Editorial

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NGM282, an FGF19 analogue, in primary sclerosing cholangitis: A nebulous matter

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Primary sclerosing cholangitis (PSC) is a chronic, cholestatic, fibroinflammatory cholangiopathy.[1–3] It is an idiopathic disorder which lacks medical therapy and consequently continues to result in life-alternating and lethal consequences in a considerable proportion of patients.[3–7] Through ongoing efforts across the research spectrum, our knowledge and awareness of PSC are greater now than ever before, yet it is difficult to controvert that fundamental understanding of PSC remains, from essentially every perspective, incomplete. It is perhaps on this basis that PSC has been regarded as the "black box" of liver disease.[8]

The ileum-derived hormone fibroblast growth factor 19 (FGF19) has gained recent and increasing attention as a potential pharmacotherapeutic avenue in liver disease, including PSC. FGF19 is a negative feedback regulator of CYP7A1 (the gene encoding cholesterol 7α-hydroxylase, the first enzyme in bile acid biosynthesis), which is transcribed in response to bile acid binding to the farnesoid X nuclear receptor. It is hypothesized that harnessing FGF19 signaling may ameliorate dysregulated bile acid metabolism and thereby attenuate hepatobiliary injury.

In this issue of *Journal of Hepatology*, Hirschfield *et al.* report their findings on the efficacy, safety, and biological activity of NGM282, a bioengineered analogue of FGF19, in a multicenter phase II trial in adults with PSC.[9] NGM282 differs from the endogenous enterokine by a 5 amino acid deletion (P24-S28) and a 3 amino acid substitution within the N-terminus (A30S, G31S, H33L); this enables preferential FGF receptor member 4 signaling such that IL-6/STAT3 mediated, FGF19-driven hepatocarcinogenesis is not triggered.[10] In said study, 62 patients in 27 centers were randomized to receive NGM282 1 mg daily (n = 21), NGM282 3 mg daily (n = 21), or placebo (n = 20), stratified according to ursodeoxycholic acid (UDCA) use. Experimental drug and placebo were provided in identical, pre-filled syringes. The treatment period was 12 weeks, followed by a 4-week follow-up period. The primary outcome was change in serum alkaline phosphatase (ALP) from baseline to week 12. Secondary and exploratory outcomes were numerous, including changes in serum liver tests and biomarkers of bile acid metabolism and fibrosis. The mean age of study participants was 43 years, 61% were male, 66% had inflammatory bowel disease, 6% cirrhosis, and 63% concomitant UDCA use. Baseline ALP was approximately 364 U/L. At the end of the 12-week treatment period, there were no significant changes from baseline ALP in any of the treatment arms. Among the secondary endpoints, there were significant reductions with NGM282 treatment in serum 7alpha-hydroxy-4-cholesten-3-one (*i.e.* C4, an indicator of CYP7A1 activity) and bile acid levels as well as in hepatic fibrosis biomarkers, namely the Enhanced Liver Fibrosis (ELF) score and N-terminal type III collagen propeptide (Pro-C3).[11,12] Low-density lipoprotein cholesterol levels did not change significantly. Adverse events (mainly injection site reaction and diarrhea) were few, transient, and mild-moderate in severity; gastrointestinal symptoms were more frequent in NGM282 treatment arms, reaching nearly 40% at the end of treatment (compared to approximately 20% at baseline and study end in the placebo arm). Four patients (1 in the NGM282 1 mg arm, 2 in the NGM282 3 mg arm, and 1 in the placebo arm) withdrew from the trial. Overall, the investigators concluded: "In patients with PSC, NGM282 potently inhibited bile acid synthesis and decreased fibrosis markers, without significantly affecting ALP levels"; while this summarizes the findings of this elegant study, a conclusion is far less clear. Indeed, several elements should be considered when interpreting the study findings and looking ahead.

The foremost matter is perhaps the lack of serum ALP reduction with NGM282 treatment. Despite an early (2–4 week) decrease in ALP (curiously greater with the 1 mg dose than the 3 mg dose), there was no trend toward improvement in ALP at 12 weeks nor evidence of a trend toward a dose response. Moreover, there was a significant numerical as well as percentage change (increase) in gamma glutamyltransferase values with NGM282 treatment at 12 weeks, particularly in patients not concomitantly receiving UDCA. The authors suggest, considering the improvements seen in the secondary outcomes as well as a recent consensus that ALP-lowering alone is not advisable as a primary efficacy outcome for PSC clinical trials,[13] that NGM282 may still "deliver clinical benefit without having an early biochemical response in ALP". This is questionable for several reasons: i) The authors stated that the early reduction in ALP with NGM282 treatment suggest that its effects "on ALP might be transient and reversed by adaptive

