NASH IN FOCUS

Current Developments in the Management of Nonalcoholic Steatohepatitis

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Drug Development for the Management of Nonalcoholic Steatohepatitis Cirrhosis

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G&H What is the prevalence of cirrhosis in patients who have nonalcoholic steatohepatitis?

NA Cirrhosis, or stage 4 fibrosis, is the last stage of the histologic progression of nonalcoholic steatohepatitis (NASH). Overall, it is estimated that between 1% and 3% of patients with nonalcoholic fatty liver disease, which includes those who have NASH, may have cirrhosis, depending upon the population. A hepatology clinic often has overrepresentation of cirrhosis vs a primary care setting, where patients typically have less cirrhosis.

G&H What is the disease burden of NASH cirrhosis?

NA Patients with NASH cirrhosis typically have the highest burden of disease in terms of developing major adverse liver outcomes (ie, ascites, hepatic encephalopathy, variceal bleeding, death, or need for liver transplant). Patients with compensated cirrhosis have the highest risk of developing these outcomes compared with patients with less-severe disease (eg, stage 2 or 3 fibrosis). Patients who have NASH cirrhosis are also at greater risk for developing hepatocellular carcinoma (HCC), which is why HCC screening is recommended in this patient population with imaging along with the serologic test alpha-fetoprotein every 6 months once a diagnosis of NASH cirrhosis is made.

G&H What is the current treatment for this patient population?

NA The US Food and Drug Administration (FDA) has not approved any treatments for NASH cirrhosis. There are currently no drugs that can reverse cirrhosis and regress stage 4 fibrosis to stage 3. Thus, the underlying cause is typically the focus of treatment for patients with NASH cirrhosis. Generally, for patients who have NASH and cirrhosis that is compensated without complications, lifestyle interventions and weight loss are recommended. However, such treatment is frequently not successful, which is why the search to develop drugs that can treat NASH cirrhosis is important. If patients start developing decompensating events such as ascites or hepatic encephalopathy, they can be treated with diuretics or with lactulose or rifaximin (Xifaxan, Salix Pharmaceuticals), respectively. Patients can also be screened for esophageal and gastric varices and treated accordingly.

G&H What are the main challenges of developing drugs for patients who have NASH cirrhosis?

NA NASH cirrhosis is advanced disease, so it is more difficult to regress stage 4 fibrosis to stage 3 than to regress stage 3 to stage 2. Drug safety is a concern because patients with cirrhosis can be at greater risk of developing drug-induced liver injury or hepatotoxicity. Within the context of a clinical trial, there may be more adverse outcomes in patients who have NASH cirrhosis, including the development of decompensation, which is part of the natural history of NASH. This makes trial design more complicated.

G&H What surrogate outcomes should be used when designing trials for the treatment of these patients?

NA Several surrogate outcomes can be looked at in clinical trials, including improvement on histology. This requires performing a liver biopsy both at baseline and at the end of treatment, and then determining histologic regression or fibrosis improvement by at least 1 stage (ie, examining the percentage of patients who regressed from stage 4 fibrosis to stage 3 or lower). This outcome has been used in several drug development programs. Data have shown that regression from stage 4 fibrosis to stage 3 is associated with a lower likelihood of developing hepatic decompensating events. Several noninvasive tests are currently available that can assess liver stiffness as a surrogate for liver fibrosis. Emerging data have suggested that liver stiffness, as determined by imaging tests, corresponds with liver outcomes. For example, higher liver stiffness predicts worse liver outcomes on magnetic resonance (MR) elastography. What still needs to be shown is that improvement in liver stiffness on MR elastography in patients who have NASH cirrhosis will also translate into improvement in liver-related outcomes. Several serologic tests can be used as secondary endpoints. In addition, the development of clinically significant portal hypertension can be measured by looking at patients who do not have esophageal varices at baseline and then determining what percentage of patients develop them. However, in my opinion, the outcome that doctors most want to see is fewer of the aforementioned major adverse liver outcomes.

