ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

Section Editor: Eugene R. Schiff, MD

Treatment of Alcoholic Liver Disease

Timothy R. Morgan, MD
Chief of Hepatology
VA Long Beach Healthcare System
Long Beach, California
Professor of Medicine
Division of Gastroenterology
University of California, Irvine
Irvine, California

G&H What are the conditions that constitute alcoholic liver disease?

TM Alcoholic liver disease has a broad clinical spectrum, from mild disease to severe, life-threatening liver injury. Alcoholic liver disease starts with fatty liver and goes on to fibrosis and cirrhosis, as well as a severe form of alcoholic liver disease known as alcoholic hepatitis. In addition, there is a very uncommon type of alcoholic liver disease known as foamy fatty change, which presents with jaundice and a high aspartate aminotransferase level. Simple fatty liver occurs in nearly all people who drink alcohol on a heavy basis, even for a relatively short period of time such as a few days. In contrast, alcohol-induced fibrosis and cirrhosis usually develop after decades of heavy drinking, as does alcoholic hepatitis. It is unclear why patients who have been drinking for decades suddenly develop alcoholic hepatitis at a certain time point, as opposed to, for example, a year or decade earlier.

G&H What are the effects of complete alcohol abstinence on alcoholic liver disease? Is cessation of alcohol sufficient for treatment?

TM Cessation of alcohol is necessary to treat alcoholic liver disease. If the patient has simple fatty liver, then cessation will allow the liver to heal and return to normal. If a patient has alcohol-induced fibrosis or cirrhosis and abstains from alcohol, damage to the liver will stop and the liver will get better, although liver scar tissue will remain. In some patients, the fibrosis seems to regress. Fibrosis regression is difficult to document and cannot be predicted in an individual patient who stops drinking. In most patients, the fibrosis remains to some degree, potentially as much as when the patient stopped drinking. For alcoholic hepatitis or foamy fatty change, stopping alcohol is necessary—and will lead to improvements in most patients—but may not be sufficient to stop the disease.

G&H How long does it take for the effects of alcohol abstinence to occur?

TM The beneficial effects of stopping alcohol start immediately, but probably are not achieved in the full sense for several weeks or longer. The exact length of time for the liver to improve is not known, and varies from patient to patient.

G&H In these patients, is there a safe threshold for resuming low alcohol consumption once their disease has improved?

TM I tell my patients who have a history of alcoholic liver disease that they cannot drink any alcohol again. I am concerned that a patient with a history of alcoholic liver disease who starts drinking small amounts of alcohol is at risk of returning to heavy alcohol use, with progression of his or her alcoholic liver disease.

G&H How effective are alcohol abstinence programs and substance abuse counseling in patients with alcoholic liver disease?

TM Alcohol treatment programs should be recommended to all patients with alcoholic liver disease. The data show that a subset of patients become abstinent. Many patients will start drinking again at some time in their lives, but participating in these programs may reduce their alcohol use or duration, or allow them to regain abstinence.

G&H How common is alcohol relapse in patients with alcoholic liver disease?

TM Alcohol relapse is fairly common. Therefore, gastroenterologists should always be aware of the possibility of relapse and question patients accordingly. It is a good idea to check their blood alcohol levels during clinic visits to assess whether they have been drinking recently.

G&H How effective are medical therapies for alcoholic liver disease?

TM Currently, there are no treatments for fatty liver, alcoholic fibrosis, or alcoholic cirrhosis other than abstinence from alcohol. The only disease for which there is specific treatment is alcoholic hepatitis. Researchers have studied corticosteroids and pentoxifylline for many years in patients with alcoholic hepatitis. Most experts recommend prednisolone at a dose of 40 mg a day for 28 or 30 days as the preferred treatment for severe alcoholic hepatitis. Some experts prefer pentoxifylline instead. The most recent data suggest that prednisolone improves survival at 1 month. However, the beneficial effects disappear by 3 to 6 months. This was especially true in the STOPAH (Steroids or Pentoxifylline for Alcoholic Hepatitis) trial.

G&H When should these drugs be started for patients with alcoholic hepatitis?

TM Generally speaking, hepatologists recommend prednisolone or pentoxifylline when the Maddrey discriminant function score is greater than or equal to 32. Some doctors use the Model for End-Stage Liver Disease (MELD) score instead and start treatment if the patient's MELD score is greater than or equal to 20. As mentioned above, the usual treatment duration is 28 or 30 days. I recommend adding magnesium, 1 pill a day, for many months. Magnesium may decrease intestinal permeability, an important component of reducing endotoxin absorption and exposure to the liver.

G&H Can these drugs be used for longer than 1 month?

TM Pentoxifylline and prednisolone are usually used only for 1 month. There are some data (although of a relatively minimal nature) on the use of pentoxifylline for a longer duration, but most doctors do not use the drug beyond 1 month for patients with alcoholic hepatitis.

G&H Since the treatment effects are not long-lasting, can the treatment be given again?

