# ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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## Therapies for Nonalcoholic Steatohepatitis

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### G&H Which types of therapies have been evaluated for nonalcoholic steatohepatitis?

**SM** Both pharmacologic and nonpharmacologic treatments have been tested in controlled trials of nonalcoholic steatohepatitis (NASH) patients. Pharmacologic treatments that have been tested include thiazolidinediones (with pioglitazone as the preferred agent), vitamin E, ursodeoxycholic acid, metformin, pentoxifylline, statins, gemfibrozil, probucol, betaine, and *N*-acetylcysteine. Nonpharmacologic treatments that have been tested include lifestyle modification, exercise, and Mediterranean diet. Not all of these studies have shown beneficial results, and different treatments have been tested in different populations (eg, diabetic and nondiabetic), making it difficult to extrapolate across these groups.

Bariatric surgery has not been tested for treatment of NASH in a controlled trial, but retrospective studies of highly selected patients who have undergone this treatment have shown excellent results. However, as there is potential for significant morbidity with surgery, the balance of benefits and harms should be considered in each patient.

### G&H What are the pros and cons of these different treatment approaches?

**SM** Lifestyle modification has many associated benefits, such as a decrease in cardiovascular risk, improvement in diabetic control and insulin sensitivity, reduction of hypertension, loss of weight, and, potentially, reduced progression to advanced liver disease. The downside is that effective lifestyle modification is labor intensive and difficult to achieve at the population level. Although trial data have shown that lifestyle modification is effective for reducing hepatic necroinflammation in selected individuals, it is likely that trial participants do not reflect the larger treatment population.

The benefit of drug therapy is improved histology, particularly steatosis and inflammation. The downside of drug therapy is the potential for side effects. For example, pioglitazone usually increases weight (on average, 4 kg with 1 year of therapy). This side effect is poorly tolerated by NASH patients, who are often overweight and have been advised repeatedly that weight loss is an essential part of their healthcare. Pioglitazone may also be associated with reduced bone mineral density and increased risk of bladder cancer, although the absolute risk (rather than the relative risk) of these side effects should be considered when making clinical decisions.

Evidence for the use of vitamin E in NASH patients comes from high-dose (800 IU) trials of this agent. These doses far exceed the average daily intake of vitamin E, which is approximately 14 IU. There has been some concern that antioxidants become pro-oxidant and cause cellular damage at supratherapeutic doses. A meta-analysis of observational studies that was published in the *Annals of Internal Medicine* in 2005 suggested that vitamin E above 150 IU/day was associated with a dose-dependent increase in all-cause mortality. However, these data were observational and may have been confounded by the chronic illness of the participants at baseline.

Therefore, clinicians must consider the balance of benefits and risks of proposed interventions for each patient. For example, the risk of progression to liver disease is greater—and probably more likely to influence overall mortality—than the risk of vitamin E therapy in patients who have severe insulin resistance, are unable to change their lifestyle, and have fibrosis on liver biopsy.

**G&H** Which treatments are most commonly used in clinical practice?

**SM** The more commonly used treatments for NASH patients are lifestyle modification, vitamin E, and pioglitazone. In addition, ursodeoxycholic acid is used more often in Europe, although there are fewer data supporting its use. The availability of glitazones is variable and depends on local regulatory factors.

**G&H** How is lifestyle modification administered at a practical level to patients with NASH?

**SM** Lifestyle modification must be detailed and constructive, and it is ideally undertaken in a multidisciplinary setting—similar to that of diabetic patients—with the involvement of dietitians, physiotherapists, psychologists, and so on. This treatment approach includes the elimination of trans fatty acids, which are thought to accelerate hepatic inflammation and to be an independent risk factor of cardiovascular disease. Another important dietary measure is the elimination of high fructose corn syrup, which is found in soft drinks and processed food. In addition, simple, calorie-dense, refined carbohydrates should be replaced with protein sources and complex carbohydrates. Exercise is also a critical component of lifestyle modification, and there is evidence that both aerobic and anaerobic activities are beneficial. Exercise alone has been shown to reduce hepatic triglycerides, visceral adipose tissue, and free fatty acids, even if it does not significantly alter the patient's weight. The use of behavioral therapies to help patients adopt these changes is poorly understood; this issue is examined in detail in a paper by Neuschwander-Tetri.

