ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Fibrosis and Cirrhosis in HCV Infection

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G&H What key circumstance is associated with slowing down progression of fibrosis, and how can this be optimized?

MS The best way to prevent fibrosis progression is to eradicate the underlying liver disease. In the case of hepatitis C virus (HCV) infection, we achieve a sustained virologic response (SVR). Several studies have demonstrated that once HCV is eradicated and SVR is achieved, the amount of scarring will be reduced and fibrosis may resolve, although it might take several years for this to occur, the same way that it took several years for fibrosis to develop.

In a report presented at the 44th annual meeting of the European Association for the Study of the Liver, which met in Copenhagen, Denmark in 2009, we showed that 50% of patients with cirrhosis who achieved SVR after treatment of HCV infection no longer had cirrhosis on liver biopsy findings 5 years later.

Similar findings are found in studies of fibrosis and hepatitis B virus (HBV) infection. In a recent study published in *The Lancet*, patients in whom HBV infection had been suppressed to an undetectable viral load for 5 years showed marked reductions in the degree of liver fibrosis, and the vast majority of patients who had had cirrhosis when antiviral therapy was initiated no longer had cirrhosis after 5 years of viral suppression.

It also has been shown in patients with fatty liver disease that significant weight reduction, either through bariatric surgery or diet, leads to a reduction in fatty liver and liver fibrosis. Therefore, the best treatment for preventing fibrosis progression is eradication of the underlying cause of the liver disease.

G&H What is the impact of liver function tests on predicting and intercepting cirrhosis in patients with chronic HCV infection?

MS Liver function tests are basically ways to assess fibrosis based on measuring other elements that correlate with fibrosis in the liver. One well-established blood test called FibroSURE (LabCorp) looks at 5 different biochemical parameters and generates a score on a scale of 0 to 1 that correlates with the degree of fibrosis. There is a lot of scatter and overlap in the data, but a FibroSURE score of more than 0.8 is highly predictive of advanced fibrosis and cirrhosis. In contrast, a score of less than 0.1 is very good at predicting no or minimal fibrosis. Unfortunately, scores between 0.1 and 0.8 tend to be less predictable regarding the degree of fibrosis. A person can have a score of 0.2 with advanced fibrosis or a score of 0.7 with mild fibrosis. Nevertheless, the FibroSURE scores at the ends of the spectrum correlate with biopsy findings about 80% of the time.

Another inexpensive tool for measuring liver function is the aspartate aminotransferase (AST)-to-platelet ratio index (APRI). It is useful because, as scarring of the liver progresses, AST levels tend to increase while the platelet counts decrease. The platelet count is a very good measure of scarring, particularly in HCV infection, with thrombocytopenia strongly correlating with cirrhosis.

In practice, if a clinician performed a FibroSURE test with a resulting score of 0.9 and also obtained a platelet count of 100,000/μL, that patient has a very high likelihood of having cirrhosis. If an ultrasound was performed and the findings were suggestive of cirrhosis and the patient also has thrombocytopenia, that is also highly suggestive of cirrhosis.

Another test is the FibroScan (Echosens/Sandhill), which has been widely utilized in Europe and Asia but has only recently been approved for use in the United States by the US Food and Drug Administration (FDA). Values of liver elasticity measured by FibroScan correlate with the degree of hepatic fibrosis.

Several tools can now be used in lieu of liver biopsy to assess the amount of scarring in liver disease, and these tests can be used over time to monitor a patient for fibrosis regression after cure. No test, however, should be used as a sole, definitive measure, including biopsy, which does not confer a 100% accuracy.

G&H How do quantitative liver function tests work in relation to other screening and prognostic modalities for HCV infection?

MS The quantitative liver function tests (QLFTs) are based on the concept that the rate at which a substance is broken down by the liver will be proportional to the degree of scarring in the liver. No QLFTs have yet been approved by the FDA, but one example is a breath test called Breath ID being developed by Exalenz Bioscience. It uses methacetin, a nonradioactive isotope that is consumed in a liquid solution and is rapidly (within 20 minutes) taken up by the bloodstream. The methacetin is broken down by the liver and exhaled in the breath. It is believed that the rate of breakdown of the product and the rate of excretion of the metabolite in the breath are proportional to the degree of liver fibrosis and could, therefore, be potentially used to diagnose cirrhosis. However, no published data yet exist that strongly support use of Breath ID in liver disease. QLFTs are largely still investigational.

