ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

Section Editor: Eugene R. Schiff, MD

Use of Angiotensin-Converting Enzyme Inhibitors in Patients With Liver Disease

Elliot B. Tapper, MD
Associate Professor
Division of Gastroenterology
University of Michigan
Ann Arbor, Michigan

G&H How do angiotensin-converting enzyme inhibitors work, and can they have an effect on liver disease?

ET Angiotensin-converting enzyme (ACE) inhibitors block an enzyme that increases the tone of certain blood vessels, which is one of the mechanisms by which the body increases blood pressure. For that reason, these agents are one of the most effective treatments for lowering blood pressure. In particular, they have been proven to preserve kidney function in patients with high blood pressure and diabetes and improve survival in patients with heart failure. This is what these medications were designed to do.

There are 3 strands of evidence that suggest that ACE inhibition may also affect liver disease. One involves animal data. When these medications are given to mice, in addition to producing the aforementioned effect on blood vessels that can be seen clinically for blood pressure, the agents also decrease the development of new blood vessels, or angiogenesis, and there is a lower risk of liver cancer. The same signaling pathway that results in higher blood pressure and angiogenesis is also involved with the development of fibrogenesis in cells making extra collagen. Thus, in these animals, less scar tissue can develop in response to simulated chronic liver diseases.

The second form of evidence involves observational data of ACE inhibitors that are prescribed for other reasons. Pleiotropy, or the idea that drugs approved or developed for other indications can have unintended benefits, is often sought for the betterment of liver disease. Patients with liver disease are often neglected and not studied as much as patients with other diseases. The hope is that off-target effects can be leveraged to help these patients. This has been seen with medications such as statins. These agents are thought to be beneficial for the liver because large databases of patients have shown that the use of statins is associated with improved liver disease outcomes.

The third form of evidence comes from clinical trials that enrolled patients with established cirrhosis and viral hepatitis. These trials were small and unblinded and did not confirm a robust antifibrotic effect. However, there was a trend toward reduction in fibrosis markers, and this finding has fueled interest.

G&H Has any other research in humans shown that ACE inhibitors have a beneficial effect on liver disease?

ET The best observational study comes from a group in Hong Kong that looked at many patients with fatty liver disease who took ACE inhibitors and found that these patients were much less likely to develop cirrhosis with decompensation or liver cancer. These observational data exemplify how off-target effects, or pleiotropy, can benefit patients with liver disease, who would not typically have access to robust programs of clinical trials designing therapies to reduce scar tissue and so on. Thus, in addition to animal data, there are large database data suggesting that there are unexpected benefits for these safe, approved drugs in patients with liver disease.

As for other research, there have been a number of smaller and older studies, and most of the human research in this area has involved patients with viral hepatitis prior to the advent of highly effective therapies. Recently, the focus has been on nonalcoholic fatty liver disease.

Interestingly, a recent randomized trial by Vos and colleagues used an angiotensin II receptor blocker, which works on the same pathway and has the same effects as an ACE inhibitor. This trial was pursued because angiotensin II receptor blockers have been linked to improved metabolic health in other studies. Unfortunately, this trial did not show an improvement in any biomarkers of nonalcoholic fatty liver disease progression in children. In a separate trial by Hirata and colleagues that compared 2 angiotensin II receptor blockers (losartan and telmisartan) with each other in adults, there was no improvement in the level of alanine aminotransferase in either arm.

There have also been efforts to conduct trials of ACE inhibitors in adults with fatty liver disease to try to apply the insights gained from animal and database research to clinical trials. However, such trials are often difficult to enroll. For example, a trial by McPherson and colleagues had to close because it could not recruit enough patients. It is not ethical to withhold an ACE inhibitor or angiotensin II receptor blocker from a patient who needs it (eg, someone who has high blood pressure or diabetes).

> The patient's medication list should be assessed regularly because a medicine that was safe and beneficial 6 months ago may not remain so if the patient's health status has changed.

Thus, further clinical trials are still needed to prove the hypothesis from animal studies that ACE inhibitors can affect liver disease. Although ACE inhibitors are frequently being used now to manage the comorbidities of patients with liver disease, whether these agents have an effect on the liver disease of these patients is uncertain at this point.

G&H Are there any concerns with using ACE inhibitors in patients with liver disease, especially those with ascites?

ET When patients have cirrhosis, they have fluid accumulating in their abdomen, or ascites, which is caused by the kidney increasing angiotensin and aldosterone to try to hold on to as much fluid as possible. The scarred liver effectively creates a traffic jam for the body's blood, slowing its return to the heart and from the heart to the kidney, which feels starved for blood. The only tool that the kidney has to preserve blood flow is to try to close some of its own off-ramps with higher angiotensin to maintain the flow of blood to the kidney. This has the side effect of increasing water retention. Patients are treated with spironolactone, which blocks the effect of a hormone downstream of the effect of ACE. However, ACE inhibitors or angiotensin II receptors do not help. They could lower blood pressure in the kidney and potentially cause kidney failure in at-risk patients. Many of my patients need an ACE inhibitor for cardiac conditions or hypertension, but there comes a point when its use is too risky because of the possibility of kidney failure, particularly if they have cirrhosis and ascites. Therefore, for patients with complex liver disease, the side effects and risks of ACE inhibitors outweigh any benefits. These agents need to be restricted to patients earlier on in the disease process, when side effects are limited and do not overshadow any potential benefits.

