NASH IN FOCUS

Current Developments in the Management of Nonalcoholic Steatohepatitis

Section Editor: Stephen A. Harrison, MD

The Future of Treatment for Nonalcoholic Steatohepatitis

Michael Charlton, MBBS
Professor of Medicine
Director, Center for Liver Diseases
The University of Chicago Medicine
Chicago, Illinois

G&H How has nonalcoholic steatohepatitis traditionally been treated?

MC No therapies have yet been approved by the US Food and Drug Administration (FDA) for the treatment of nonalcoholic steatohepatitis (NASH). Thus, therapy has mostly been lifestyle-based, often directed at achieving weight loss with exercise and a diet that is low in cholesterol, saturated fats, and fructose, such as the Mediterranean diet. However, most patients find lifestyle interventions difficult to sustain long term.

G&H Besides lifestyle interventions, have pioglitazone and vitamin E been used much?

MC In surveys of practitioners who treat people with NASH and other forms of fatty liver disease, pioglitazone has not been used very much, despite having been shown to be effective in high-quality prospective studies, including ones published in *The New England Journal of Medicine*. The possible risk of cancer as well as the side effect of weight gain have limited the use of pioglitazone in this patient population. As for vitamin E, it can be effective, but there is some concern about long-term prostate cancer risk and insulin resistance.

G&H Why are so many different targets and drugs currently being investigated for the treatment of NASH?

MC NASH involves different aspects of several processes, including inflammation, fibrosis, and fat or lipid accumulation. Some drugs operate on all 3 of these important elements of liver injury, while other drugs are very specific to just 1 element, reflecting the complexity of the disease. For example, drugs can target mechanisms that are important in lipid accumulation, such as the ability of liver cells to form new fat, or de novo lipogenesis, in the liver. Other drugs have been targeted at decreasing inflammation. One such drug is selonsertib (Gilead), which inhibits a very specific pathway known as apoptosis signaling-regulating kinase 1. Selonsertib is a fairly targeted anti-inflammatory drug, although it turned out not to be effective in late-phase clinical trials. Other drugs can have a more global effect. The NASH drug that is the most advanced in terms of clinical trial research is the farnesoid X receptor (FXR) agonist obeticholic acid (Ocaliva, Intercept Pharmaceuticals). This drug acts on a nuclear receptor that has very broad effects on lipid metabolism, inflammation, and, subsequently, fibrosis. Obeticholic acid recently finished its phase 3 study and is currently under review by the FDA.

G&H What are some of the most promising drugs in development for the treatment of NASH?

MC There are many promising drugs, but the most important ones to consider are those in phase 3 development. As previously mentioned, obeticholic acid is the furthest along in development and could, theoretically, receive approval by the FDA soon. Also promising is the peroxisome proliferator–activated receptor (PPAR) agonist elafibranor (GFT505, Genfit), which will soon report

interim phase 3 results. This drug has very broad effects involving both lipid and glucose metabolism, as well as downstream effects on inflammation and fibrosis. Other promising drugs in phase 3 trials are aramchol (Galmed Pharmaceuticals), which is a stearoyl-CoA desaturase 1 inhibitor, and cenicriviroc (Allergan), which likely has primarily anti-inflammatory effects. Among thyroid hormone receptor β agonists, MGL-3196 (Madrigal Pharmaceuticals) is furthest along and looks promising. However, there are no data on longer-term safety or the impact on clinical endpoints, such as liver failure, involving any of the drugs in advanced development.

In addition, one of the most interesting therapeutic approaches, in my opinion, involves drugs that are well established in other indications that are common among patients with NASH. An example involves glucagon-like peptide-1 (GLP-1) agonists and sodium-glucose cotransporter-2 (SGLT2) agonists, which are used in many patients for diabetes and promote weight loss. SGLT2 agonists are cardioprotective as well.

G&H Which other NASH drugs are being studied that target lipid or glucose metabolism, and why are these approaches important?

