ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Emerging Research on MGL-3196 for the Treatment of Nonalcoholic Steatohepatitis

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G&H What is the mechanism of action of MGL-3196?

ZY MGL-3196 (Madrigal Pharmaceuticals) is a thyroid hormone receptor β agonist. Thyroid hormone receptors can be classified as α receptors and β receptors. Activating the α receptor results in all of the symptoms associated with too much thyroid gland activity. On the other hand, thyroid hormone receptor β agonism appears to affect metabolic processes by lowering serum lipids such as low-density lipoprotein (LDL) cholesterol, serum triglycerides, and other metabolic factors. There is a possibility that these changes could lower liver fat and reduce the toxicity of fat in the liver of patients with nonalcoholic fatty liver disease (NAFLD). Thus, by engaging the thyroid β receptor, the patient does not experience symptoms of thyrotoxicosis, or the toxic effect of the thyroid hormone, which is mediated through the α receptor. Essentially, the primary mechanism of action of this drug suggests potentially improving the patient's lipid profile and hepatic fat.

G&H Why is this therapeutic approach being studied for nonalcoholic steatohepatitis?

ZY Nonalcoholic steatohepatitis (NASH) is the progressive subtype of NAFLD, which is an umbrella term for liver diseases associated with metabolic conditions such as visceral obesity, dyslipidemia, type 2 diabetes, and hypertension. Thus, more severe metabolic abnormality puts a patient at risk for progressive NASH. Additionally, it appears that lipotoxicity in the liver can be one of the mechanisms associated with the development of NASH and, potentially, its progression. For example, if a patient has an accumulation of fat in the liver, which is considered to be the initial step in the pathogenesis of NAFLD, other steps or "hits" can damage the liver cells, leading to the development of NASH and chronic injury to the liver, which results in the accumulation of scar or fibrotic tissue and, ultimately, cirrhosis. Thus, dyslipidemia or lipotoxicity could potentially play an important role in the development of NASH in some patients. That is the reason that the improvement of the lipid profile and, potentially, lipotoxicity is being explored as a target for NASH treatment.

G&H What was the design of the phase 2 study on MGL-3196 for the treatment of NASH?

ZY Results from the phase 2 trial were presented at last year's American Association for the Study of Liver Diseases meeting. In a double-blind, placebo-controlled trial, patients were randomized to 2 different doses of MGL-3196 or placebo for 36 weeks. The primary endpoint assessed a number of parameters but primarily liver fat measured by magnetic resonance imaging proton density fat fraction (MRI-PDFF) at week 12 as well as week 36. There were also several key secondary endpoints at weeks 12 and 36 that involved changes in liver biopsy, making it necessary for patients to undergo a screening liver biopsy as well as a liver biopsy at week 36. These secondary endpoints were histologic changes in terms of resolution of NASH and improvement of fibrosis; the achievement of

more than 30% reduction of fat by MRI-PDFF at weeks 12 and 36; and the improvement of liver enzymes, serum fibrosis markers, and lipid profiles at weeks 12 and 36.

G&H What were the characteristics of the NASH patients who were studied?

ZY Patients were required to have NASH proven by histology in liver biopsy, some fibrosis but not cirrhosis, and at least 10% liver fat on MRI-PDFF. It turned out that a number of patients had diabetes (approximately 32% of the placebo group and approximately 42% of patients who received MGL-3196). Study participants had the typical profile of NAFLD patients. Their mean body mass index was between 34 and 36. Their mean lipid profile was suggestive of dyslipidemia, with LDL cholesterol ranging between 111 and 117 and serum triglycerides between 161 and 178.

G&H What were the key study findings?

ZY The primary endpoint of the study was met, as there was a highly significant reduction in liver fat in patients who received either dose of MGL-3196 compared with placebo. Reduction in MRI-PDFF was 36% at week 12 and 37% at week 36 with the lower dose; 42% and 49%, respectively, with the higher dose; and 8% and 10%, respectively, with placebo.

In addition, patients who received the drug experienced improvement in their lipid profile. Liver enzymes (alanine aminotransferase, aspartate aminotransferase, and even γ-glutamyltransferase) improved more in the active arm. Liver biopsy also showed at least some improvement in important NASH histologic endpoints. Several noninvasive markers of fibrosis also showed improving profiles.

G&H What were the main adverse events and side effects?

ZY The adverse events were mostly mild and a few were moderate, but they were equal across the arms and compared with placebo. The side effects were nonspecific, such as loose stool. There were no significant concerns with the drug, including effects involving cardiovascular and diabetes biomarkers, thyroid-stimulating hormone, bone mineral density, or heart rate.

G&H Were there any limitations with the use of this drug?

