Treatment of Nonalcoholic Fatty Liver: Present and Emerging Therapies

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Abstract

Treatment of patients with nonalcoholic fatty liver has typically been focused on the management of associated conditions such as obesity, diabetes mellitus, and hyperlipidemia as well as discontinuation of potentially hepatotoxic drugs. Nonalcoholic fatty liver associated with obesity may resolve with weight reduction, although the benefits of weight loss have been inconsistent. Appropriate metabolic control for patients with diabetes mellitus or hyperlipidemia is always recommended but not always effective in reversing nonalcoholic fatty liver. Promising results of pilot studies evaluating ursodeoxycholic acid, gemfibrozil, betaine, N-acetylcysteine, and -tocopherol suggest that these medications may be of potential benefit in the treatment of patients with nonalcoholic fatty liver. These medications, however, need first to be tested in well-controlled trials with clinically relevant end points and extended follow-up. A better understanding of the pathogenesis and natural history of this condition will help to identify the subset of patients with nonalcoholic fatty liver at

risk of progressing to advanced liver disease and, hence, the subgroup of patients who should derive the most benefit from medical therapy. In this article, we review (1) the existing medical therapy for patients with nonalcoholic fatty liver, (2) the emerging data from clinical trials evaluating potentially useful medications, and (3) the potential therapeutic implications of recent studies on the pathogenesis of this liver disease.

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Introduction

Nonalcoholic fatty liver (NAFL) is a medical condition that may progress to end-stage liver disease with the consequent development of portal hypertension and liver failure.[1,[2]] In some patients, however, NAFL follows a relatively benign course and remains stable for many years, and it will probably never progress in some others.[3,[4]] Thus, the decision to intervene with medical therapy should be aimed at arresting disease progression and, ideally, be restricted to the NAFL patients at risk of developing advanced liver disease. Unfortunately, because the natural history of NAFL remains unknown and risk factors to predict disease progression over time have not been identified, the decision whether to treat remains a matter of clinical judgment.

The spectrum of NAFL is wide and ranges from simple fat accumulation in hepatocytes (fatty liver) without biochemical or histological evidence of inflammation

or fibrosis, to fat accumulation plus necroinflammatory activity with or without fibrosis (steatohepatitis), to the development of advanced liver fibrosis or cirrhosis (cirrhotic stage).[1,[2],[5]] All these stages are histologically indistinguishable from those produced by excessive alcohol consumption, drugs, or hepatotoxins (Table 1). Other liver diseases including viral or autoimmune hepatitis and metabolic or hereditary liver diseases should be appropriately excluded.

Because the pathogenesis of NAFL remains unknown, the management of this condition is empirical. Treatment of patients with NAFL has typically been focused on the management of associated conditions such as obesity, diabetes mellitus, and hyperlipidemia as well as discontinuation of potentially hepatotoxic drugs known to produce NAFL.

Treatment of Associated Conditions

Metabolic and Hereditary Conditions

A large body of clinical and epidemiological data gathered during the last three decades indicates that obesity and type 2 (non-insulin-dependent) diabetes mellitus are major associated conditions or predisposing factors leading to the development of NAFL.[1,[6]-9] Hence, it is reasonable to believe that the prevention or appropriate management of these conditions would lead to improvement or arrest of the liver disease.

NAFL may resolve with weight reduction, although the benefits of weight loss have been inconsistent. An early report described two patients whose biopsy showed

steatosis, necroinflammation, and fibrosis that significantly improved following 11 and 20 kg weight loss over 1 year.[10] In another report, five obese patients stopped eating for some time and lost 14-30 kg within 1 month. The hepatic fat content decreased in three of them, but fibrosis became more prominent in four of the five patients.[11] In another series, 14 patients maintained a mean weight loss of nearly 65 kg for 1.5 years and in more than half the liver biopsy findings normalized.[12]

Another case series of 39 obese patients reported a marked biochemical improvement, particularly in the patients who lost more than 10% of body weight.[13] Liver biopsies were not performed in any of these patients. In another series,[14] 41 morbidly obese patients with NAFL had a median weight loss of 34 kg during treatment with a very low calorie formula diet (388 kcal/day). The degree of fat infiltration improved significantly. However, a fifth of the patients, particularly those with more pronounced reduction of fatty changes and faster weight loss, developed slight portal inflammation or fibrosis. None of the patients losing less than 230 g per day or approximately 1.6 kg per week developed fibrosis. A significant improvement in liver biochemistries was noted regardless of the histological changes. In a more recent study,[15] liver biochemistries and the degree of fatty infiltration improved significantly in 15 obese patients with NAFL who were treated with a restricted diet (25 cal/kg/day) plus exercise for 3 months. Improvement in the degree of inflammation and fibrosis also occurred in some patients.