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mechanisms to re-establish a new equilibrium"; while this could be true, it would not explain the lack of ALP reduction in the 3 mg NGM282 arm, nor is it clear how such mechanisms would cause de-reversal of ALP reduction at a later time point. Thus, it remains to be seen if ALP reduction would in fact be achieved with longer treatment. ii) While ALP-lowering is not by itself deemed a well-validated primary efficacy outcome, one wonders if its absence suggests inefficacy. iii) In a similar vein, histological improvement observed with NGM282 (also referred to as M70) treatment in a murine model of PSC correlated with ALP reduction.[14] iv) Some of the improvements noted in the secondary outcomes may have been by chance; without diving too deeply into probability theory, a familywise error rate should be entertained considering the issue of independence (or lack thereof) of outcomes from one another and the uncertainties surrounding surrogate markers in PSC,[15,16] particularly for assessing therapeutic response.[13,17] Regardless, what is curious in the present study (and ostensibly a promising but underexplored facet) is the significant reduction in ALP (as well as other outcomes, including alanine aminotransferase and aspartate aminotransferase) in the subgroup of patients with baseline C4 <2 ng/ml; this may be an important (albeit *post hoc*) finding given patients with low baseline levels of C4 have been recently found to be at greater risk of aggressive disease.[18]

Several other points merit mention. The sample was impressively heterogeneous, including patients with dominant strictures, small duct disease, autoimmune hepatitis, and cirrhosis; though this yields a sample that is more reflective of all comers with PSC, it can likewise result in difficult-to-interpret results and type II error. Second, a significant reduction was observed in the ELF score (and its individual components) in patients receiving NGM282 treatment compared to placebo, and *post hoc* analysis revealed that patients with a baseline ELF score >9.8 (higher risk of disease progression[11]) intriguingly experienced a greater reduction in ELF score than those with a lower baseline ELF score; whether this could indicate that the drug may be more effective in patients with an aggressive PSC phenotype (analogous to what may be suggested by the greater improvements observed in patients with baseline C4 <2 ng/ml) or simply that patients with a higher ELF score had more room for reduction remains unknown. The same query can be applied to the finding that reductions in Pro-C3 with NGM282 were significantly greater compared to placebo and most pronounced in patients with Pro-C3 >20 ng/ml at baseline. Third, with respect to anti-fibrotic effects, NGM282 does appear to demonstrate potent target engagement, but are these adequate, especially in light of the absence of significant ALP reduction, to decrease the incidence of cholangiocarcinoma or improve survival? Likewise, it is unknown if the NGM282-mediated improvements in non-invasive fibrosis biomarkers translate into significant changes at the histological level in patients with PSC; this may be assessed in future studies. In addition, though the fibrosis biomarkers used in this study have been shown to be of (baseline) prognostic value, it remains to be seen if changes caused by pharmacologic (or other) interventions represent a valid surrogate endpoint for clinical trials; for example, patients who are obese at the time of idiopathic pulmonary fibrosis diagnosis may have shorter survival compared to those who are not obese, but that does not ensure that a drug which causes weight loss would improve survival in idiopathic pulmonary fibrosis. Fourth, in terms of patient reported outcomes, these were seemingly not measured as study endpoints, but based on adverse event reporting, NGM282 did not worsen pruritus or fatigue; it would be interesting to know if the putative anti-fibrotic and other therapeutic effects could lessen symptoms of PSC or otherwise improve quality of life.[4] Lastly, cholangiographic changes were not assessed as a study endpoint; given these (or histologic changes in the case of small duct PSC) represent a hallmark of disease diagnosis and progression, the evaluation of a potential therapeutic intervention should include biliary imaging and/or histopathology.

The intricacies and uncertainty in assessing prospective pharmacotherapies in PSC notwithstanding, the present study has convincingly shown that NGM282, at the very least, effectuates inhibition of the classic pathway of *de novo* bile acid synthesis in patients with PSC, as evidenced by significant reduction in serum C4 levels; however, in the context of the design, overall findings, and limitations of the study, it would be premature to surmise that NGM282 has veritable clinical benefit in PSC, though it does open doors to further research. Future trials of NGM282 in patients with PSC, if performed, should examine longer term treatment and cholangiographic and/or histopathological endpoints (in addition to biochemical) which can more comprehensively reflect the complex nature of PSC and recapitulate its multifaceted pathobiology.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

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Supplementary data

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