ZY According to a subgroup analysis that was presented at this year's meeting of the European Association for the Study of the Liver, the group that responded better consisted of patients who had experienced a reduction in their fat content by MRI-PDFF. In other words, if a patient did not improve fat by MRI-PDFF, response to the drug was not as good as in those patients who responded by MRI-PDFF. Thus, MRI-PDFF responders had better histologic improvement.

G&H Could this drug potentially be used in all NASH patients?

ZY There is not a specific group of patients that I would say is absolutely not a candidate for future treatment with this type of drug. However, we need much more safety and efficacy data, especially in patients with cirrhosis. In fact, we do not have any data yet on MGL-3196's use in patients with cirrhosis. As mentioned, multiple pathways lead to the NASH phenotype. In this context, the question is how many patients with NASH that providers see in their clinical practices will fit the pathogenic profile that will respond to this drug. Additionally, I look at this drug as a potential component of combination regimens that are being considered for the treatment of NASH.

G&H How might MGL-3196 be used as part of a combination regimen for NASH?

ZY It is important to remember that NASH is not like liver diseases such as hepatitis C that are treated for a limited period of time and then cured. I think that NASH will more likely be treated like diabetes, which requires long-term management. It seems to me that the best treatment approach would be to use a combination of 2 or 3 drugs for perhaps 6 months or a year to treat NASH patients with significant fibrosis in order to reduce their steatohepatitis and improve their hepatic fibrosis, which is the most important predictor of mortality. Then, patients would be placed on some form of maintenance therapy for the long term. Such a management plan would need to target multiple different pathways in NASH (eg, the disease has inflammatory, metabolic, proapoptotic, and profibrotic pathways). I think that combining drugs that can potentially address different targets in one regimen will enhance the efficacy of treatment, which, ultimately, should lead to improvement of fibrosis as the most important surrogate of liver-related mortality. To me, that is the most important endpoint. There are a number of agents that could potentially be used in combination with a thyroid hormone receptor β agonist.

G&H How does MGL-3196 compare with the thyroid hormone receptor β agonist VK2809?

ZY It is probably unfair to compare the 2 drugs, which have a similar profile but have not been looked at head-to-head in a randomized, controlled trial. No liver biopsy data have been presented yet for VK2809 (Viking Therapeutics). On the other hand, it appears that VK2809 leads to strong fat reduction as determined by MRI-PDFF. However, it is unclear exactly how this drug will compare with MGL-3196 in terms of additional efficacy endpoints and safety profile. In my view, both drugs seem to be very promising as a part of combination regimens.

G&H What are the next steps of research?

ZY For MGL-3196, phase 3 clinical trial data are needed on efficacy as well as safety for more than 36 weeks of use. A phase 3 trial was initiated very recently.

In addition, greater awareness is needed in the general gastroenterology community, as well as in other specialties, regarding the importance of NASH as a liver disease and how it can impact patients' lives. NASH is rapidly becoming the most common liver disease worldwide, the most common indication for liver transplantation, and one of the leading causes of liver cancer. Treatment of NASH in the future will likely not be just the responsibility of one specialty; the disease will be managed by a team that will include gastroenterologists, hepatologists, diabetologists, nutritionists, exercise specialists, and, in some cases, bariatric surgeons and bariatric endoscopists.

Finally, I am convinced that we will not be able to address the increasing burden of NASH unless a public health approach is used to address its root causes, obesity and diabetes, which are becoming worldwide epidemics. Thus, parallel to the development of pharmacologic therapies, there has to be a push toward the national policies of government and perhaps even the World Health Organization to address the causes of NASH.

Dr Younossi has received research funds and/or serves as a consultant to Allergan, Bristol-Myers Squibb, Echosens, Gilead Sciences, Intercept, Merck, Novartis, Novo Nordisk, Quest Diagnostics, Siemens, Shionogi, Terns, and Viking.

Suggested Reading

Harrison SA, Guy CD, Bashir M, et al. In a placebo controlled 36 week phase 2 trial, treatment with MGL-3196 compared to placebo results in significant reductions in hepatic fat (MRI-PDFF), liver enzymes, fibrosis biomarkers, atherogenic lipids, and improvement in NASH on serial liver biopsy [abstract 0014]. Presented at the American Association for the Study of Liver Diseases meeting; November 9-13, 2018; San Francisco, CA.

Harrison SA, Moussa S, Bashir M, et al. MGL-3196, a selective thyroid hormone receptor-beta agonist significantly decreases hepatic fat in NASH patients at 12 weeks, the primary endpoint in a 36 week serial liver biopsy study. *J Hepatol.* 2018;68(suppl 1):S38.

Loomba R, Neutel J, Bernard D, et al. VK2809, a novel liver-directed thyroid receptor beta agonist, significantly reduces liver fat in patients with non-alcoholic fatty liver disease: a phase 2 randomized, placebo-controlled trial [abstract LB-4]. Presented at the American Association for the Study of Liver Diseases meeting; November 9-13, 2018; San Francisco, CA.