Information regarding the effect of weight loss in obese children with NAFL is

sparse. In a case series report,[16] seven out of nine obese children with NAFL who adhered to treatment with hypocaloric diet and exercise lost about 500 g per week. Weight loss led to improvement in serum aminotrasferase levels and degree of hepatic steatosis evaluated by ultrasonography. Posttreatment liver histology normalized in the only child who underwent liver biopsy. In a more recent series,[17] 33 obese children with abnormal liver tests related to NAFL underwent 6 months of treatment with a moderately hypocaloric diet (mean 35 cal/kg/day; carbohydrates 65%, protein 12%, fat 23%) plus aerobic exercise (6 hours/week) to obtain a weight loss of about 500 g per week. Liver tests became normal in all children who lost weight, whereas the degree of steatosis evaluated by ultrasonography improved significantly or normalized in all children who lost 10% of body weight. In another report,[18] six obese children with NAFL had improvement in serum aminotransferases with weight loss after a mean follow-up of 18 months.

Thus, weight loss, particularly if gradual, may lead to improvement in liver histology. However, rate and degree of weight loss required for normalization of liver histology have not been established. It seems that the means by which weight loss is achieved is important and may play a critical role in determining whether more severe liver damage will develop. In patients with a high degree of fatty infiltration, pronounced reduction of fatty changes and fast weight loss may promote portal inflammation and fibrosis. Similarly, starvation or total fasting may lead to development of pericellular and portal fibrosis, bile stasis, and focal necrosis.[11,14] This paradoxical effect seen in

some patients may be due to increased circulating free fatty acid levels derived from fat mobilization and, thus, a greater rate of exposure of the liver to an unusually high amount of free fatty acids. Furthermore, liver tests, in particular serum aminotransferase levels, usually improve or normalize with weight loss and they are poor predictors of worsening of liver damage related to weight loss.

Different caloric restrictions have been evaluated. A formula providing 600-800 cal/day with 45-100 g of high-quality animal proteins, less than 100 g carbohydrate, and less than 10 g fat in adults seems to be reasonable, particularly for patients who are 30% overweight.[19] This low-calorie diet has been recommended by some authors only after a more conventional 1200-calorie diet has been tried and proved unsuccessful. Diet to produce weight loss should always be prescribed in an individual basis and considering the patient's overall health. Patients who have obesity-related disease such as diabetes mellitus, hyperlipidemia, or cardiovascular disease require close medical supervision during weight loss to adjust the medication dosage as needed. Further studies are necessary to determine the most appropriate content of the formula to be recommended for obese patients with NAFL.

Medications used to reduce appetite result in weight reduction in many patients.[20] These medications are associated with rare but potentially serious side effects, including pulmonary hypertension.[21] It remains to be proved whether the risk-to-benefit ratio of these medications justifies their use in patients with NAFL.

Obese patients with type 2 diabetes mellitus should be enrolled in a low-calorie diet

and exercise program. In patients with diabetes and hyperlipidemia, good laboratory control is always recommended but not always effective in reversing NAFL. In obese ob/ob mice, an animal model of NAFL,[22] metformin, an oral hypoglycemic medication, led to improvement in liver tests and degree of steatosis. Hence, metformin may deserve evaluation in humans with NAFL. Patients with insulin-dependent diabetes mellitus and hepatomegaly will show improvement in symptoms of hepatomegaly when appropriate control of hyperglycemia is achieved.

Gastric and intestinal bypass, popular weight-reducing surgical procedures in the 1960s and 1970s, have been almost abandoned, mainly because of the high frequency of severe NAFL followed by liver failure.[23,24] The development of NAFL in obese patients undergoing intestinal or gastric bypass may be due to a combination of additive factors including protein/calorie malnutrition, increased fluxes of and liver exposure to free fatty acids, and bacterial overgrowth in the defunctionalized intestinal segment. In this regard, enteral and parenteral supplementations of amino acids and proteins are of proven benefit.[25] Also, in a series of 33 obese patients undergoing intestinal bypass,[26] metronidazole given at random intervals after surgery led to a significant improvement or normalization of the degree of steatosis.

