MASH IN FOCUS

Current Developments in the Management of Metabolic Dysfunction-Associated Steatohepatitis

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Fibroblast Growth Factor 21 Agonists for the Treatment of Patients With Metabolic Dysfunction-Associated Steatohepatitis

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G&H Why are fibroblast growth factor 21 agonists being studied for the treatment of metabolic dysfunction-associated steatohepatitis?

PN Fibroblast growth factor 21 (FGF21) agonists are being studied in metabolic dysfunction-associated steatohepatitis (MASH) because they are thought to be effective agents in managing multiple aspects of the pathogenesis of this condition. The value of a therapy impacting multiple pathways is that for a complex condition such as MASH, an effect may be produced that would otherwise be missed if only a single pathway was targeted. In other words, the targeting of multiple pathways is far more likely to be effective than the targeting of a single pathway alone.

Historically, there were concerns of tachyphylaxis, where the effect of the therapies may wane, although that does not appear to be a real consideration with the more recently tested compounds.

G&H How do these agents work?

PN FGF21 agonists act on a number of different receptors. The agents act on the 1c receptor, which is in the brain, reducing consumption of sweet foods or drinks and alcohol. FGF21 agonists also act on the 1c receptor in adipose tissue, where they increase insulin sensitivity, glucose uptake, and the secretion of adiponectin, resulting in a reduction in lipolysis. Additionally, these agents act on the 2c receptor in the liver, where they reduce lipotoxicity and the secretion of very low-density lipoprotein, as well as decrease de novo lipogenesis. FGF21 agonists also increase fatty acid oxidation. The sum total of these effects is a reduction in oxidative stress and, therefore, a decrease in liver injury, inflammation, and fibrosis. Finally, it is thought that FGF21 agonists also act on the 1c and 3c receptors in muscle, increasing insulin sensitivity there as well as the oxidation of free fatty acids and ultimately reducing oxidative stress.

G&H Are there any potential drawbacks or limitations to using this approach in MASH patients?

PN Historically, there were concerns of tachyphylaxis, where the effect of the therapies may wane, although that does not appear to be a real consideration with the more recently tested compounds. The other potential limitation involves the effects of FGF21 agonists on bone mineral density, where there appears to be a signal with some of these agents suggesting an increase in bone turnover. This may be relevant when considering that many patients

who are affected by this condition are women in particular who are postmenopausal.

G&H What efficacy and safety data are currently available on the FGF21 agonist efruxifermin?

PN The bivalent Fc-FGF21 analogue efruxifermin was shown to be effective in HARMONY, a multicenter, randomized, double-blind, placebo-controlled, phase 2b trial in patients with MASH and histologic stage F2 or F3 fibrosis. The drug was administered once a week via subcutaneous injection. The primary endpoint of at least 1 stage of fibrosis improvement without MASH worsening after 24 weeks of treatment was met in both dose groups (39% in the 28 mg efruxifermin group and 41% in the 50 mg efruxifermin group vs 20% in the placebo group). At week 96, 46% and 75% of patients in the 28 mg and 50 mg efruxifermin dose groups, respectively, had at least a 1-stage improvement in fibrosis without worsening of MASH, compared with 24% in the placebo group. Thus, augmentation of liver signals was seen with more prolonged treatment. The most frequent adverse events were diarrhea and nausea, and serious adverse events were reported in 4 patients in the 50 mg group. Five patients discontinued treatment owing to their adverse events.

In addition, in the randomized, placebo-controlled, double-blind, phase 2b SYMMETRY trial, efruxifermin was shown to be effective in patients with cirrhosis who were treated for 96 weeks, resulting in a reduction in fibrosis. However, statistical significance was not achieved for the primary endpoint of fibrosis improvement at 36 weeks in this trial.

G&H Could you discuss any recent research on the FGF21 agonist pegozafermin?

PN Another drug in development is pegozafermin, which is a long-acting glycopegylated FGF21 analogue that has been shown to be effective in patients with MASH and F2 to F3 fibrosis in a phase 2 trial. In the multicenter, double-blind, randomized, placebo-controlled, phase 2b ENLIVEN trial, treatment with pegozafermin led to improvements in fibrosis (22%, 26%, and 27% in the 15 mg, 30 mg, and 44 mg pegozafermin groups, respectively). Resolution of nonalcoholic steatohepatitis (now known as MASH) was achieved by 37%, 23%, and 26% of the 15 mg, 30 mg, and 44 mg pegozafermin groups, respectively. The drug was administered subcutaneously weekly or every 2 weeks, depending on the dose. Nausea and diarrhea were the most common adverse events. The drug is now being tested in patients in a phase 3 clinical trial with advanced fibrosis and also cirrhosis.

G&H What other FGF21 agonists are in development in MASH?

PN Efimosfermin (formerly BOS-580) is an engineered FGF21 variant with a long half-life. Administered monthly, this drug has been shown to improve markers of liver injury and to have a favorable safety profile in early-phase studies. In a multicenter, randomized, double-blind, placebo-controlled, phase 2a trial, 89% of patients who received efimosfermin for whom data were available experienced at least a 30% reduction in hepatic fat fraction at week 12. Sixty-six percent of patients experienced treatment-emergent adverse events, which were usually mild to moderate and spontaneously resolved. The most frequent treatment-emergent adverse events were gastrointestinal, namely nausea, vomiting, and diarrhea.

The tolerability profile of adding efruxifermin to glucagon-like peptide-1 receptor agonist therapy appeared comparable with the tolerability profile of either drug alone.

G&H Could you discuss research on the use of FGF21 agonists in combination with glucagon-like peptide-1 receptor agonists?

PN This is an interesting combination because it involves combining therapies that have different modes of action, thereby producing multiple impacts on the pathogenesis of the condition. There are a number of ongoing trials looking at these combinations, and those data should be reported soon, hopefully demonstrating their effectiveness. One trial that has reported so far was a double-blind, placebo-controlled, phase 2b study that examined the use of efruxifermin in patients with MASH, fibrosis, and type 2 diabetes who were taking a glucagon-like peptide-1 receptor agonist (semaglutide, dulaglutide, or liraglutide). The tolerability profile of adding efruxifermin to glucagon-like peptide-1 receptor agonist therapy appeared comparable with the tolerability profile of either drug alone. The addition also significantly decreased hepatic fat fraction as well as noninvasive markers of fibrosis in patients with MASH and type 2 diabetes.

G&H What are the next steps in research in this area?

PN The next steps with FGF21 agonists are completion of the phase 3 clinical trials in patients with significant and advanced fibrosis, as well as in patients with cirrhosis. Also, further results of combination studies of glucagon-like peptide-1 receptor agonists with FGF21 agonists are awaited. Another aspect that will be important is a better understanding of the safety profile of FGF21 agonists, in particular whether there is a true signal on bone mineral density.

Disclosures

Professor Newsome has served on the speakers bureau for Eli Lilly, Echosens, Ipsen, and Novo Nordisk and has received consulting fees from Akero, Aligos, Boehringer Ingelheim, Sagimet, Madrigal, Novo Nordisk, Shionogi, and 89bio.

Suggested Reading

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