NASH IN FOCUS

Current Developments in the Management of Nonalcoholic Steatohepatitis

Section Editor: Stephen A. Harrison, MD

Emerging Treatments for Patients With Nonalcoholic Steatohepatitis

Vlad Ratziu, MD, PhD
Professor of Hepatology
Sorbonne Université
Hôpital Pitié - Salpêtrière
Institute of Cardiometabolism and Nutrition
Paris, France

G&H What have been the challenges of drug development in nonalcoholic steatohepatitis?

VR One challenge has been that drug trials need to be very long because the natural course of nonalcoholic steatohepatitis (NASH) is rather slow, and histologic changes, especially clinical improvements, may take time to occur when patients are on therapy. There are also no easy surrogate markers that can be measured in order to understand whether a compound is effective in a clinical trial.

Another challenge has been that NASH trials require liver biopsy to be performed at the beginning of the study as well as at the end of the study; thus, liver biopsy is used to determine trial eligibility as well as the efficacy of a drug, which is defined histologically. Requiring each trial participant to undergo an invasive procedure repeatedly has made recruitment more difficult. This requirement has also made it hard to find clinical trial sites that are familiar with such procedures and can perform them at a high enough volume for trials to be completed quickly.

It has also been challenging that, in later-phase clinical trials, the demonstration of efficacy has relied on histologic assessment. Histologic assessment is associated with a number of drawbacks, including pathologic variability among readers, variability in interpreting histologic definitions, and use of a method that has intrinsic sampling variability.

G&H What lessons have been learned that have allowed recent compounds to advance further in development than in the past?

VR We have learned that for a development program to be successful, it is important not to go fast and skip any steps; it is necessary to go step-by-step and demonstrate extensively the efficacy of a drug in earlier phases before embarking on a large late-phase trial that requires liver biopsies to be performed several times.

Another lesson that has been learned is that NASH trials are still feasible despite their difficulties and the long duration they require. Several very large (>2000 patients) phase 3 trials have been completed. There are currently several very promising molecules with multiple pleiotropic effects that can be beneficial for patients with NASH, and the pipeline is very robust and vibrant for NASH compounds. The first positive results from these trials are now starting to be seen and the first fruits of this very long development process are being harvested.

G&H What appears particularly exciting about obeticholic acid and resmetirom, which are furthest along, and what is the likelihood of approval for each?

VR What is exciting about obeticholic acid (Ocaliva, Intercept Pharmaceuticals) is that this compound has repeatedly shown histologic benefit, particularly in terms of fibrosis reversal, both in the phase 2b FLINT trial as well as in the phase 3 trial's first interim analysis and, later on, extended analysis. It is especially reassuring for the drug to demonstrate an antifibrotic effect repeatedly and in different patients. Also, the antifibrotic effect in the phase 3 trial of obeticholic acid has been shown using

different pathologists, minimizing the possibility of inter-reader variability.

Another important aspect is that many patients have now been treated for a long time with this molecule. More than 8000 patients have been exposed to obeticholic acid. The side effects have now been well established, and most can be easily controlled for. At least in the NASH population, the safety profile is largely reassuring, which is good.

This drug has the ability to induce fibrosis reversal and delay progression of fibrosis, increasing the proportion of patients who undergo reversal of fibrosis and reducing the proportion of patients who experience worsening of fibrosis. Thus, obeticholic acid appears to be a very promising novel therapy for NASH, which these patients have completely lacked. I am confident that the clinical need for a drug such as obeticholic acid would be a major argument in favor of its approval by regulatory authorities. Most of the side effects can be identified early on, and some of them can be mitigated. Even if a small number of patients have tolerability issues, that should not prevent the larger number of patients from obtaining access to a drug that might benefit them.

As for resmetirom (Madrigal Pharmaceuticals), what is exciting is its innovative mode of action, which appears to be limited to and operated in the liver itself, hence resulting in a very good safety and tolerability profile. Clear histologic benefits of the most distinctive features of steatohepatitis (ie, disease activity, fibrosis) have been demonstrated in a very large phase 3 trial. Other collateral benefits, such as improvement in the lipid profile, have also been shown repeatedly. Therefore, this drug could have a significant beneficial impact on patients with NASH, which is very encouraging. Given the current data, I do not see any reason that a drug such as resmetirom would not be made available for patients with NASH.

Nevertheless, it should be noted that there is clearly a proportion of patients with NASH who do not respond to any of the compounds that have reached phase 3 development based upon the histologic endpoints currently being used. Thus, more work needs to be performed to identify nonresponders early on and to understand whether patients who do not respond to one drug might benefit from treatment with a different compound, whether alone in monotherapy or in combination with the initial drug.

G&H Beyond obeticholic acid and resmetirom, what other NASH therapies are in phase 3 development?