Patients receiving long-term total parenteral nutrition may develop NAFL partially because of choline deficiency. Choline supplementation has been reported to improve or revert hepatic steatosis.[27,28] Similarly, bacterial overgrowth in the resting intestine along with the lack of enteral stimulation has been implicated in the genesis of liver

damage, including NAFL, in patients receiving long-term total parenteral nutrition. Polymyxin B, a nonabsorbable antibiotic that specifically binds to the lipid A-core region of lipopolysacharide[29] and metronidazole,[30] has been shown to improve significantly the degree of fatty infiltration and reduce the production of tumor necrosis factor in rats receiving total parenteral nutrition.

Drugs and Hepatotoxins

Several drugs and environmental exposure to some hepatotoxins (Table 1) have been recognized as potential causes of NAFL. They should always be sought in patients with NAFL because their withdrawal, when possible, usually leads to resolution of the liver disease.

Promising Pharmacological Therapy

Because rapid weight loss may worsen NAFL, use of medications that can directly reduce the severity of liver damage independent of weight loss is a reasonable alternative. However, pharmacological therapy directed specifically at the liver disease has only recently been evaluated in patients with NAFL. Most of these studies have been open-label and published in abstract form (Table 2).

The decision to intervene with pharmacological therapy aimed at the underlying liver disease is based on the anticipated risk of progression to severe liver disease. Pharmacological therapy may be of particular benefit for patients who lack risk

factors or associated conditions such as the nonobese, nondiabetic patients as well as the patients who do not lose weight or cannot maintain long-term weight reduction, as usually happens in most obese patients.

Clofibrate is a lipid-lowering drug that decreases the content of hepatic triglyceride in rats with ethanol-induced hepatic steatosis. Because of this, a pilot study was performed to evaluate the usefulness of clofibrate (2 g/day) in the treatment of patients with nonalcoholic steatohepatitis.[8] After a year of treatment, no significant changes in liver tests or degree of steatosis, inflammation, or fibrosis were found.

In one study,[31] 46 patients with nonalcoholic steatohepatitis were randomized to treatment with gemfibrozil at 600 mg per day for 4 weeks or no treatment. A significant improvement in aminotransferase levels was noted with gemfibrozil compared with baseline values, which did not occur in the untreated patients. The patients' weight remained unchanged during treatment and improvement in liver tests seemed to be independent of baseline triglyceride levels.

Ursodeoxycholic acid (UDCA) is the epimer of chenodeoxycholic acid and appears to replace endogenous bile acids, some of which may be hepatotoxic, with the nonhepatotoxic ursodeoxycholic acid. UDCA has membrane-stabilizing or cytoprotective and immunological effects. Three open-label pilot studies have evaluated the therapeutic benefit of UDCA in patients with NAFL. In one of these studies, 24 patients with nonalcoholic steatohepatitis8 received UDCA at a dose of 13-15 mg/kg/day for 12 months, which led to a significant improvement in liver tests

and the degree of hepatic steatosis compared with baseline. In another study,[32] liver tests normalized or significantly improved after 6 months of treatment with UDCA at 10/mg/ kg/day in 13 patients with steatohepatitis. In the latest study,[33] 31 patients with nonalcoholic steatohepatitis were randomized to UDCA (10 mg/kg/day) plus low-fat diet or low-fat diet alone for 6 months. Normalization of liver tests was significantly more common among patients treated with UDCA plus diet than diet alone. On the basis of these promising results, a large scale, placebo-controlled trial of UDCA in NAFL patients is now under way.

Betaine, a normal component of the metabolic cycle of methionine, increases S-adenosylmethionine levels, which in turn protect the liver from ethanol-induced triglyceride deposition in rats.[34] In a recent study, betaine at 20 g/day was given to eight patients with nonalcoholic steatohepatitis. After a year of treatment, a significant improvement in serum aminotrasferase levels was noted as well as a marked improvement in the degree of steatosis, necroinflammatory activity, and fibrosis.[35]

N-Acetylcysteine is a glutathione prodrug that increases glutathione levels in hepatocytes, which in turn constrains hepatocyte production of reactive oxygen species and, hence, protects against oxidative stress in the liver. Recently,[36] 11 patients with nonalcoholic steatohepatitis were treated with N-acetylcysteine (1 g/day) for 3 months. A significant improvement in aminotransferase levels was found at the end of treatment.

