THE EFFECTIVE PHYSICIAN

Alcoholic Liver Disease

BY WILLIAM E. GOLDEN, M.D., AND ROBERT H. HOPKINS, M.D.

Background

Fermented beverages and associated liver disease date back almost 12,000 years. The American College of Gastroenterology and the American Association for the Study of Liver Diseases recently produced a practice guideline on this common, chronic impairment.

Conclusions

Nearly two-thirds of Americans drink some form of alcohol, and nearly 7.5% of the adult population meets criteria for alcohol abuse and/or alcohol dependence. Across societies, for every 1 liter increase in per capita annual consumption of alcohol, there is a 14% increased incidence of cirrhosis in men and an 8% increase in women. Alcohol is responsible for more than 40% of deaths from liver disease.

Histologic injury from alcohol is usually staged into three groups: fatty liver (steatosis), alcoholic hepatitis, and chronic hepatitis with fibrosis or cirrhosis. More advanced injury is associated with Mallory's hyaline and megamitochondria.

A standard alcoholic drink contains 12 g of alcohol. Of those who drink 60 g/day, 90% develop fatty liver. Fibrotic changes occur in 40%-60% of drinkers who consume 40-80 g/day over 25 years. In general, the risk of cirrhosis is increased with long-term ingestion of more than 60 g/day in men and 20 g/day in women. African Americans and Hispanic men have higher rates of cirrhosis than do whites with similar ingestion patterns.

Fatty liver is usually asymptomatic and reversible by 4-6 weeks of abstinence. Nevertheless, about 10% of these drinkers who achieve abstinence will progress to fibrosis.

Patients who develop alcoholic hepatitis have a worse prognosis. Symptomatic disease is often associated with progressive fibrosis leading to cirrhosis. Abstinence may or may not affect the long-term histology and persistence of alcoholic hepatitis.

Implementation

"Safe" ingestion of alcohol is considered to be less than 170 g/week for men and 110 g/week for women.

The medical community has underrecognized problem drinkers, and these patients often minimize their behavior. Patterns of medical visits may suggest alcohol overconsumption as a unifying background diagnosis. Structured screening tools such as the CAGE, MAST, and AUDIT questionnaires can be helpful in identifying patients who would benefit from counseling and intervention.

Physical examination in patients other than those with advanced cirrhosis is usually nonspecific. Palpation of the liver can be normal and is not reliable for estimating liver volume. Comorbid conditions that coexist with alcoholic liver disease include cardiomyopathy, muscle wasting, neuropathy, and pancreatic insufficiency.

There are no standard laboratory tests to identify patients with problem drinking. Many patients have elevated gamma-glutamyl-transpeptidase (GGT) and macrocytosis. An AST/ALT ratio over 3 is highly associated with alcoholic liver disease.

Liver biopsy is not necessary for managing alcoholic liver disease, although approximately 20% of patients have a secondary or comorbid hepatic diagnosis. Biopsy should be considered if the results could alter subsequent therapy.

The Maddrey discriminant function (MDF) can identify patients at high risk of short-term mortality. The MDF is equal to 4.6 (patient's prothrombin time – control time)/total bilirubin (mg/dL). Patients with scores higher than 32 can have 1-month mortality over 30%.

Serial calculation of the Model for End-Stage Liver Disease (MELD) scores can also be useful to stage and assess risk in patients with advanced liver disease.

Patients with alcoholic hepatitis benefit from strict abstinence and nutritional support. Patients with severe hepatitis (MDF over 32) might benefit from a month of 40 mg/day of prednisolone or 400 mg 3 times a day of pentoxifylline. Colchicine or propylthiouracil should not be used in the treatment of alcoholic liver disease.

Abstinence can result in significant improvement after 3 months. It improves histology, reduces portal pressure, and improves survival of patients throughout the spectrum of liver injury. Patients with chronic hepatitis C should pursue complete abstinence, as persistent alcohol abuse has been noted to increase the risk of cirrhosis 30-fold.

More than two-thirds of patients with consumption issues relapse in the first year of abstinence. Disulfiram is poorly tolerated and no longer a first-line agent to support abstinence. Naltrexone is useful for short-term craving for alcohol, but is potentially hepatotoxic itself. Acamprosate has been effective in helping patients maintain abstinence. These drugs should be used in combination with counseling for effective interventions.