G&H Are there any other side effects or safety issues associated with the use of ACE inhibitors?

ET Anyone who takes ACE inhibitors can develop a dry cough. This well-known side effect occurs approximately 10% of the time. These patients are often switched to angiotensin II receptor blockers, which do not produce the same side effect. Another side effect, though rare, is angioedema, in which the tongue may become so large that the patient cannot talk and may choke. In addition, liver injury, inflammation in the liver, and high alanine aminotransferase levels may occur. However, liver injury is rare. It is usually mild and will resolve when the injurious medication is stopped.

G&H Why are ACE inhibitors being used in patients with liver disease more often now than in the past?

ET Once cirrhosis develops, ACE inhibitors are generally avoided. What has changed is that the average person with cirrhosis is different. In the past, it used to be a frail man in his 50s or 60s with alcohol-related liver disease and low blood pressure. Today, the average patient with cirrhosis can be young and with a higher acuity of illness. At the same time, the predominant cause of cirrhosis is nonalcoholic fatty liver disease. That means that patients are developing cirrhosis as a consequence of the metabolic syndrome, which is defined in part by high blood pressure. Cirrhosis used to be classically associated with

low blood pressure. Now, many patients with cirrhosis conventionally have high blood pressure. In fact, their kidneys are entirely different and may continue to benefit from ACE inhibitors for much longer into their disease course. However, the threshold where benefit gives way to risk is uncertain.

G&H Might a particular ACE inhibitor be best in patients with liver disease? Are there any significant differences among the ACE inhibitors currently available?

ET I believe that the answer is no to both questions. In certain animal studies, a particular type of ACE inhibitor may have a more robust effect on angiogenesis. However, without clinical trials confirming these findings in patients, no such preference is justifiable.

G&H How should patients with liver disease who are taking ACE inhibitors be monitored?

ET Liver disease complicated by cirrhosis is a dynamic condition in which the therapeutic window can vary with time for any given treatment. When a patient has cirrhosis, he or she should be followed routinely by a gastroenterologist or hepatologist. The patient's medication list should be assessed regularly because a medicine that was safe and beneficial 6 months ago may not remain so if the patient's health status has changed. For example, I might see a patient with diabetes and nonalcoholic steatohepatitis cirrhosis who is taking an ACE inhibitor. However, when I see the patient 6 months later, he or she might require frequent paracentesis and might have had several falls at home. These are signs that the patient's blood pressure needs to be improved at home by reducing the burden of antihypertensive drugs. It is more common for me to stop an ACE inhibitor than start one, but I only stop it when the therapeutic window has narrowed as a function of the progression of the patient's underlying liver disease.

Disclosures

Dr Tapper has done consulting for Takeda, Madrigal, Ambys, Axcella, Mallinckrodt, Lipocine, Novo Nordisk, Novartis, and Allergan, and has received grants from Bausch and Gilead.

Suggested Reading

Hirata T, Tomita K, Kawai T, et al. Effect of telmisartan or losartan for treatment of nonalcoholic fatty liver disease: Fatty Liver Protection Trial by Telmisartan or Losartan Study (FANTASY). *Int J Endocrinol*. 2013;2013:587140.

Kim G, Kim J, Lim YL, Kim MY, Baik SK. Renin-angiotensin system inhibitors and fibrosis in chronic liver disease: a systematic review. *Hepatol Int*. 2016;10(5):819-828.

McPherson S, Wilkinson N, Tiniakos D, et al. A randomised controlled trial of losartan as an anti-fibrotic agent in non-alcoholic steatohepatitis. *PLoS One*. 2017;12(4):e0175717.

Siddiqui MT, Amin H, Garg R, et al. Medications in type-2 diabetics and their association with liver fibrosis. *World J Gastroenterol*. 2020;26(23):3249-3259.

Stokkeland K, Lageborn CT, Ekbom A, et al. Statins and angiotensin-converting enzyme inhibitors are associated with reduced mortality and morbidity in chronic liver disease. *Basic Clin Pharmacol Toxicol*. 2018;122(1):104-110.

Vos MB, Van Natta ML, Blondet NM, et al; NASH Clinical Research Network. Randomized placebo-controlled trial of losartan for pediatric NAFLD. *Hepatology*. 2022;76(2):429-444.

Zhang X, Wong GL, Yip TC, et al. Angiotensin-converting enzyme inhibitors prevent liver-related events in nonalcoholic fatty liver disease. *Hepatology*. 2022;76(2):469-482.

Zhu Q, Li N, Li F, et al. Therapeutic effect of renin angiotensin system inhibitors on liver fibrosis. *J Renin Angiotensin Aldosterone Syst*. 2016;17(1):1470320316628717.