# ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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## Glucagon-Like Peptide-1 Receptor Agonists and Cirrhosis

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**G&H** What is the impact of glucagon-like peptide-1 receptor agonists on the risk of progression to cirrhosis or decompensation?

**SJ** The hallmark ESSENCE trial showed that the glucagon-like peptide-1 receptor agonist (GLP-1RA) semaglutide was able to cause a statistically significant improvement in metabolic dysfunction-associated steatohepatitis (MASH) resolution as well as fibrosis improvement by 1 stage in patients without cirrhosis, highlighting the ability of this medication to reverse the disease and related liver damage before cirrhosis develops. An earlier study has shown that patients with metabolic dysfunction-associated steatotic liver disease (MASLD) and diabetes who were started on a GLP-1RA were less likely to develop cirrhosis and cirrhosis-related complications (liver decompensation, liver cancer, or need for liver transplant) compared with patients started on another diabetes medication (dipeptidyl peptidase-4 inhibitor [DPP-4i]). When stratified by specific GLP-1RAs, only semaglutide was associated with decreased risk of progression to cirrhosis. Interestingly, the beneficial effect of GLP-1RA therapy in reducing cirrhosis-related complications was only noted when treatment was started prior to the development of cirrhosis. Another retrospective study involving close to 2 million people suggested that GLP-1RA therapy was associated with reduced risk of liver cancer, although the results were most pronounced in patients without liver disease. Real-world prospective data from the TARGET-NASH database showed that patients with MASH who were not on GLP-1RAs were 1.69 times more likely to progress from compensated to decompensated cirrhosis compared with patients using GLP-1RAs. It is not clear if these patients initiated GLP-1RA therapy before or after cirrhosis was diagnosed. Thus, these data demonstrate a strong association between GLP-1RA usage and a reduced risk of cirrhosis development or complications in patients with MASH, but it is not clear if the beneficial effect remains if patients are started on GLP-1RA therapy after cirrhosis is diagnosed.

**G&H** Should patients with non-MASH liver disease take a GLP-1RA to reduce the risk of progression to cirrhosis or decompensation?

**SJ** The majority of research involving GLP-1RAs in liver disease has been done in patients with MASLD or MASH. There are some small studies showing potential effects of GLP-1RAs on hepatitis C viral replication as well as improving hepatitis C–related dysglycemia, but the clinical significance of these findings is unclear. However, it is important to recognize that patients who have been diagnosed with liver diseases other than MASH may also have concurrent MASLD/MASH. With up to 35% of the population affected by MASLD, it is not surprising that this disease can coexist with other liver disease such as viral hepatitis, alcohol-related liver disease, and other chronic liver diseases. Importantly, it has been shown that MASLD can synergize with other liver diseases in accelerating and promoting liver injury. This highlights the need for all patients with MASH to be screened for other concomitant liver disease. In patients with such a dual diagnosis, GLP-1RAs may have benefit.

**G&H** Could these agents potentially help reverse fibrosis in patients who have cirrhosis?

**SJ** Despite the excitement from the population-based

studies previously mentioned, there are no definitive data demonstrating that GLP-1RAs can reverse liver fibrosis in patients with cirrhosis. A phase 2 study of weekly semaglutide therapy in patients with MASH cirrhosis did not show a statistically significant reduction in liver fibrosis by 1 stage or more, despite demonstrating significant improvement in MASH resolution. Similarly, at The Liver Meeting last year, results were presented from the WAYFIND study, which investigated the use of a combination therapy of semaglutide with 2 other agents in patients with MASH cirrhosis. When read by a central pathologist, the semaglutide-containing arms (including semaglutide alone) did not demonstrate a statistically significant reduction in liver fibrosis by 1 stage or more, despite demonstrating significant improvement in MASH resolution. Therefore, thus far, it has yet to be demonstrated that semaglutide is able to reverse fibrosis in patients with cirrhosis the way the drug has been able to do in patients with F2 and F3 fibrosis, again highlighting the importance of early initiation of GLP-1RA therapy to prevent the development of cirrhosis.