**G&H** Could you briefly review some of the key studies on the treatment of NASH patients?

**SM** The PIVENS study, which was published in the *New England Journal of Medicine* in 2010, was a methodologically robust study of 247 patients with biopsy-confirmed NASH who were randomized to 1 of 3 arms: placebo, pioglitazone (30 mg), or vitamin E (800 IU). The study enrolled nondiabetic patients and ran for 96 weeks, with an end-of-treatment liver biopsy. The endpoint was a composite histologic score that included improvement in hepatocellular ballooning and no increase in fibrosis. Both drug arms showed histologic improvement; however, only vitamin E was statistically significant (with the adjusted *P*-value of <.025). Patients in the pioglitazone arm gained more weight than patients in the other arms. Other side effects (eg, fractures) were not significantly different; however, this trial, like most trials, was not powered to detect safety outcomes. A major limitation of this study is that it did not enroll diabetic patients; thus, it is unknown whether these study findings can be applied to diabetic patients.

Promrat and associates examined a combination of behavioral strategies, exercise, and portion-controlled meals in 31 NASH patients in a randomized trial. They found that improvement in steatohepatitis was proportional to weight loss, but no improvement in fibrosis was seen.

**G&H** Is the available evidence adequate to support current clinical practice? If not, what factors have limited researchers' abilities to gather more data?

**SM** More data are needed on clinical outcomes. All of the trials that have been conducted to date have relied heavily on change in liver fibrosis as a surrogate marker for clinical progression, but the validity of this assumption is not known. Moreover, performing large-scale trials with start-of-treatment and end-of-treatment biopsies is demanding, expensive, and may cause potential harm to patients. The development of a biomarker for fibrosis is a research priority, and several promising biomarkers have recently been developed.

**G&H** Which therapies are most cost-effective for the treatment of NASH?

**SM** The pharmacologic treatments of vitamin E and pioglitazone are both likely cost-effective in NASH patients. To examine this issue, my colleagues and I developed a Markov model with a lifetime horizon, inserted rates of NASH disease progression that have been reported in the literature, and applied risk reduction of fibrosis progression with pharmacologic treatment that were obtained from trial and meta-analysis data. We modeled a cohort of NASH patients with advanced fibrosis, as this patient group is likely to progress faster than NASH patients with no or minimal fibrosis. The outcome measure of the study was quality-adjusted life-years, which is the outcome measure preferred by health economists, as it can be compared across different diseases and can, therefore, facilitate direct comparison of the value-for-money of healthcare interventions. The results of our model indicated that both vitamin E and pioglitazone treatments are cost-effective in NASH patients.

Currently, nonalcoholic fatty liver disease is the most common liver disease in developed countries and is expected to be the leading cause for liver transplantation in the United States by 2020; therefore, the assessment of which therapies are effective, as well as cost-effective, is an important issue at the population level.

## G&H What further research is needed regarding therapies for NASH patients?

**SM** Ideally, long-term data on drug therapies are needed. Most trials in this area have been undertaken for less than 2 years, and NASH is a chronic, slowly progressive disease. We need information on how well histologic improvement (eg, fibrosis) predicts a reduction in the progression to adverse liver-related outcomes.

There is also little information available on patient preferences for treatment. In all chronic conditions, adherence to therapy is very important; therefore, studying patient preferences would help improve treatment outcomes. In addition, more formal quality-of-life studies are needed in NASH patients to determine whether quality of life improves with pharmacologic treatment or lifestyle modification. The PIVENS study was 1 of the few studies to assess quality of life using the SF-36 form. This study found no significant difference in quality of life with placebo, pioglitazone, or vitamin E. Although quality of life was not a primary outcome measure in this study—and thus may have been underpowered—at least it provided some data on this issue.

In addition, genetic polymorphisms that predict disease development and treatment response would be informative and would have the potential to change how patients are treated. As findings from the current work on this issue are conflicting, further research is awaited.

Finally, research translation remains challenging, but it is increasingly expected of researchers and academics and is important in NASH therapies in order to bring treatments from the bench to the bedside.

## Suggested Reading

Mahady SE, George J. Management of nonalcoholic steatohepatitis: an evidence-based approach. *Clin Liver Dis*. 2012;16:631-645.

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