Non-Alcoholic Fatty Liver Disease

Update on Clinical Management

Lisa J. Yoo, D.O.
Gastroenterologist
Regional Gastroenterology

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is characterized by excessive fat deposition in the liver, in the absence of other causes of liver disease. It affects more than 25% of the world's population. Dr. Lorenzo Galindo of the Department of Pathology at Lancaster General Hospital and Dr. Emma Furth of the Hospital of the University of Pennsylvania discussed the pathophysiology and histo-pathology of NAFLD in this Journal in 2015.[1] The current article will focus on clinical diagnosis and management, especially regarding pharmacotherapy with newer drugs.

The NAFLD disease spectrum ranges from non-alcoholic fatty liver (NAFL), when there is fat in at least 5% of hepatocytes without inflammation, to non-alcoholic steatohepatitis (NASH), in which there is not only 5% hepatic steatosis, but also lobular inflammation, ballooning, and acidophilic degeneration of hepatocytes with or without fibrosis. It ranges all the way up to cirrhosis and hepatocellular carcinoma (HCC).[2] NASH is the second leading indication for liver transplantation in the United States after hepatitis C infection, and likely will become the No. 1 indication for transplantation.[3] The rising incidence of obesity has led to a dramatic rise in NAFLD-related HCC, at an annual rate of 9%.[4] Though NAFLD is histologically similar to alcoholic liver disease, with steatosis on imaging or history, it lacks other causes of fat accumulation or a history of alcohol overuse, and the diagnosis is made clinically.

EPIDEMIOLOGY

In the United States, NAFLD is, or shortly will become, the leading cause of chronic liver disease. It is estimated that in 2015 there were 83 million cases of NAFLD in the U.S., with a prevalence rate of 25.8% among all ages.[5] Approximately 20% of NAFLD patients develop NASH during their clinical course, but only 10% will have advanced fibrosis.[6]

CLINICAL FEATURES AND DIAGNOSIS

Clinical predictors of NASH include age over 45 years old, obesity, visceral adiposity, and diabetes mellitus type 2. The most common presentations are incidental elevations of aminotransferases in asymptomatic individuals, detection of steatosis on imaging, or a new diagnosis of cirrhosis in the absence of alcohol use or chronic viral hepatitis.[7] Screening of high-risk populations with metabolic syndrome, diabetes, and obesity is not recommended for patients or family members, as there are inadequate data about the reliability of diagnostic screening tests, or the cost-effectiveness and long-term benefits of treatment options.[4]

Fibrosis remains the main determinant of outcomes among NAFLD patients.[8] Several scoring methods are utilized to stage liver fibrosis with the most common being the METAVIR and Ishak scores. The METAVIR scores fibrosis from stage 0 to 4, with stage 4 being cirrhosis; Ishak scores fibrosis from stage 0 to 6, with stage 5 signifying incomplete, or early cirrhosis, and stage 6 being established cirrhosis.[8] (See also Galindo and Furth.[1])

Although the gold standard for NAFLD diagnosis is liver biopsy, it is invasive and has the potential for complications. Consequently, many noninvasive biomarkers and radiologic modalities are being developing for aid in diagnosis. The NAFLD fibrosis score (NFS), FIB-4, aspartate aminotransferase/platelet ratio index, and serum biomarkers (FibroTest, and Hepascore) are serologic markers commonly used in clinical practice for noninvasive assessment of fibrosis.[9] Among radiologic techniques, elastography (FibroScan) with measurement of liver stiffness is an accurate and simple modality for the assessment of fibrosis in the ambulatory setting, but this technique is less reliable in the setting of ascites, and has limited ability to discriminate between earlier stages of fibrosis.[4]

In sum, a combination of serologic and radiologic markers is recommended to identify patients

at risk for NASH and/or advanced fibrosis, but liver biopsy may be required when these markers are indeterminate in staging the disease.

MANAGEMENT

The goals in managing patients with NAFLD include treatment of liver disease and its complications, control of risk factors for the disease, stabilization of disease, and prevention of the progression of fibrosis.[4] The most critical needs are to cultivate awareness and education among primary care providers, identify higher risk patients, and develop effective and safe treatments to improve fibrosis. The only consistently proven treatment for NAFLD is lifestyle modification including diet, exercise, maintainable weight loss, and control of associated metabolic comorbidities, including obesity, diabetes mellitus type 2, and hyperlipidemia.

In a meta-analysis of eight randomized control trials (RCT), 94% of adults able to lose at least 5% of body weight had improvement in hepatosteatosis, while body weight reduction of 7% was also associated with improvement of their NAFLD Activity Score, or NAS.[10] (The NAS was developed as a tool to measure changes in NAFLD during therapeutic trials.[11]) Unfortunately, only half of patients were able to reach at least 7% weight loss at 12 months. A dose-response curve demonstrated that the greater the degree of weight loss, the more significant the histopathologic improvement,[12] so that a 10% weight loss was associated with improvement in NASH features, including portal inflammation and fibrosis.[4]

Dietary Modification

The specific macronutrient composition of the diet is less relevant than the end result of maintainable weight loss. Studies suggest that a 30% decrease in caloric intake, or approximately 750-1,000 kcal/day, resulted in improvement in hepatosteatosis.[13] The Mediterranean diet, which is higher in monounsaturated fatty acids than a high-fat, low-carbohydrate diet, showed no significant weight loss after six weeks, but MRI demonstrated significant improvement in steatosis.[13] Prospective, long-term trials with histopathological results are needed before specific macronutrient diets can be recommended.