### **G&H** Can GLP-1RAs affect the risk of all-cause mortality in cirrhotic patients?

**SJ** The aforementioned population-based studies demonstrating a decreased risk of progression to or decompensation of MASH cirrhosis with GLP-1RA use also demonstrate decreased all-cause mortality in GLP-1RA users. Patients with MASH started on a GLP-1RA had a reduction in the hazard ratio for all-cause mortality compared with patients started on a DPP-4i (11%-12%). However, this finding only met statistical significance when GLP-1RA therapy was initiated prior to the diagnosis of cirrhosis. The TARGET registry demonstrated that among all patients with MASLD or MASH, including those with cirrhosis, there was a 2.28-fold increase in the hazard ratio for all-cause mortality for patients who were not on GLP-1RA therapy compared with those who were. Unfortunately, the difference in mortality for just patients with MASH cirrhosis was not reported. These data suggest the potential for GLP-1RA therapy to reduce mortality in patients with MASH, with a more prominent effect noted when treatment is started prior to a diagnosis of cirrhosis.

### **G&H** Are there any safety concerns with using these agents in the setting of compensated cirrhosis?

**SJ** Any weight loss, including weight loss induced by a GLP-1RA, can result in muscle mass loss that can lead to sarcopenia. This has been well described in the obesity medicine literature. That is why most obesity medicine providers are very adamant about recommending a high-protein diet with associated resistance training while achieving weight loss. This becomes even more critical when a patient has cirrhosis, as sarcopenia has been clearly linked to increased risks of liver decompensation and death. Thus, in a patient with very well-compensated cirrhosis (Child-Pugh class A), GLP-1RAs can be used cautiously while being very cognizant about protein intake, strength training, and monitoring for signs of muscle mass loss.

Additionally, GLP-1RAs can be associated with gallbladder and biliary issues, including cholecystitis and pancreatitis. Although these can often be managed conservatively with drug discontinuation in the general population, the stakes are higher for patients with cirrhosis, as surgical interventions such as cholecystectomy may be high risk and pancreatitis-associated shock could induce acute-on-chronic liver failure.

### **G&H** Do you have any other guidance for managing cirrhotic patients taking GLP-1RAs?

**SJ** It should be pointed out that GLP-1RAs are not currently approved for the treatment of MASH in patients with cirrhosis; these agents are only approved for the treatment of patients with MASH who have stage 2 or 3 fibrosis. However, there are many patients who are taking GLP-1RAs for other indications, such as obesity and diabetes, who may also have compensated cirrhosis. I think the continuation of these medications should be individualized to the patient. As discussed, keeping patients with compensated cirrhosis on GLP-1RA therapy might reduce their risk of liver decompensation and all-cause mortality (especially if it was initiated prior to the diagnosis of cirrhosis). However, if this results in significant muscle mass loss in a cirrhotic patient, GLP1-RA therapy should be discontinued as the risk likely outweighs the benefit at that point. It should be noted that in most of the population-based studies previously mentioned, it was not the dose of GLP-1RA therapy but the duration that was most closely associated with positive outcomes, suggesting that a dose reduction could potentially still provide clinical benefit in preventing disease progression while minimizing excessive weight or muscle loss.

If a patient with cirrhosis is going to remain on GLP-1RA therapy for diabetes or obesity, there needs to be a focus on a high-protein diet that avoids severe calorie restrictions or prolonged fasting along with an aggressive strength training regimen. Our liver clinic is fortunate to have an integrated hepatologist-run obesity program where we treat many patients who have compensated cirrhosis with careful weight loss that is achieved with

or without GLP-1RAs. In our experience, this approach can help maintain reasonable muscle mass even in the presence of moderate weight loss related or unrelated to GLP-1RA therapy. Obviously, this approach should be pursued with caution and with careful monitoring of subjective markers of muscle mass (body composition with bioelectrical impedance, cross-sectional imaging [psoas muscle size], or anthropometric measurements). It is also important to recognize that patients with sarcopenia have difficulty gaining muscle mass, even with resistance training, so it is critical to try to avoid sarcopenia rather than reverse it. It may be reasonable to collaborate with a dietitian, physiatrist, and/or obesity medicine provider who understands the unique needs of cirrhotic patients to prevent muscle mass loss while on GLP-1RA therapy.

> … I would not recommend the use of GLP-1RAs in patients with decompensated cirrhosis and would discontinue them in patients with cirrhosis who develop liver decompensation.

Finally, there may be certain patients with cirrhosis on GLP-1RA therapy who are more predisposed to the potential GLP-1RA–related complications previously described, including those patients who cannot tolerate a high-protein diet (because of chronic kidney disease, gout, dietary restrictions), are predisposed to gastrointestinal adverse effects (because of gastroparesis), are unable to exercise, or have a history of severe gallbladder or pancreatic disease.