MC I think the best inhibitor of lipid metabolism is actually weight loss. Drugs that act on GLP-1 lead to weight loss in the range of 5% to 15%, depending on the patient, agent, and dose. With weight loss, there is also delipidation or loss of liver fat. Drugs that directly affect liver fat formation include acetyl-CoA carboxylase (ACC) inhibitors. Several are currently being studied, including firsocostat (Gilead), which is relatively advanced in clinical development. Other agents that inhibit lipogenesis within the liver, including through decreasing the activity of ACC, are fibroblast growth factor (FGF) 19 and 21 agonists. A recent phase 2 study in over 70 patients taking aldafermin (NGM Bio), an injectable FGF19 agonist, showed encouraging histologic effects. Aldafermin is the first drug to demonstrate statistically significant, even if numerically modest, effects on the FDA composite regulatory endpoints of fibrosis improvement and resolution of NASH when compared to placebo. Aldafermin has previously been reported to produce dyslipidemia (increased low-density lipoprotein and triglyceride-rich lipoprotein levels), effects that will need to be followed closely in larger studies, as cardiovascular disease is the most common cause of mortality in patients with NASH, far outpacing liver disease.

In terms of targeting glucose metabolism, some of the most popular agents are currently PPAR-γ and mixed agonists. These include pioglitazone, as well as several drugs in development that have some of the properties of pioglitazone in terms of glucose and anti-inflammatory effects but without some of the side effects such as weight gain.

G&H Which agents are being studied to specifically target fibrosis in NASH patients?

MC It is important to keep in mind that turning off liver fat formation slows down or stops liver inflammation, which leads to fibrosis in the liver. Thus, one of the drugs that has been the most successful at producing antifibrotic effects is obeticholic acid. Even though this drug is not a direct antifibrotic, it was shown to have an antifibrotic effect in a clinical trial with biopsies. One of the trial endpoints was reversal of fibrosis by at least 1 stage without worsening of NASH, which obeticholic acid achieved at a frequency that was significantly higher than that of the placebo control group. A number of direct antifibrotics, such as simtuzumab (Gilead), have been studied in phase 2a or 2b trials but have not been successful.

G&H Are any immune modulators currently being investigated to treat NASH patients?

MC There are a handful of immune modulators, including the anti-CD3 monoclonal antibody foralumab (Tiziana Life Sciences), which is in phase 1 development, and several c-Jun N-terminal kinase antagonists, which are currently in phase 2 development. However, in terms of approaches, immune modulation has been secondary; reducing liver fat, and thereby reducing inflammation, has been the more common approach.

G&H What are the most significant challenges of developing NASH drugs?

MC One challenge is that clinical trial endpoints have been inconsistent. Another is that histologic endpoints are inherently imprecise with frustratingly poor reproducibility when different pathologists look at the same biopsy or even when expert pathologists look at the same biopsy twice. This introduces a level of uncertainty and reproducibility that requires large numbers of patients to determine whether a drug is working.

In addition, there is tremendous variability in the placebo response in part, I suspect, because the nutritional approach among sites and providers varies enormously. In my opinion, people who receive effective nutritional advice for reducing cholesterol and fructose intake, for example, are more likely to experience a benefit than people who are not receiving much nutritional education.

The lack of accepted and validated noninvasive tests and, consequently, the continuing need for biopsies make up another challenge. The FDA needs to continue to work

with investigators and sponsors in developing noninvasive tests that can be used at least in phase 2a and 2b portions of clinical trials, and perhaps even phase 3 portions, once tests are shown to be predictive of outcomes or to correlate with histology.

> The most likely way forward is combination therapy with different mechanistic approaches.

Finally, artificial intelligence and software analysis of biopsies are now emerging as more reproducible ways of assessing histologic response. These emerging technologies should be rapidly adopted to help improve ease of patient participation in studies, as well as the interpretability of study results.

G&H Are there any other reasons that improvements are needed regarding NASH endpoints?

MC NASH is a major health concern. It is the most common indication for liver transplantation for women and the second-most common for men. It is also the most common cause of liver cancer, which is the most rapidly increasing type of cancer in the United States. We do not have the luxury of time to use outdated methodologies to assess the efficacy of drugs. We need to figure out a better way to assess whether a drug is safe and has a good chance of being effective so that patients can have access to treatments that can bend the curve of their disease and move them closer to health.

G&H What are some promising nonpharmacologic treatment approaches currently being studied in NASH patients?

MC An interesting treatment is duodenal mucosal resurfacing, in which patients can obtain many of the benefits of weight loss surgery by bypassing the duodenum. A company has a technique in which heat is used to ablate the duodenal surface, and the effects last for at least a year. Encouraging data on fatty liver disease patients were recently presented.

