

ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

Section Editor: Eugene R. Schiff, MD

Overview of Current and Emerging Therapeutic Approaches to Nonalcoholic Steatohepatitis



Stephen A. Harrison, MD
 Medical Director, Pinnacle Clinical Research
 San Antonio, Texas
 Visiting Professor of Hepatology
 Radcliffe Department of Medicine
 University of Oxford, Oxford, United Kingdom

G&H What role do diet and exercise play in the treatment of nonalcoholic steatohepatitis?

SH Diet and exercise are the cornerstone of therapy for patients with fatty liver disease, whether it is nonalcoholic fatty liver or the more advanced form of the disease, nonalcoholic steatohepatitis (NASH), which is characterized by hepatic steatosis, inflammation, and ballooning degeneration or dying hepatocytes with or without fibrosis. It is well known that a weight loss of 10% improves all aspects of NASH from the easiest component to improve (fat) to the hardest (fibrosis).

Based upon the available data, it appears that eating a relatively hypocaloric diet (ie, reducing daily caloric intake by at least 500 calories per day) and augmenting that with 3 to 4 days of exercise (both aerobic and anaerobic) for approximately 1 hour each time has a significant effect on NASH. However, the ideal dietary composition for NASH patients as well as the ideal amount, type, and duration of exercise are unclear. Some research has suggested that patients on a Mediterranean diet (ie, a diet rich in polyunsaturated and monounsaturated fatty acids) tend to do better than patients on a low-fat diet, but more research is needed. My colleagues and I recommend that NASH patients limit their processed carbohydrate intake. I routinely tell patients to avoid foods such as potatoes, rice, bread, tortillas, pasta, pizza, and chips and, if they must have those foods, to limit them to 1 meal per week and try to stick to their diet the rest of the time. In addition, patients should eliminate fructose-containing

beverages. If these steps are followed, I have found that patients lose weight relatively quickly and find themselves with more energy and a reduced appetite. They do not

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develop the insulin surges that routinely occur when carbohydrates are eaten, which make patients tired in the afternoon and do not fill them up.

G&H Are both dietary modification and exercise needed, or would dietary modification possibly be enough?

SH Dietary modification alone would probably be enough, which is good news for people who are restricted in their ability to exercise (eg, patients with rheumatoid arthritis or severe osteoarthritis who are limited in what they can do for exercise). However, my colleagues and I try not to have NASH patients implement dietary modification or exercise in isolation. We tell patients that a lifestyle change is needed, even if exercise consists of small

steps, such as getting into the habit of taking the stairs instead of an elevator or parking their car further away from an entrance so that they have to walk an extra 100 or 200 steps. With these new habits, they are increasing their exercise without realizing it.

G&H Is lifestyle modification usually sufficient for the treatment of NASH?

SH It appears that achieving and maintaining a 10% weight loss is sufficient for most patients to experience histopathologic improvement of their liver disease, at least for patients who do not have cirrhosis. Thus, achieving and maintaining a 10% weight loss remains the goal for every overweight or obese NASH patient. The problem is that very few people are able to achieve a 10% weight loss, and even fewer patients are able to maintain it. Thus, pharmacotherapy has to be considered to augment weight loss and lifestyle change in the majority of NASH patients.

G&H Does vitamin D or E supplementation have a role in the management of NASH?

SH It is very common for patients with fatty liver to be vitamin D–deficient. However, there have been no well-designed, prospective, randomized, clinical trials to date that I am aware of that have shown that vitamin D supplementation has an impact on the histopathology of NASH.

Alternatively, and somewhat surprisingly, vitamin E at doses up to 800 IU per day has shown a benefit on the histopathology of patients with NASH. This was seen in the PIVENS trial, which compared vitamin E to pioglitazone and placebo. However, vitamin E supplementation has not been studied in cirrhotics or diabetics, so more research is needed. In addition, there has been some concern because data have suggested that all-cause mortality is increased in patients who take long-term vitamin E supplementation; also, a large prospective trial showed a possible increased risk for prostate cancer. However, it should be noted that the number needed to treat to develop prostate cancer was quite high. Thus, the odds of prostate cancer occurring in an individual patient are quite low, although patients should be made aware of this possibility.

G&H What types of pharmacologic approaches are currently in the pipeline for treatment of NASH?

SH There has been a tidal wave of new therapies for NASH that have been coming into clinical trials over the past several years. Five phase 3 trials are currently

underway, and many more compounds are in phase 2 trials. This speaks to the complex pathogenesis of fatty liver disease and the multiple different pathways that are

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involved in the activation and propagation of this disease. The main components of fatty liver are steatosis, necroinflammation, and fibrosis, and there are currently multiple drugs in development that target all of those components. Some of these drugs are direct antifibrotic agents, and others are antimetabolic agents that target steatosis and the necroinflammatory pathway together. Other drugs are purely anti-inflammatory.

