ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Preventative Hepatology and the Reduction of All-Cause Mortality in Liver Disease

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G&H Why is preventative hepatology important and a growing area of study and interest?

JP Preventative hepatology is important because so much of chronic liver disease is potentially modifiable. There is a growing interest in trying to see what can be done to prevent liver disease progression or, in a patient with cirrhosis, prevent progression to decompensated cirrhosis or hepatocellular carcinoma (HCC). There are several different potential risk factors for developing cirrhosis. If providers intervene to modify any of these factors early, it may be possible to prevent the development of cirrhosis. For example, hepatitis B and C are very treatable now, but most people do not know that they are infected; therefore, just diagnosing people and treating them early can prevent cirrhosis and long-term complications of these viruses. Another example involves patients with metabolic dysfunction-associated steatotic liver disease (MASLD). If providers can intervene at early disease stages, before advanced fibrosis or cirrhosis has developed, it may be possible to prevent many cases of decompensated cirrhosis, the need for liver transplantation, or the development of HCC.

G&H How should providers decide which patients with liver disease require a more aggressive preventative approach?

JP Preventative approaches can be divided into nontherapeutic, behavioral modification lifestyle approaches and therapeutic approaches. In general, nontherapeutic approaches can be beneficial regardless of stage. However, when talking about more aggressive approaches, noninvasive tools are very helpful in risk-stratifying patients; such tools can help providers identify which patients are at the greatest risk of liver-related adverse events. Especially when considering the use of therapeutics, it is important to tailor prescriptions to the patients who are going to derive the most benefit, as all agents have potential side effects and toxicity. In addition, some medications are contraindicated in patients with more advanced hepatic dysfunction and decompensated cirrhosis. Thus, providers have to be mindful of who they are prescribing a medication for; prescribing one medication to all patients can result in potential toxicity.

In terms of tools for such assessment, noninvasive tools are preferred when possible. These include noninvasive serum indices such as the Fibrosis-4 index as well as vibration-controlled transient elastography and magnetic resonance elastography. Usually, the decision of which tool to use is based on the resources that are available to the provider.

G&H How and why might therapeutic agents such as statins be able to prevent liver disease progression and reduce all-cause mortality in liver disease, even though they are not prescribed for those purposes?

JP The answer may depend on the agent and also potentially the underlying liver disease. A lot of observational data have shown that statin use is associated with a lower risk of liver disease progression as well as a lower risk of

the development of cirrhosis, decompensation, and even HCC in patients with liver disease. What is particularly interesting about these observational data is that they appear to be consistent across different types of liver disease and not just in terms of decreasing those liver-related complications but also reducing all-cause mortality. In a systematic review and meta-analysis by Kamal and colleagues, which included 9 observational studies, the pooled hazard ratio for mortality with statin use was 0.67 (95% CI, 0.46-0.98).

For liver diseases such as MASLD and metabolic dysfunction-associated steatohepatitis, these effects make a lot of intuitive sense. A leading cause of mortality in patients with MASLD is cardiovascular disease, and statins decrease the risk of cardiovascular events. However, observational studies have found decreased adverse outcomes in statin users not just in MASLD but also in viral hepatitis, for example. We do not know why exactly. Statins have pleiotropic effects, and there are a variety of reasons they might decrease fibrosis and portal hypertension; more research is needed. One of the caveats of these data is that they come from observational studies, so rigorous randomized controlled trials are needed because of concern for selection bias or bias by indication. Providers might not prescribe statins to patients who are sicker or who have more advanced liver disease.

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Randomized controlled trials are needed before providers can universally recommend prescribing statins to patients with chronic liver disease in the absence of another indication. Several studies are also being conducted to evaluate the safety and efficacy of statins in reducing liver-related outcomes in patients with cirrhosis, including one being performed through the US Department of Veterans Affairs (NCT03654053) and another one through the National Institutes of Health–funded Liver Cirrhosis Network (NCT05832229) (although this one is not yet recruiting).

G&H Has research looked into whether other therapeutic agents such as nonselective beta blockers might also produce such effects?