It should also be noted that research is still being conducted on dietary therapy for NASH, particularly involving coffee and the Mediterranean diet.

G&H Will combination therapy likely be needed for the treatment of NASH?

MC In my opinion, combination therapy will be essential. The data that are available on monotherapies have been encouraging, but not impressive. The majority of patients have not achieved histologic endpoints, even in the most successful studies to date. The most likely way forward is combination therapy with different mechanistic approaches. As previously mentioned, obeticholic acid may be approved soon. I could foresee combining that drug with one that has a different mechanism, such as a thyroid hormone receptor β agonist or a GLP-1 agonist. Drugs that are known to be safe and effective in their own right would also be appealing in combination.

G&H Are you aware of any trials of combination therapies currently underway?

MC Yes. There is an increasing number of companies and studies that are incorporating combination therapies. For instance, Gilead has tried several of its drugs in combination. There did seem to be a benefit to adding, for example, an FXR agonist to an ACC inhibitor. This approach might be investigated further. Terns Pharmaceuticals also has a pipeline of different agents that are being studied in combination, such as an FXR agonist with a thyroid hormone receptor β agonist.

G&H In your opinion, what would be the ideal combination?

MC Currently, I think the agent most likely to emerge as a cornerstone therapy is obeticholic acid because it is the furthest along. Among drugs with good datasets leading up to phase 3 investigation, I think that the thyroid hormone receptor β agonist MGL-3196 and the injectable FGF19 agonist aldafermin look encouraging. I also think that the GLP-1 agonist semaglutide (Ozempic, Novo Nordisk), which is approved by the FDA as an oral agent for diabetes and weight loss, is also very appealing in combination. In addition, there are several novel therapies in preclinical stages that are intriguing, so I think NASH treatment will be increasingly interesting over time.

G&H How long will NASH treatment likely be needed?

MC Treatment will likely be needed for years. If a patient with, for example, stage 3 fibrosis (ie, bridging fibrosis, which is a relatively advanced disease) takes a drug for 1 year, there are 3 possible outcomes from the liver disease perspective. In the first scenario, the patient could be a

little worse after a year of treatment, but it would need to be considered whether the patient would have been even worse without taking the drug. In the second scenario, the patient could appear the same after treatment, but it would need to be considered whether the drug prevented the patient from becoming worse. Finally, the patient could be better after treatment. In each of these 3 scenarios, a case could be made for continuing therapy for a disease that takes years to progress. An increasing body of evidence points to a fairly rapid return of liver inflammation markers toward pretreatment levels when treatment is stopped. If liver fibrosis and scar tissue are reversed, it is not known how long that reversal lasts and how long a particular therapy is needed. I suspect that NASH therapies will be used for similar durations as therapies for diabetes. These issues will keep the field busy for years to come.

G&H How will the effectiveness of these new treatments be monitored?

MC No one has an appetite for serial biopsies, so we will have to move toward noninvasive tests. These tests could be transient elastography with FibroScan (Echosens), magnetic resonance imaging with proton density fat fraction, magnetic resonance elastography, or a blood test (eg, the Enhanced Liver Fibrosis score). Two large groups of researchers, one from Western Europe and one from North America, are currently examining blood-based biomarkers that might identify people in terms of their severity of disease, as well as their response to therapy over time.

G&H What are the priorities of research?

MC The first priority is the identification of a biomarker that predicts histology and outcomes, with the latter type of prediction being more important than the former. Knowing that a patient will have a poor outcome, such as a liver-related event or death from cardiovascular disease, is vital. The second priority is identifying agents that can change those outcomes to the benefit of the patient. The third priority is developing better screening and surveillance methods to identify people with NASH and, among those millions of people, the ones who are at the highest risk of progression. Only a small proportion of those patients have been identified. Most people with NASH and fatty liver disease are currently undiagnosed.

Dr Charlton has served as a consultant for Novartis, Pfizer, Gilead, Intercept Pharmaceuticals, Metacrine, Siemens, NGM Bio, ProSciento, Celgene/Bristol Myers Squibb, Fractyl, HistoIndex, and Terns Pharmaceuticals. He has received research support from Novartis, Pfizer, Gilead, Intercept Pharmaceuticals, and Celgene/Bristol Myers Squibb

Suggested Reading

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