Exercise

Large RCTs have not assessed the effect of exercise on NASH histopathology. The optimal duration and intensity of exercise is also uncertain. However, a meta-analysis did indicate an improvement in hepatosteatosis with exercise, but not in ALT levels.[4] Data do suggest patients who maintain physical activity more than 150 minutes per week, or increase activity levels by more than 60 minutes per week, have a more pronounced decrease in serum aminotransferases, independent of weight loss.[4] These data are supported by a large Korean population study showing that regardless of BMI, over a five-year period of follow-up, moderate exercise five times per week, such as carrying light loads, riding a bike at a steady pace, or playing tennis for at least 10 minutes, was associated with the greatest benefit in preventing NAFLD, or improving it in patients who had it.[14] The combination of dietary modifications and exercise is more effective than either alone.[15]

PHARMACOLOGICAL MANAGEMENT

Patients with NAFLD without steatohepatitis or fibrosis have an overall good prognosis regarding the liver, so pharmacological therapy aimed at treating liver disease should be limited to biopsy-proven NASH with fibrosis. Many pharmacologic options have been studied, but no FDA-approved drug currently exists for the management of NAFLD.

Metformin

Metformin is not recommended for treating NASH in adult patients. Several studies in NASH patients examined its effect on aminotransferases and/or liver histology. Two meta-analyses concluded that although serum aminotransferases improved, metformin did not improve liver histology.[16,17]

Thiazolidinediones

Thiazolidinediones are ligands for the nuclear transcription factor peroxisome proliferator-activated receptor gamma (PPAR)-c affecting glucose and lipid metabolism.[18] Studies with pioglitazone showed improvement in insulin sensitivity and aminotransferases, steatosis, inflammation, and ballooning.[4] The NAFLD Activity Score (NAS) improved in 73% of pioglitazone-treated patients, compared with 24% of placebo-treated patients ($P < 0.001$). Improvement in fibrosis was also seen among patients randomized to pioglitazone ($P = 0.08$).[19] In a recent study, 101 patients with biopsy-proven NASH and either prediabetes or diabetes mellitus type 2, were treated with a hypocaloric diet (500-kcal/day less than weight-maintaining caloric intake) and pioglitazone (45 mg/day) or placebo for

18 months, followed by an 18-month open-label phase with pioglitazone treatment.[20]

The primary outcome was a reduction of 2 points in the NAS in treated patients, without worsening of fibrosis.[21] Fifty-eight percent achieved a 2 point reduction and 51% had resolution of NASH (both $P < 0.001$) with improvement in fibrosis ($P = 0.039$). Overall there was no significant difference in adverse events between groups, but compared with placebo, pioglitazone showed greater weight gain of about 2.5 kg at 18 months, and a total of 3kg over 36 months. The weight gain was likely from improved adipose tissue insulin action, and increased adipocyte triglyceride synthesis.

Pioglitazone has also been shown to have benefit for patients with NASH without diabetes. A RCT of pioglitazone 30mg/day versus placebo over 12 months in 74 patients with NASH, showed that steatosis did not improve significantly, but treatment did improve hepatocellular injury and fibrosis.[21]

In the PIVENS trial (Pioglitazone versus Vitamin E versus Placebo for the Treatment of Nondiabetic Patients with Nonalcoholic Steatohepatitis), a large, multicenter RCT in nondiabetic patients with NASH, 247 patients were randomized to pioglitazone (30 mg/day), vitamin E (800 IU/day), or placebo for 24 months.[22] There were histological benefits associated with pioglitazone, but it did not meet the primary endpoint of improvement in NAS by 2 points with at least 1 point improvement in hepatocellular ballooning and 1 point improvement in either the lobular inflammation or steatosis score, and no increase in the fibrosis score.

Population-based studies that looked at bladder cancer due to pioglitazone therapy have reported either positive or negative associations. However, a large study by Lewis et al followed patients aged 40 years for up to 16 years, and found no statistically significant association, even with increasing duration of therapy.[23] Also of concern is bone loss, which may occur in women treated with thiazolidinediones.[23]

Pioglitazone has been shown to improve liver histology in patients with and without diabetes mellitus type 2 with biopsy-proven NASH, but risks and benefits should be extensively discussed with each patient before initiating therapy.[4] Since more data about safety and efficacy are needed, pioglitazone should not be used to treat NAFLD without biopsy-proven NASH.

Glucagon-Like Peptide-1 Analogues

There has also been interest in the potential use of glucagon-like peptide-1 (GLP-1) agonists in patients with NAFLD and NASH. In an RCT of 52 patients with biopsy-proven NASH, liraglutide administered once-daily for 48 weeks was associated with greater resolution of steatohepatitis and less progression of fibrosis.[24] Nonetheless, these drugs are not recommended for therapy due to associated gastrointestinal side effects.