Reference

O'Shea R.S., et al. Alcoholic liver disease. Hepatology 2010;51:307-28.

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New HCV Drugs May Be Worth the Wait

BY SHERRY BOSCHERT

SAN FRANCISCO — Because new medications for hepatitis C are expected to be approved within 2 years, some experts are waiting to treat selected patients.

"Over the last year, I've moved increasingly toward deferred treatment, which is a change for me," Dr. Norah A. Terrault said. "We clearly will have drugs that are going to work better" when used with the current standard regimen of pegylated interferon (peg-IFN) and ribavirin, she said at a meeting on HIV management sponsored by the University of California, San Francisco.

Approval is anticipated in 2011 for two protease inhibitors—telaprevir and boceprevir—that have been in phase III clinical trials for the treatment of hepatitis C virus (HCV), said Dr. Terrault, director of the Viral Hepatitis Center at the university. Using either of these drugs as add-on therapy with peg-IFN plus ribavirin should "push our sustained viral response rates up over 50% consistently," she said. (See box.)

Clinicians should weigh the pros and cons of immediately treating HCV in patients who are coinfected with HIV, Dr. Terrault suggested. Coinfected patients tend to have accelerated progression of HCV disease with more liver-associated morbidity and mortality, compared with patients who have HCV but not HIV. Treating HCV in coinfected patients may improve the patient's ability to take highly active antiretroviral therapy to combat HIV.

On the other hand, patient characteristics or comorbidities may make it nearly impossible for some patients to tolerate the toxicities associated with peg-IFN and ribavirin. In general, coinfected patients tolerate HCV therapy less well than monoinfected patients. Interactions between HCV drugs and antiretrovirals may necessitate a change in HIV therapy. Clinicians must be comfortable with helping patients get through HCV therapy for it to succeed, Dr. Terrault said.

The main reason to consider deferring HCV therapy, however, is that "better treatments are, I think, just around the corner," she said.

All of the new HCV treatments in the pipeline are being developed primarily for genotype 1 HCV, so Dr. Terrault does not defer HCV therapy for coinfected patients with genotypes 2 or 3 HCV. Patients with low levels of HCV RNA (less than 600,000 IU/mL) are most likely to achieve a sustained viral response to HCV therapy regardless of genotype, so she still offers HCV therapy to this group. She also offers HCV treatment to patients with advanced fibrosis (bridging fibrosis or cirrhosis) because "they can't wait for new treatments," she said.

Dr. Terrault also treats acute HCV in coinfected patients who are on stable antiretroviral therapy with no active opportunistic infections and CD4 counts over 200 cells/mm^3. ■

Disclosures: *Dr. Terrault has been a consultant to Schering-Plough Corp., which is developing boceprevir, and to three other companies. She has received grants from Vertex Pharmaceuticals Inc., which is developing telaprevir, and from two other companies.*

Therapies in The Pipeline

New treatments for HCV are being developed in several drug classes.

Preliminary data from phase III clinical trials of the two new treatments closest to market entry—the protease inhibitors telaprevir and boceprevir—suggest improved response rates and added toxicities when used with peg-IFN and ribavirin.

Based on early results with telaprevir, she anticipates that 69% of treatment-naive patients will achieve a sustained viral response to treatment with 12 weeks of triple therapy (telaprevir, peg-IFN, and ribavirin) followed by 12-36 weeks of peg-IFN and ribavirin. This regimen could produce response rates of up to 39% in patients who had not responded to previous treatment with peg-IFN and ribavirin, and up to 76% in patients who had relapsed from previous therapy with peg-IFN and ribavirin.

The boceprevir treatment regimen starts with 4 weeks of peg-IFN and ribavirin followed by 24-44 weeks of triple therapy by adding boceprevir. Dr. Terrault anticipates a sustained viral response at 48 weeks in up to 74% of previously untreated patients with genotype 1 HCV and no HIV. No data are available on the use of boceprevir in treatment-experienced patients.

"This is add-on treatment, so you still have peg-interferon and ribavirin side effects, and now you have protease inhibitor side effects," she noted. Telaprevir most commonly causes anemia, rash, or pruritus. Boceprevir most commonly causes anemia, neutropenia, or dysgeusia.