TM The treatment is not given again unless the patient resumes alcohol consumption and returns with an exacerbation of alcoholic hepatitis.

G&H Are any new therapies being studied for alcoholic hepatitis?

TM Several new therapies have been studied in patients with alcoholic hepatitis. One is granulocyte colony-stimulating factor (GCSF). In several studies from India, the use of GCSF along with either prednisolone or pentoxifylline, depending on the study, improved short-term (2-3 months) survival. In my opinion, studies of GCSF should be performed in the United States or in the Western world to confirm its effectiveness in a Western population before the therapy can be broadly recommended. One of the potential advantages of GCSF is its reported safety.

N-acetylcysteine (NAC) has also been studied for the treatment of alcoholic hepatitis. In a meta-analysis, NAC by itself did not improve survival in alcoholic hepatitis. However, one study showed that treatment with prednisolone and NAC was better than treatment with prednisolone alone at 1 month, although the survival benefit was lost by 6 months. In my opinion, additional clinical trials of NAC are needed before it can be recommended for patients with alcoholic hepatitis.

G&H What is the role of early liver transplantation in alcoholic liver disease?

TM Patients with alcoholic cirrhosis who have been abstinent for 6 months or more are potential candidates for liver transplantation as long as they meet the other criteria for transplantation. The recidivism rate among abstinent alcoholic cirrhotic patients is roughly 10%. Alcohol use after transplantation is often minimal and does not affect organ survival; however, in a small number of patients, there is a significant return to alcohol use. Nevertheless, abstinent patients with decompensated alcoholic cirrhosis are generally considered to be suitable candidates for liver transplantation if they have fulfilled all of the standard components of the transplant evaluation process.

In contrast, transplanting patients with alcoholic hepatitis who have less than 6 months of abstinence is a difficult issue that is under study at several sites. These patients are currently being considered for transplantation

at a number of transplant centers. There have been several trials in which transplant teams evaluated patients with alcoholic hepatitis who had not been abstinent for very long and transplanted select patients, with very good survival reported at 1 and 2 years. Thus, some data do support transplanting select patients with alcoholic hepatitis with less than 6 months of alcoholic abstinence.

G&H Why is the issue of early liver transplantation more complicated in patients with alcoholic hepatitis?

TM Knowing which patients with alcoholic hepatitis are transplant candidates is difficult. In a study by Dr Philippe Mathurin and colleagues in France, the results of which were published in the *New England Journal of Medicine* in 2011, one of the major criteria for liver transplantation was that the alcoholic hepatitis was the patient's first episode of decompensated alcoholic liver disease. Studies in the United States have not been as strict in requiring that the episode of alcoholic hepatitis be the patient's first decompensation, which might explain why there was a slightly higher incidence of recidivism in at least 1 of the studies conducted in the United States.

Early liver transplantation of patients with alcoholic hepatitis is complicated because of perceived issues among the donor population that the donated liver may be given to a recipient who might end up drinking alcohol again. Because livers are scarce commodities, some in the transplant community feel that the organs should be reserved for the people who will take care of them the best. The ongoing uncertainty regarding the reliability of recently abstinent patients with alcoholic hepatitis to take care of their liver likely influences the decision of transplant teams across the United States to transplant patients with alcoholic hepatitis. In studies that were performed in France and the United States, roughly 1 in 10 patients with alcoholic hepatitis was a potential transplant recipient, and perhaps half of these patients ended up receiving a liver transplant.

Overall, transplanting patients with alcoholic hepatitis has a relatively small effect on the use of donor livers. In most publications, less than 5% of the livers were used for patients with alcoholic hepatitis. Nevertheless, the transplantation of patients with alcoholic hepatitis who have not been abstinent for very long remains a complicated issue with no clear consensus.

G&H What research is currently underway in this area?

TM In the United States, the National Institute on Alcohol Abuse and Alcoholism is funding 4 consortia to study alcoholic hepatitis. These consortia are looking at new treatments for alcoholic hepatitis and are also performing basic science and translational research into the pathophysiology and mechanisms of liver injury in alcoholic hepatitis. The consortia have been active for 4 or 5 years and have published some preliminary findings thus far.

Dr Morgan has no relevant conflicts of interest to disclose.

Suggested Reading

Crabb DW, Bataller R, Chalasani NP, et al; NIAAA Alcoholic Hepatitis Consortia. Standard definitions and common data elements for clinical trials in patients with alcoholic hepatitis: recommendation from the NIAAA Alcoholic Hepatitis Consortia. *Gastroenterology*. 2016;150(4):785-790.

Mathurin P, Moreno C, Samuel D, et al. Early liver transplantation for severe alcoholic hepatitis. *N Engl J Med*. 2011;365(19):1790-1800.

Thursz M, Morgan TR. Treatment of severe alcoholic hepatitis. *Gastroenterology*. 2016;150(8):1823-1834.

Thursz MR, Richardson P, Allison M, et al; STOPAH Trial. Prednisolone or pentoxifylline for alcoholic hepatitis. *N Engl J Med*. 2015;372(17):1619-1628.