Vitamin E, -tocopherol, a potent antioxidant particularly effective against membrane lipid peroxidation, suppresses tumor necrosis factor- (TNF-), interleukin-1 (IL-1), IL-6, and IL-8 expression by monocytes and/or Kupffer cells and inhibits liver collagen 1(I) gene expression.[37] A case series study reported the results of treatment with -tocopherol in 11 children with NAFL. -tocopherol (vitamin E) at 400-1200 IU orally per day was given for 4 to 10 months and led to a significant improvement in liver tests.[38]

The encouraging results of pilot studies with gemfibrozil, UDCA, betaine, N-acetylcysteine, and -tocopherol in the treatment of NAFL (Table 2) and animal studies with metformin suggest that these agents deserve further evaluation in clinical trials. However, in order to make solid recommendations concerning routine administration of any of these (or other) medications in the treatment of patients with NAFL, further, well-controlled clinical trials are clearly necessary. These studies must have enough power, have adequate duration of follow-up, be analyzed on an intention-to-treat basis, and must also include clinically relevant end points. The simple improvement or normalization of liver tests and/or ultrasonography findings in most of the pilot studies reported to date (Table 2) does not necessarily imply that these agents will have a real effect on the natural history of this liver disease. Similarly, although improvement of liver histology may be a more accurate surrogate marker of a better long-term prognosis, a beneficial medication for NAFL patients should be safe and well tolerated and prove beneficial in delaying the development of

liver-related complications and improvement of long-term survival.

Given the slowly progressive nature of NAFL, hundreds of patients with this condition would need to be enrolled in prospective clinical trials and be followed up for a number of years, perhaps decades, in order to see a real effect of a medication on long-term survival. It may be unrealistic to believe that such a study is feasible and will be appropriately funded. The identification of NAFL patients at risk of progressing to end-stage liver disease may lead the "high-risk" patients who, in theory, are expected to derive the most benefit from medical therapy to enroll in therapeutic trials.

Future Directions

In order to develop effective medical therapy for patients with NAFL, further work is clearly needed to enhance our understanding of the pathogenesis and natural history of this condition. Some lines of evidence, albeit still inconclusive and some derived from studies of alcohol-induced liver disease, suggest that oxidative stress/lipid peroxidation, bacterial toxins, overproduction of TNF-, alteration of hepatocyte ATP stores, and Cyp2E1 enzyme activity may play a role in the genesis of NAFL.

Acute or chronic hepatic steatosis, regardless of the cause, is associated with lipid peroxidation, which seemed to increase with the severity of steatosis.[39] Malondialdehyde, an end product of lipid peroxidation, activates hepatic stellate cells, stimulating collagen production and fibrogenesis. Malondialdehyde may also contribute to inflammation by activating nuclear factor-kB (NF-kB), which regulates the

expression of proinflammatory cytokines such as TNF- and IL-8.[40] Another end product of lipid peroxidation, 4-hydroxynonenal, is a strong chemoattractant for neutrophils. Furthermore, the risk factors for development of NAFL, namely obesity with rapid weight loss and type 2 diabetes mellitus, lead to increased circulating levels of free fatty acids with consequent enhanced concentration in the liver. Free fatty acids per se are potentially cytotoxic[41] and may also increase cytochrome P450 CYP2E1 activity, as shown in a rat model of NAFL using a diet deficient in methionine-choline.[42]

This evidence suggests that oxidative stress and lipid peroxidation may, in part, be one of the critical factors involved in the genesis and probably in the progression of NAFL. If this concept is valid, further therapeutic strategies may be directed to its inhibition. In support of the role of oxidative stress and lipid peroxidation in the pathogenesis of NAFL is the demonstration that -tocopherol, a potent antioxidant, improved liver tests in children[38] with NAFL. Both -tocopherol and silymarin, a flavanoid isolated from milk thistle with antioxidant, antifibrotic, and membrane-stabilizing effects,[43] are currently being evaluated in the treatment of adult patients with NAFL.