JP There has been a lot of research on the use of nonselective beta blockers in patients with cirrhosis. These agents are mainly used as primary prevention for variceal bleeding in patients with known esophageal varices. Additionally, new guidance endorses the use of nonselective beta blockers in patients with clinically significant portal hypertension in order to decrease the risk of decompensation. However, their use in patients with compensated cirrhosis without clinically significant portal hypertension is not indicated because these agents do not reduce the risk of varices development or clinical decompensation when given at this earlier stage. In addition, there are some subpopulations in whom providers want to stop or hold the use of nonselective beta blockers; for example, when patients are in the hospital because they have refractory ascites, acute kidney injury, or spontaneous bacterial peritonitis, nonselective beta blockers can be detrimental. However, if these patients improve, providers might cautiously restart the use of nonselective beta blockers. Similarly, in patients with decompensated cirrhosis who are taking statins, there is concern for the risk of rhabdomyolysis. Therefore, there is a point when these agents may be beneficial and also a point when they could be detrimental; nuance is needed when using these agents.

G&H How should sarcopenia and frailty, which are common in end-stage liver disease and older patients, be measured?

JP In 2021, the American Association for the Study of Liver Diseases released the first practice guidance on malnutrition for healthy and sarcopenic patients with cirrhosis, which recommended that all patients with cirrhosis undergo assessment of frailty and/or sarcopenia. There are several methods to assess frailty, but the guidance statement does not weigh in on which is the optimal one. Thus, there is no consensus on the best way to assess frailty. In the clinic where I work, medical assistants are trained to measure frailty using objective measurements. The Liver Frailty Index (https://liverfrailtyindex.ucsf.edu) can be performed at the patient's bedside relatively easily so that is our standard practice for evaluating frailty.

Likewise, there is no standard recommendation for what to use for sarcopenia measurement. Sarcopenia is more challenging to formally measure than frailty because bedside measurement reproducibility is low. Imaging can be used, including computed tomography or computerized axial tomography (CAT), which is the most validated

and reproducible method. Although CAT scan is not recommended for obtaining muscle mass measurements alone because of exposure to radiation, sarcopenia can be measured from scans performed for HCC surveillance. Magnetic resonance imaging can also be used and can measure skeletal muscle mass, although it has not been validated in patients with cirrhosis.

G&H How can patients be engaged to prevent or reverse sarcopenia and frailty?

JP Providers should engage patients as early as possible to prevent them from becoming frail or sarcopenic. When first meeting patients with cirrhosis, providers should assess the nutritional status of these patients and try to encourage them to obtain sufficient nutrition and protein as well as encourage them to remain physically active. Providers should also educate patients and their caregivers regarding primary prevention of these conditions.

If patients have already become frail, providers should become a bit more aggressive with management. Nutritionists are usually engaged at this point and even physical therapists if possible. My colleagues and I typically recommend calorie intake of at least 35 kcal/kg and protein intake of 1.2 to 1.5 g/kg daily and counsel patients to minimize fasting and eat frequent small meals/snacks. Physical activity recommendations can be personalized, but we generally recommend 150 minutes of aerobic activity and 2 to 3 days of resistance training per week. If a patient is very frail, providers should engage in rehabilitation management to try to reverse frailty or sarcopenia. Some patients will need intensive nutritional support and might need a feeding tube to help with nutrition.

G&H Do you have any nontherapeutic recommendations for reducing all-cause mortality in liver disease or preventing liver disease progression?

JP My biggest recommendation is addressing the modifiable risk factors, such as minimizing alcohol, addressing metabolic comorbidities, and screening for hepatitis B or C. The Centers for Disease Control and Prevention already recommended screening all patients with liver disease for hepatitis B and C, but now also recommends universal hepatitis B and C screening. It is also important that gastroenterologists and hepatologists vaccinate their patients if they are not immune to hepatitis A or B, and educate patients about MASLD and its risk factors. I talk with my patients about their diet and lifestyle, as well as the importance of trying to remain active and avoiding simple sugar and high-fructose corn syrup.

G&H What are the next steps in research in this area?

JP In terms of therapeutic measures, much of the data on statins and other medications are based on observational studies that have been very heterogeneous with different types of liver disease. Rigorous randomized controlled trials are needed before providers can recommend the use of these agents unless patients have other indications.

Any preventative strategy (therapeutic or not) can only be effective if adopted. Implementation science, which involves the study of strategies that promote the uptake of evidence-based research into routine use, is an important growing field in hepatology. Diet and exercise are important but are very difficult to adhere to on a regular basis. How can providers help patients achieve the lifestyle modifications that we are asking of them, and what are the most effective strategies? Likewise, providers can tell patients not to drink alcohol, but how can we assist them? These are areas that are very important for research in the future.

Disclosures

Dr Price has no relevant conflicts of interest to disclose.

Suggested Reading

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