FGF-19 agonism for NASH: a short study of a long disease

Non-alcoholic steatohepatitis (NASH) has emerged as the most common cause of liver disease worldwide and is on a trajectory to become the most common indication for liver transplantation.1,2 Interest in developing effective therapies for NASH has been proportional. Since its original scientific description, NASH has been a histologically defined disease, characterised by hepatic steatosis and inflammation with variable presence and severity of Mallory’s hyaline, balloon degeneration, and, most important clinically, fibrosis.3 Steatosis and inflammation, and thereby fibrosis, are thought to be causally related through hepatic lipotoxicity.4

Many of the therapeutic agents currently in development for NASH, such as the agonists of the endocrine fibroblast growth factor (FGF) family (FGF-19 and FGF-21), have hepatic delipidation as a primary mechanism of intended effect. The pleiotropic effects of FGF-19, including inhibition of bile acid synthesis from cholesterol via cytochrome P450 7A1, and inhibition of insulin-induced hepatic lipogenesis, make FGF-19 agonism an attractive potential therapeutic mechanism.5,6

It is thus with great interest that the field has awaited the results of the phase 2A, 12 week, randomised, double-blind, placebo-controlled study assessing the efficacy and safety of NGM282, a recombinant FGF-19 agonist, reported in The Lancet by Stephen Harrison and colleagues.7 Study size was modest (n=82). At 12 weeks, 20 (74%) of 27 patients who received 3 mg NGM282 and 22 (79%) of 28 patients who received 6 mg NGM282 met the primary endpoint of a 5% or more decrease in absolute liver fat content, compared with two (7%) of 27 patients in the placebo group. A substantial proportion of patients (seven [26%] in the 3 mg dose group, 11 [39%] in the 6 mg dose group, and none in the placebo group) normalised liver fat content. The differences in liver fat content between study groups were highly significant. NGM282 also significantly reduced serum aminotransferase concentrations, with decreases in aminotransferases correlating with changes in liver fat content. The speed and magnitude of hepatic delipidation achieved in the treatment groups are unequivocally impressive, setting a new efficacy benchmark for pharmacotherapy of these aspects of NASH. The concomitant and correlative changes in a broad array of biomarkers of inflammation and fibrosis are also encouraging.

These exciting results notwithstanding, there are some important considerations in interpreting the results of this phase 2 trial. The first is the side-effect profile of NGM282, with three (11%) patients in the 3 mg dose group and three (11%) in the 6 mg group requiring early discontinuation of study drug (vs none in the placebo group). More patients experienced a grade 2 or 3 adverse event than normalised liver fat content. Adverse events were mostly gastrointestinal in nature, including high frequencies of diarrhoea, abdominal pain, and nausea. One patient in the 3 mg dose group experienced pancreatitis. FGF-19 agonism has diverse gastrointestinal effects, including altered intestinal motility, believed to be mediated in part by FGF-19 inhibition of bile acid synthesis.8 Bile acid synthesis, as measured by C4 (7α-hydroxy-4-cholesten-3-one) activity, was attenuated by 80–90% in the NGM282 groups, with the degree of attenuation correlating with decrease in liver fat content. The significant increases in cholesterol and LDL cholesterol (LDL-C) recorded in the NGM282 groups are also worthy of consideration. While the reported effect of large versus small particle LDL-C on risk of cardiovascular mortality and events is variable, the potential for increased risk of cardiovascular disease with FGF-19-induced dyslipidaemia will be an important consideration as cardiovascular disease is a much more common cause of mortality in patients with NASH than liver disease.9

Finally, NASH is most commonly a hepatic manifestation of obesity and metabolic syndrome, both chronic conditions. Liver-related clinical events occur in a minority of patients with NASH in whom fibrosis had progressed to cirrhosis over decades. In this context, 12 weeks, while enough to show lowering of liver fat content, is a physiological blink of an eye. Studies of much longer duration that show a clinically relevant sustained benefit of treatment (transaminase concentrations returned toward baseline 4 weeks after cessation of treatment with NGM282), net of adverse events, are clearly needed. The adverse event profile and physiological effects (eg, of diminished bile acid pool) associated with NGM282 suggest longer periods
of administration might be difficult at the doses used in this study. In summary, the findings of Harrison and colleagues show encouraging efficacy of a novel and potentially important therapeutic approach to NASH.

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