G&H How do genetics influence the risk of liver decompensation?

MS Genetics probably influence the risk of liver decompensation much more than we realize. Say 2 people are infected with HCV—or any other liver disease—at the same time in the same circumstances. After 30 years, 1 person may have cirrhosis while the other has mild, stage 1 or 2 fibrosis. What determined the degree of disease progression in these 2 persons? Genetics are a strong possibility.

We know what mechanisms cause liver damage. The resultant inflammation causes the release of cytokines that then cause stellate cells to secrete fibrotic matrix proteins. This step is probably genetically modulated to a degree such that some persons will secrete more fibrotic proteins than others for a given level of inflammation. In general, histologic studies strongly suggest that the rate of fibrosis progression—at least in the context of HCV infection—is driven by inflammation.

Several studies have tried to screen populations for genes that modulate the rate at which fibrosis progresses. A few candidate genes have been identified, but having one of these genes does not necessarily mean that the gene carrier is destined for the development of cirrhosis in the context of liver disease. At this stage of the game, the only biomarkers that could be useful for a clinician in monitoring fibrosis progression would be an FDA-approved product, which would be FibroSURE or FibroScan, used in conjunction with measurement of platelets or the APRI.

G&H What other avenues for optimization of care are possibly being overlooked?

MS In terms of treatment of HCV infection, it is hard to tell. The paradigm has completely changed from what it was several years ago. We are now in an era in which antiviral drugs combined with interferon and ribavirin are incredibly potent at suppressing the virus, and 2 new direct-acting antiviral agents, simeprevir (Olysio, Janssen) and sofosbuvir (Sovaldi, Gilead), were just approved this past November and December, respectively.

G&H What have the sofosbuvir trials taught us about management of patients with HCV and cirrhosis?

MS Sofosbuvir has been shown to be incredibly potent at suppressing HCV. It is rapid-acting, and HCV becomes undetectable in nearly all treated patients within 4 weeks of initiating treatment. The next generation of drugs for HCV infection will be so potent at suppressing the virus and will do this so fast that viral kinetics will no longer have a role in predicting SVR. This is particularly true of the oral combinations. Now that we are using multiple oral antiviral drugs that provide cure rates of more than 90%, it may be very difficult to tease out why the remaining 5% or 10% of patients do not achieve cure.

G&H What are your thoughts about vitamin supplementation on fibrosis and risk of cirrhosis?

MS The data are very mixed and not conclusive. The strongest data, which are consistent but sparse, suggest that vitamin E may reduce the fat content in patients with fatty liver disease. This, in turn, may reduce fibrosis progression. At this stage of the game, eating healthy and maintaining health is probably a better strategy for averting liver fibrosis than vitamin supplementation. Interestingly, the strongest data about the antifibrotic effects of food concern coffee. Data from several studies now suggest that drinking 2 cups of coffee a day reduces fibrosis progression in the liver. The most useful study

on this comes from the National Institutes of Health HALT-C (Hepatitis C Antiviral Long-term Treatment against Cirrhosis) trial. Patients completed detailed diet questionnaires that included questions on coffee and tea consumption. A strong relationship between coffee consumption and lack of cirrhosis was found.

G&H What suggestions can you give to clinicians about optimizing care of patients with HCV infection who are at risk for cirrhosis?

MS The most important thing that clinicians need to understand about HCV infection is that the vast majority of infected patients have not been identified. For this reason, clinicians need to follow the recommendations of the Centers for Disease Control and Prevention and US Preventive Services Task Force about screening the high-risk birth cohort—anyone born between 1945 and 1965—for HCV infection. We now have treatments that can cure most persons infected with HCV. Identifying and treating those persons in the general population who have HCV infection will make a significant impact on the health of our population. Anyone who presents to a gastroenterologist for colon cancer screening fits into the birth cohort for HCV screening and should be screened for HCV at that time.

Dr Shiffman has no relevant conflicts of interest to disclose.

Suggested Reading

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