On the basis of the fact that metronidazole and polymyxin B may prevent the development of NAFL in obese patients undergoing intestinal bypass[26] and in rats receiving total parenteral nutrition,[29,30] a role of endotoxin/cytokine-mediated injury has been suggested as a contributing factor in the development of NAFL. It has been

shown that genetically obese mice are very sensitive to the effect of lipopolysaccharide (LPS) in developing NAFL.[44] The messenger RNA (mRNA) of interferon-, which sensitizes hepatocytes to TNF- toxicity, was overexpressed, whereas mRNA of IL-10, which is inhibitory to TNF- effects, was reduced. In this model, the phagocytic activity of Kupffer cells was reduced, presumably favoring the development of systemic endotoxemia and release of proinflammatory cytokines. If this concept is valid, intestinal decontamination and administration of soluble cytokine receptors and neutralizing anticytokine antibodies as well as drugs with anti-TNF- activity (i.e., pentoxifylline, anti-TNF- antibodies) may warrant further evaluation as therapies for patients with NAFL.

ATP stores in hepatocytes of mice[45] and humans[46] with steatosis seem to be potentially vulnerable to depletion compared with those of nonobese controls. Hence, treatment efforts primarily directed toward protecting hepatocytes ATP stores might be potentially benefit in NAFL patients. Similarly, Cyp2E1 activity may contribute to hepatotoxicity in mice and humans with NAFL.[42,47] Treatment strategies to limit its activity, such as dietary modifications (fat-reduced diet), may be beneficial.

The role of iron in the pathogenesis of NAFL remains uncertain. Anecdotal reports suggested that increased iron stores might lead to more severe liver disease in NAFL patients.[48,49] Studies with larger populations of patients with NAFL, however, have clearly shown that this is not always the case.[2,9,50] Nevertheless, serum iron studies should always be performed in patients with NAFL, and an iron stain with

quantification of hepatic iron is also recommended for patients with abnormal serum iron studies. If excessive iron and perhaps also the HFE gene mutation are shown in a patient with NAFL, serial phlebotomies, which may improve liver biochemistries,[51,52] may be a therapeutic option.

Type 2 diabetes mellitus and obesity are well-known conditions associated with resistance to normal peripheral actions of insulin. Hepatic steatosis was found in 50% of patients with unexplained hepatic iron overload plus at least one of the components of the "insulin resistance syndrome" including truncal obesity, type 2 diabetes mellitus, and hypertriglyceridemia.[53] Hence, it is reasonable to speculate that the use of medications that improve insulin sensitivity may benefit the liver disease of patients with NAFL associated with insulin resistance conditions. Thiazolidinediones are a new class of antidiabetic drugs that selectively enhance or partially mimic certain actions of insulin, causing an antihyperglycemic effect frequently accompanied by a reduction in circulating concentrations of insulin, triglycerides, and nonesterified fatty acids.[54] Troglitazone, a thiazolidinedione derivative, was given to six patients with nonalcoholic steatohepatitis for 2-4 months.[55] Alanine aminotransferase levels normalized in four of the six patients and remained in the normal range during 3 months of off-drug follow-up. Troglitazone (Rezulin) may produce hepatocellular liver damage[56] and is now no longer available in the United States. Other thiazolidinedione agents (i.e., darglitazone, rosiglitazone) may deserve further evaluation in NAFL patients.

When Should Patients with NAFL be Treated?

The decision whether to treat an individual patient with NAFL should be primarily dictated by knowing the potential risk of progression to end-stage liver disease. However, because no prospective, longitudinal clinical studies have been performed, the clinical course of this condition remains unknown, and hence treatment recommendations remain speculative.

An attempt at gradual weight loss as well as a concerted effort to maintain appropriate control of serum glucose and lipid levels is a useful first step in the management of NAFL patients. Perhaps this, along with appropriate exclusion of other liver disease, may be the only treatment recommendation for NAFL patients with pure steatosis and no evidence of inflammation or fibrosis, who seem to have the best prognosis[3,4] within the spectrum of NAFL. NAFL patients with steatohepatitis, particularly those with fibrosis on liver biopsy, may have a worse prognosis; they should be monitored closely, have a greater effort made for adequate metabolic control, and be offered enrollment in well-controlled clinical trials evaluating the potential benefit of promising medications. For the NAFL patients with cirrhotic stage and decompensated disease, liver transplantation is a potential life-extending therapeutic alternative.