VR The glucagon-like peptide-1 (GLP-1) agonist semaglutide (Ozempic, Novo Nordisk) is in a phase 3 trial and has the advantage of producing substantial weight loss. Several GLP-1–based therapies that are dual GLP-1–glucose-dependent insulinotropic polypeptide or GLP-1–glucagon agonists will soon enter phase 3 trials (eg, tirzepatide [Mounjaro, Lilly], cotadutide [AstraZeneca]). Also, pan–peroxisome proliferator-activated receptor agonists such as lanifibranor (Inventiva) are in phase 3 development, as are inhibitors of lipogenesis such as aramchol (Galmed Pharmaceuticals).

G&H Given the large number of drugs in phase 2 development, which mechanisms appear to be the most exciting?

VR That is difficult to determine. Many of the mechanisms are exciting from a pathogenesis point of view; however, even if the drugs make sense biologically, they may fail to show clinical or histologic efficacy. Therefore, even if there is excitement about inhibiting a particular pathway of injury, it is still necessary to wait and see whether that mechanism will be sufficient. There is no guarantee of effective histologic efficacy because of the many redundancies among the numerous pathways in the pathogenesis of NASH.

> The major challenge in future drug development is replacing histologic endpoints as defined by conventional microscopy.

Having said that, clearly the drugs that induce weight loss can be extremely useful and are also utilized for other medical benefits. Drugs that block the necroinflammatory process associated with steatohepatitis and inhibit lipotoxicity in the liver might also be very exciting. Drugs that inhibit de novo lipogenesis could prove to be particularly useful as well. It has been disappointing that most, if not all, of the purely antifibrotic drugs that have been tested have not shown efficacy. Further research is certainly needed to devise pharmacologic agents meant to interfere with the fibrogenic process, which could also be efficacious on histologic endpoints.

G&H Why does combination therapy make sense for patients with NASH?

VR Combination therapy makes sense for a number of reasons. One reason is the complexity of the pathogenic

pathways that are in play for NASH. Another reason is that the rate of response to any particular agent, including the 2 most advanced agents, is still relatively low (<33%). As with other complex, metabolically driven diseases such as arterial hypertension and diabetes, NASH will need to be treated with multiple agents, whether from the start or sequentially or because the beneficial effect of a single agent might become insufficient after some time.

G&H What types of agents might form the ideal combination therapy for patients with NASH?

VR A theoretical answer is that the combination should ideally be able to control for metabolic dysfunction and, at the same time, have a direct impact on the lipotoxic/inflammatory process in the liver with, if possible, a direct inhibition of the fibrogenic process. Clinically speaking, at least in patients who are heavily overweight or obese, drugs that induce weight loss would be very important if their efficacy is not only mediated by weight loss.

G&H What have trials of NASH combination therapies reported thus far?

VR Interestingly, the early combination trials all had negative findings. However, these findings could be explained by the fact that the individual components of those combinations were not particularly effective. There are now ongoing trials combining fibroblast growth factor–21 agonists with GLP-1–based agonists, which will be particularly interesting to follow. These trials will likely produce positive findings because each component of the combination has shown efficacy on its own.

G&H Are there any promising nonpharmacologic treatments under investigation for patients with NASH?

VR Bariatric surgery is being studied because it can clearly have a beneficial impact on the liver's condition along with other overall survival benefits and metabolic clinical benefits. However, this invasive procedure is reserved for a relatively small population of patients with NASH. Endoscopic procedures such as endoscopic duodenal mucosal resurfacing or intragastric balloons meant to induce weight loss are also being studied.

G&H Are there any additional challenges that may be seen in future drug development for NASH?

VR The major challenge in future drug development is replacing histologic endpoints as defined by conventional microscopy. One possible option may be using noninvasive biomarkers that could demonstrate short- and long-term clinical benefits. Another possibility may be using artificial intelligence–based digital pathology, which allows for an automated, quantitative, reproducible measure of histologic changes in the liver, including early patterns of change that are not visible through conventional microscopy.

G&H How close is the use of such noninvasive tests?

VR I think they are still at least several years away. One of the major challenges is that it is not yet possible to demonstrate that changes in noninvasive biomarkers caused by a pharmacologic intervention truly reflect changes in histology and predict clinical outcomes. This may still take 5 to 10 years. It may be that a faster way of achieving this is to use histology-based assessment of efficacy measured through artificial intelligence–based digital pathology. In the end, a combination of both noninvasive biomarkers and digital pathology could also be envisioned as a very thorough way of measuring changes in liver health.

Disclosures

Professor Ratziu has done consulting for Novo Nordisk, Terns Pharmaceuticals, Madrigal Pharmaceuticals, ENYO Pharma, Poxel, Bristol Myers Squibb, Intercept Pharmaceuticals, NGM Bio, and Pfizer. He has also received research grants (to his institution) from Gilead Sciences and Intercept Pharmaceuticals.

Suggested Reading

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