Interestingly, we have recently learned that the abnormalities seen on liver biopsy from fatty liver are dynamic and can each change relatively quickly with appropriate intervention. According to this year's European Association for the Study of the Liver (EASL) meeting, one drug (NGM282, NGM Bio) was studied for 12 weeks with paired liver biopsy at baseline and at week 12, and showed that all of the components of fatty liver (fat, inflammation, ballooning, and fibrosis) can be reduced during that short time period. The treatment landscape for fatty liver disease will be revolutionized if we learn that targeting the drivers of fibrosis has a positive and profound impact on fibrosis itself and see that a fibrosis benefit does not necessarily require waiting years. This is important because, currently, fibrosis portends the worst prognosis; once cirrhosis is achieved, morbidity and mortality from fatty liver disease increase.

G&H What pharmacologic approaches are currently under phase 3 investigation for the treatment of NASH?

SH We have learned that bile acids play a role in fatty liver disease. One of the ways that farnesoid X receptor (FXR) agonists work is by stimulating fibroblast growth factor (FGF) 19, which inhibits CYP7A1, the rate-limiting enzyme that converts cholesterol to bile acids.

This inhibition can be determined by measuring C4. One of the ways to assess target engagement is to measure C4 levels. We learned at the recent EASL meeting that bile acids are associated with the severity of both NASH and fibrosis. Thus, it makes sense that reducing the bile acid pool may have a positive impact on fatty liver disease. A drug that uses this mechanism is the FXR agonist obeticholic acid (Ocaliva, Intercept Pharmaceuticals), which is in phase 3 trials.

Another drug in phase 3 development is elafibranor (GFT505, Genfit), which is a peroxisome proliferator-activated receptor (PPAR) α - and δ -agonist. Essentially, this agent modulates steatosis and the metabolic parameters of fatty liver disease. It increases oxidation of fatty acids and decreases the development of cholesterol in the liver, de novo lipogenesis, and several other pleiotropic mechanisms.

There are two phase 3 studies being conducted on the apoptosis signal-regulating kinase 1 (ASK1) inhibitor selonsertib (Gilead). One study is in F3 fibrosis patients (ie, patients who have bridging fibrosis and who are at high risk for cirrhosis). The other study comprises cirrhotic patients who have not yet developed hepatic decompensation; these patients have evidence of cirrhosis but still essentially function as normal individuals. ASK1 inhibition works through reactive oxygen species-mediated signaling to target inflammation and fibrosis.

Finally, the other NASH drug in phase 3 development is the C-C chemokine receptor type (CCR) 2/5 antagonist cenicriviroc (Allergan). CCR 2 and 5 promote recruitment of macrophages following liver injury and activation of collagen-producing hepatic stellate cells. This phase 3 study is essentially just looking at fibrosis, not the improvement of NASH. Likewise, the studies on the ASK1 inhibitor are just looking for improvement in fibrosis. In contrast, the obeticholic acid and elafibranor studies are looking for either resolution of NASH or a fibrosis benefit.

G&H What phase 2B studies are currently being conducted on NASH drugs?

SH One phase 2B study involves the FGF21 agonist BMS-986036 (Bristol-Myers Squibb). Like the ASK1 inhibitor, this agent is being studied in 2 different cohorts of patients: an F3 population and a well-compensated cirrhotic NASH population. Fibrosis benefit, not NASH resolution, serves as the primary endpoint.

Another phase 2B study focuses on the antidiabetes drug semaglutide (Ozempic, Novo Nordisk), which is the second generation of the antidiabetes drug liraglutide (Victoza, Novo Nordisk). A relatively large phase 2B trial is being conducted in NASH patients with

F1 to F3 fibrosis with a primary endpoint of NASH resolution with no worsening of fibrosis. This drug lowers hemoglobin A1C, which is often a problem in NASH patients, and induces weight loss. The diabetes trials reported a mean weight loss of approximately 13%, which meets the 10% weight loss goal associated with improvement in NASH patients.

A different treatment approach under phase 2B investigation involves MSDC-0602 (Cirius Therapeutics), the mitochondrial target of the thiazolidinedione modulator that is undergoing a large 1-year trial in F1 to F3 fibrosis patients with NASH. Essentially, this agent modulates the molecule that takes pyruvate into the mitochondria. By doing this, it is thought that PPARs can be upregulated in a positive way without having any of the related side effects. In particular, PPAR γ (pioglitazone) is usually associated with weight gain and, potentially, small bone fracture risk and unmasking of diastolic dysfunction in patients. MSDC-0602 may offer the positive effects of pioglitazone without the side effects.