Vitamin E

Vitamin E (a-tocopherol) is an antioxidant and has been investigated as a treatment for NASH. However, comparison between trials is difficult due to varying criteria for enrollment, different medication doses, uncertainty about formulations which could affect bioavailability, and limited histological data to assess outcomes. Also, most studies were relatively underpowered and did not meet Consolidated Standards of Reporting Trials (CONSORT) criteria for clinical trials. Despite limitations, it can be summarized that:

(1) Vitamin E is associated with a decrease in aminotransferases in patients with NASH;

(2) Studies that evaluated histological endpoints indicated that vitamin E improves steatosis, inflammation, and ballooning and resolution of steatohepatitis in a proportion of nondiabetic NASH adults, and

(3) Vitamin E did not have an effect on hepatic fibrosis. In the PIVENS clinical trial, the primary endpoint was achieved in a significantly greater number of participants receiving vitamin E compared with placebo (42% vs. 19%; $P < 0.001$, number needed to treat = 4.4).[22]

Notwithstanding its apparent benefits, there are concerns about the long-term safety of vitamin E. One meta-analysis suggested that a dose greater than 800 IU/day was associated with increased all-cause mortality, but this meta-analysis has been criticized for excluding several studies with low mortality and concomitant use of vitamin A and other drugs. Also, smoking was not considered.[4]

In sum, vitamin E at a daily dose of 800 IU/day improves liver histology in nondiabetic adults with biopsy-proven NASH, and may be considered for this patient population, but as always, risks and benefits should be discussed extensively with each patient before commencing therapy. Until further data supporting its effectiveness become available, vitamin E is not recommended to treat NASH in diabetic patients, NAFLD without liver biopsy, NASH cirrhosis, or cryptogenic cirrhosis.

Bariatric Surgery

Bariatric surgery can improve or eliminate comorbid disease in most patients, and improves long-term survival and death from CVD and malignancy, the two most common causes of death in NAFLD.[25] There are no RCTs of bariatric surgery in NASH, but there are several retrospective and prospective cohort studies, and two large, single-center studies with follow-up liver biopsies. These demonstrated significant improvement in prevalence and severity of steatosis and ballooning at one and five years following bariatric surgery, including gastric band, bilio-intestinal bypass, and gastric bypass.[26]

Foregut bariatric surgery could be considered in otherwise eligible obese individuals with NAFLD or NASH; however, further studies of risks, benefits, and results are needed to consider foregut bariatric surgery as a recommended option to specifically treat NASH.

Ursodeoxycholic Acid, Omega-3 Fatty Acids, and Miscellaneous Agents

Several studies explored ursodeoxycholic acid (UDCA) in conventional or high doses, to improve aminotransferases and steatosis in NAFLD patients, and liver histology in NASH patients. A single, large, multicenter RCT showed UDCA offered no histological benefit over placebo in patients with NASH.[27] UCDA is not recommended for treatment of NAFLD or NASH.

Omega-3 fatty acids have been considered to treat NAFLD in both animal models and humans, but the interpretation of human studies was limited by small sample sizes and methodological flaws.[28] Two recent studies failed to show convincing therapeutic benefit for omega-3 fatty acids in patients with NAFLD or NASH.[4] Omega-3 fatty acids should not be used as a specific treatment of NAFLD or NASH, though they may be considered to treat hypertriglyceridemia in patients with NAFLD.

Current Medication Trials

Currently, several medications are undergoing trials to evaluate their potential benefits in NAFLD. Obeticholic acid (OCA; NCT02548351) and elafibranor (NCT02704403) are being tested in phase 3 registration trials (REGENERATE).[29]

OCA, a farnesoid X receptor agonist, was evaluated over a 72-week period in a large, multicenter, phase 2b clinical trial (FLINT). Steatohepatitis and fibrosis improved in 35% of treated patients, compared with 13% of patients in the placebo arm, but the drug was associated with dyslipidemia and itching.[30]

Elafibranor, a dual PPARa/d agonist was evaluated over a 12-month study period in a phase 2 study, and improved NASH without worsening fibrosis (GOLDEN-505).[31]

Further safety and efficacy data are needed, and these drugs should not be used off-label for treatment of NASH.

CONCLUSION

NAFLD is quickly becoming a leading etiology of chronic liver disease. The crucial goals in managing patients with NAFLD include not only treatment of the liver disease and its complications, but also control of risk factors, stabilization of disease, and prevention of progression of fibrosis. It is of the utmost importance that we identify higher risk patients and develop treatments for improvement in fibrosis. Many pharmacologic options have been and are being studied, but no FDA-approved drug currently exists for management of NAFLD. Currently, the only consistently proven treatment is lifestyle modification, including diet, exercise, maintainable overall weight loss, and control of metabolic comorbidities, including obesity, diabetes mellitus type 2, and hyperlipidemia. These patients require multidisciplinary treatment plans and long-term care.

Lisa Yoo, D.O.
Regional Gastroenterology
2112 Harrisburg Pike, Suite 202
Lancaster, PA 17601
717-869-4600
lisajyoo@gmail.com

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