Because these patients have the most advanced disease, combination therapy very likely will give them the best chance to respond to treatment and maximize efficacy.

G&H What trials are currently underway examining drugs for the treatment of patients with NASH cirrhosis?

NA A number of clinical trials are currently underway in patients with NASH cirrhosis. The farnesoid X receptor (FXR) agonist obeticholic acid (Ocaliva, Intercept) has been shown to lead to fibrosis improvement by 1 stage in a significant percentage of patients with NASH and stage 2/3 fibrosis. The REVERSE trial is currently examining the use of obeticholic acid in patients with NASH cirrhosis, and the results should be released by the end of this year. If the trial has positive results, obeticholic acid could be one of the first drugs to be approved to treat patients with NASH cirrhosis. The ALPINE 4 trial is studying the fibroblast growth factor (FGF)-19 agonist aldafermin (NGM Biopharmaceuticals) in patients with NASH cirrhosis, with the endpoint of improvement on histology as determined by improvement by 1 stage of fibrosis or more. This study is currently enrolling patients, and the results are expected next year. There is also an open-label trial on resmetirom (MGL-3196; Madrigal Pharmaceuticals), a thyroid hormone receptor beta agonist, in patients with NASH cirrhosis. The FGF-21 agonist efruxifermin (Akero Therapeutics) underwent a proof-of-concept study with a small sample size that showed that 33% of patients with NASH cirrhosis who received the drug experienced reversal of cirrhosis and regression from stage 4 fibrosis to stage 3 in 16 weeks. A dedicated NASH cirrhosis trial is expected to start with this therapeutic compound hopefully before the end of this year.

Another trial designed for patients with NASH cirrhosis that is currently in the enrollment phase involves belapectin (GR-MD-02; Galectin Therapeutics). To enroll in this study, NASH patients need to have cirrhosis, high liver stiffness, thrombocytopenia, and other signs of clinically significant portal hypertension (eg, splenomegaly); however, patients cannot have varices at baseline. Patients will undergo endoscopy at the end of the study to determine the percentage who developed varices. Thus, the primary endpoint is endoscopic as opposed to histologic.

Several studies are investigating combination therapies in patients with NASH cirrhosis. For example, one study is examining 3 drugs in combination: the glucagon-like peptide-1 agonist semaglutide (Ozempic, Novo Nordisk), the FXR agonist cilofexor (Gilead), and the acetyl-CoA carboxylase inhibitor firsocostat (Gilead). The study endpoint is improvement of fibrosis on liver histology.

G&H Do you think that combination therapy will likely be needed for the treatment of patients with NASH cirrhosis?

NA Because these patients have the most advanced disease, combination therapy very likely will give them the best chance to respond to treatment and maximize efficacy. As long as new safety signals are not introduced, I think that combination therapy is a good way to improve response. The best response rates in terms of resolution

of NASH, whether in cirrhotic or noncirrhotic patients, have ranged from 25% to nearly 60%, showing that there is room for improvement.

Most NASH drug programs are now thinking of developing their own cirrhosis trials, likely because of the alternative pathway that the FDA has given for obtaining full drug approval.

G&H Thus far, how safe do these drugs appear to be in this sick patient population?

NA Because this is a sick patient population, safety is very important. To date, these drugs have been well tolerated, and there have not been any concerning safety signals. One caveat is that I would not use obeticholic acid to treat patients with NASH cirrhosis who have signs of clinically significant portal hypertension.

G&H Are most of the NASH drugs in development being studied in patients who also have cirrhosis?

