weight in 8 weeks on the MCD diet in the current study. This is in stark contrast to fatty liver disease in humans, which is associated with obesity (14). Nevertheless, the potent ability of B1344 to prevent a diet-induced progression to NASH certainly warrants follow-up investigations.

Collectively, the study by Cui et al. is an important step forward in evaluating FGF21 analogs for the treatment of NAFLD/NASH. Recently, another long-acting FGF21 analog called pegbelfermin was evaluated in patients with biopsy-confirmed NASH (15). While pegbelfermin reduced hepatic fat up to 30%, NASH end points were not assessed with liver biopsies (15). Since liver fat and NASH do not always correlate (16), it is significant that Cui et al. now provide histological evidence that long-acting FGF21 analogs can improve NASH in nonhuman primates. To understand whether this is the case in humans

will be the next step in the quest to develop a pharmacotherapy for fatty liver disease.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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