In addition, a phase 2B trial is being conducted on the antiapoptotic drug emricasan (Conatus) in F1 to F3 fibrosis NASH patients with an endpoint of resolution of NASH or fibrosis. This drug is also being studied in two phase 2B trials in cirrhotic patients examining various severity levels of cirrhosis. The primary endpoint of these trials is hepatic venous pressure gradient (HVPG) drop (a marker of portal hypertension), not necessarily resolution of NASH by biopsy.

Recently, phase 2A/B data were presented on MGL-3196 (Madrigal), a thyroid hormone receptor β agonist. This agent is mainly localized to the liver and has only β activity (not α activity). Fatty liver patients are typically relatively hypothyroid. This drug helps the liver convert T4 to T3, thus increasing β oxidation of fatty acid and burning off fat. Study results are expected very soon, and based on these findings, the US Food and Drug Administration (FDA) may allow MGL-3196 to enter phase 3 development.

Phase 2B data were also recently presented at the EASL meeting for the antifibrotic drug GR-MD-02 (Galectin), which was administered in 2-week infusions in approximately 160 patients. This study showed that if patients did not have esophageal varices or did not have clinically significant portal hypertension by HVPG measurement at baseline, then the drug had a benefit on HVPG. The manufacturer is heading to the FDA to present a phase 3 plan but needs additional funding.

A drug that recently finished a large phase 2B trial of over 200 patients is aramchol (Galmed); study results should be released within the next several months. This agent is a synthetic fatty acid/bile acid conjugate that functions as a partial inhibitor of stearyl-CoA

desaturase 1 and upregulates the ABCA1 reverse cholesterol transporter.

G&H Are there any different treatment approaches being studied in phase 2A trials?

SH There are a plethora of phase 2A studies looking at various treatment approaches, including combination therapies incorporating different mechanisms of action to increase the synergistic effects of the drugs on fatty liver disease. For example, Gilead is currently studying several therapies in combination. Data were presented at the recent EASL meeting showing that, at 12 weeks, the drugs were safe to combine. The data did not show significant synergistic effects on noninvasive biomarkers, but that was not the purpose of the study. A 1-year phase 2B study with paired liver biopsies is ongoing looking at these drugs in different combinations.

Another treatment approach in phase 2A development involves an FGF19 analogue (NGM282) that is nontumorigenic and is administered in a daily injection (3 mg). Data from 19 patients on open-label NGM282 were presented at the recent EASL meeting showing significant improvements in magnetic resonance imaging–proton density fat fraction. Indeed, 60% of patients normalized liver fat completely at 12 weeks. Liver biopsies also showed significant improvement, with 42% of patients improving fibrosis by at least 1 stage at 12 weeks, and 3 patients having a 2-stage improvement (from F3 to F1).

Other ongoing phase 2A studies involve a PPAR δ -agonist (CymaBay); PPAR α - and γ -agonist (Zyodus); PPAR α -, δ -, and γ -agonist (Inventiva); apical sodium-dependent bile acid transporter inhibitor (Shire); the immune globulin (Immuron); and various FXR agonists (separately being studied by Novartis, Enanta, and Gilead).

G&H What are the most important next steps in research for NASH treatment?

SH There are many NASH drugs in the pipeline. The next step is getting these studies enrolled and obtaining the

results. Thus, disease awareness is vital. This means implementing an awareness campaign to primary care doctors, endocrinologists, and gastroenterologists to look for this liver disease in their patients, particularly those who are diabetic. We know that 70% to 75% of diabetics have fatty liver; approximately half of these patients have NASH, and approximately half of those have more advanced liver disease. Thus, screening for NASH in diabetics could help enrollment in NASH studies.

In the future, I think we will have single agent therapy that will be able to treat the majority of NASH patients, but combination therapies, similar to hepatitis C drugs, will be needed in other patients. An important next step is continuing to combine NASH drugs to see which populations would receive a better benefit from combination therapy over monotherapy.

Within the past 12 months, Dr Harrison has served on the speakers bureau for AbbVie and Alexion; served as a consultant to or on the advisory board for Echosens, Allergan, Metacrine, Perspectum, Prometheus, Galmed, Capulus, CiVi Biopharma, Corcept, Madrigal, Pfizer, NGM Bio, BMS, Gilead, Intercept, HistoIndex, Cirius, Axcella, Genfit, Novo Nordisk, Novartis, PPD, Medpace, IQVIA, CymaBay, and the Chronic Liver Disease Foundation; and has received grant/research support from Gilead, Intercept, Genfit, Cirius, NGM Bio, Novo Nordisk, Novartis, Galmed, Immuron, Galectin, Madrigal, Conatus, Pfizer, BMS, Prometheus, and Tobira/Allergan.

Suggested Reading

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