NA Most NASH drug programs are now thinking of developing their own cirrhosis trials, likely because of the alternative pathway that the FDA has given for obtaining full drug approval. Most of the NASH drugs currently in advanced stages of development are being evaluated in patients with fibrotic NASH but not cirrhotic NASH. The classic pathway for obtaining conditional approval of a drug was to show efficacy on histologic endpoints when performing an interim analysis at 12 or 18 months. In addition, patients had to be followed for 5 to potentially 7 years to look at the major adverse liver outcomes previously discussed. This past January, the FDA announced that to obtain full approval, a study could be performed based on histologic endpoints for NASH fibrosis, not cirrhosis, and that instead of following these patients for years, a separate trial could be designed dedicated to NASH cirrhosis to show improvement in major adverse liver outcomes. This change generated renewed interest in designing NASH cirrhosis clinical trials, and most drug developers who did not have an active NASH cirrhosis trial are now contemplating one and trying to put together protocols to help their program obtain full FDA approval.

G&H Have the many past drug failures in NASH provided any lessons for drug development in NASH cirrhosis?

NA Much has been learned from programs that failed in achieving their primary endpoints. We learned about the natural history of NASH cirrhosis and the rate of developing decompensating events. We also learned about the value of noninvasive tests in patients with cirrhosis. If 2 patients with cirrhosis have different liver stiffness measurements (eg, 20 kilopascals [kPa] vs 30 kPa), they will have different outcomes and prognoses. Even within the realm of cirrhosis, liver stiffness predicts worse outcomes as it increases.

In addition, we learned about other biomarkers, such as the Enhanced Liver Fibrosis score, which has prognostic value. We learned that some patients with NASH cirrhosis develop decompensation faster than originally thought. In one program, approximately 20% of patients developed major adverse liver outcomes within 2.5 years, which was faster than what was previously reported in the medical literature (3%-5% per year). Thus, there appears to be a fast-progressing subgroup of patients with cirrhosis.

We also learned that improving NASH cirrhosis on histology and regressing stage 4 fibrosis to stage 3 is associated with better outcomes. The data that led to this conclusion were generated by 2 studies by Gilead (one on selonsertib and the other on simtuzumab). Neither of these drugs showed efficacy, so the programs were terminated. When looking at patients who had improvement on liver biopsy, the likelihood of them developing liver-related events decreased almost 7-fold, validating the use of regression on histology as a potential endpoint in clinical trials.

G&H What are the priorities of research in terms of drug development for NASH cirrhosis?

NA Having effective and safe therapy is the ultimate goal. I think that identifying patients with compensated NASH cirrhosis is key. Many of these patients are undiagnosed, so it is important to find patients who are qualified for these trials, design proper trials that will show either histologic or endoscopic benefit, and ideally design large trials that will follow patients for a long period of time and show improvement in major adverse liver outcomes, overall mortality, and major adverse cardiac events. Small steps sometimes lead to large accomplishments, and focusing

initially on noninvasive tests and histologic improvement may be helpful. As we progress in these programs, it is important to use outcomes as the endpoint and make sure that patients are followed for a long period of time to be able to see enough of these outcomes to establish if a drug has beneficial effects over placebo.

Once patients with NASH cirrhosis are identified, they should be considered for clinical trials. In the near future, I would like to see trial design based on noninvasive tests such as MR elastography because such tests can indicate if a patient has cirrhosis or not without needing an invasive procedure such as biopsy. Investigators could assess response noninvasively and attempt to correlate it with outcomes. I think this would increase the number of patients enrolled in studies, avoid complications related to liver biopsy, and expedite drug development for this highly susceptible patient population with the highest unmet need for treatment.

Disclosures

Dr Alkhouri has served as an advisory board/review panel member for 89bio, Echosens, Enyo, Gilead, Intercept, LG Chem, Perspectum, Pfizer, and Zydus; has received grant/research support from 89bio, Akero, Allergan, Bristol Myers Squibb, Corcept, Galectin, Genentech, Gilead, Hepagene, Intercept, Madrigal, NGM Biopharmaceuticals, Novo Nordisk, Pfizer, Poxel, Viking, and Zydus; and has been a speaker for AbbVie, Alexion, Echosens, Gilead, and Intercept.

Suggested Reading

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