In summary, GLP-1RAs can be safe in patients with well-compensated cirrhosis and can potentially help prevent liver decompensation, according to population-based studies. However, it is critically important to be cognizant of and monitor for any GLP-1RA–related complications, including muscle mass loss or hepatobiliary complications.

### G&H Is there any role for using GLP-1RAs in the setting of decompensated cirrhosis?

**SJ** Patients with decompensated cirrhosis are at highest risk for complications related to both hepatobiliary issues and sarcopenia. There is also no clear evidence demonstrating a potential benefit of GLP-1RA therapy in patients with decompensated cirrhosis. Thus, based on the data currently available, I would not recommend the use of GLP-1RAs in patients with decompensated cirrhosis and would discontinue them in patients with cirrhosis who develop liver decompensation.

### G&H Do you have any other advice for cirrhotic patients using these agents?

**SJ** I think it is important that patients with MASH have a frank discussion with their doctors if they are started on GLP-1RA therapy before or after the diagnosis of cirrhosis. The discussion should include the goals of therapy (glycemic control, weight loss, prevention of liver decompensation), mechanisms to monitor and prevent complications (gallbladder and pancreatic issues, excessive weight loss, muscle loss, and other standard GLP-1RA–related complications described in the prescribing information), and maximization of tolerability. Patients should be counseled to self-monitor for complications and the efficacy of the therapy with consideration of therapy discontinuation if potential risks are outweighing benefits or if there are early signs of liver decompensation.

### G&H What further research is needed regarding GLP-1RAs in patients with cirrhosis?

**SJ** As discussed, there appears to be a pattern of outcomes where GLP-1RA therapy seems to be most beneficial in the precirrhotic phase with benefits that appear to extend into the cirrhotic phase. However, these effects appear to be attenuated when the medication is started in patients who are already cirrhotic. It will be important to understand why GLP-1RAs can readily reverse fibrosis in patients with precirrhotic disease with seemingly less prominent effects in patients with cirrhosis. Similarly, it is not clear why GLP-1RA therapy is able to reduce liver decompensation and death, but these effects are seemingly attenuated when the therapy is initiated in patients already diagnosed with cirrhosis.

There are also several interesting areas of research for MASH-related GLP-1RA therapy in general. One of the more hotly debated questions in recent years is the exact mechanism by which GLP-1RAs influence MASH disease progression and regression. Although GLP-1 receptors have been described on human hepatocytes, the clinical significance of this is unclear and is an area of ongoing research. It is thought that the majority of the effects of GLP-1RAs on the liver are indirect via its effects on inducing weight loss, improving glycemic control, and possibly other mechanisms. A fascinating study presented at The

Liver Meeting last year demonstrated that semaglutide's effect on MASH resolution (and possibly liver fibrosis) was partially independent of its effect on both weight loss and A1c improvement. It will be interesting to see if there are other metabolic effects of GLP-1RA therapy that can also mediate MASH reversal and fibrosis improvement. Importantly, maximizing weight loss–independent effects of GLP-1RA therapy that can treat MASH may be highly beneficial for patients with cirrhosis to maximize the effects on MASH while minimizing weight loss–related muscle mass loss.

Another issue that will hopefully be investigated further involves the central effects of GLP-1RAs on central reward pathways that can affect cravings and addiction. Anecdotal data have described significant reduction in compulsive behaviors, including reduced alcohol use and even gambling, in patients who are on these medications. Consistent with this, low-dose semaglutide was associated with significantly reduced amount of alcohol consumed, drinks per day, and weekly alcohol cravings. I think a large part of why people struggle with weight gain and have difficulty with weight loss is the underrecognition and undertreatment of addictive behaviors when it comes to food intake, especially with sugars and highly palatable ultra-processed foods that are common in the American diet. Understanding the mechanistic role of GLP-1RAs on modulating these reward/addiction pathways could have widespread implications on not just obesity and metabolic syndrome–related disease such as MASH, but other lifestyle-influenced disorders, including alcohol-related liver disease. Interestingly, there is an ongoing clinical trial that is investigating the potential for a combination of semaglutide and other agents to treat patients with MetALD, a new disease entity that involves both metabolic dysfunction and alcohol-related steatotic liver disease.

***Disclosures***

*Dr Janardhan is a consultant for Novo Nordisk and Madrigal Pharmaceuticals.*

## Suggested Reading


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