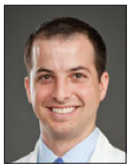
# ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

Section Editor: Eugene R. Schiff, MD

## Liver Transplant in Patients With Primary Sclerosing Cholangitis



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**G&H** What is primary sclerosing cholangitis?

**DG** Primary sclerosing cholangitis (PSC) is an autoimmune disease that affects bile ducts within the liver or outside of it. In almost all cases, these bile ducts are large enough to be seen on imaging. This is unlike primary biliary cholangitis, which is an autoimmune disease that affects bile ducts that are microscopic (ie, bile ducts that can only be seen via biopsy).

**G&H** What is the first line of therapy for patients with PSC?

**DG** The first line of therapy for these patients, and the only medical therapy currently available, is ursodeoxycholic acid. There are some data showing that this drug improves liver enzymes; however, there are only limited data showing its ability to prevent or slow the progression of PSC. In addition, ursodeoxycholic acid has not been shown to reduce the risk of PSC recurrence.

**G&H** For patients with PSC, what is the usual time frame from diagnosis to liver transplant?

**DG** For many years, the literature suggested that the time from diagnosis to the need for transplant or development of bile duct cancer was in the range of 10 to 15 years. However, those data were based on transplant centers with very sick populations. Data published approximately 2 years ago suggested that when looking at the broader population, this time frame was more likely 20 to 25 years. This is because researchers looked at the broader population, not just the sickest patients, who were being referred to advanced centers. Therefore, the prognosis may not be as dismal as thought in the past.

**G&H** What is the ideal time for liver transplant in these patients?

**DG** The ideal time for liver transplant could be viewed from a few different perspectives. Just like with any other disease, liver transplant is indicated when PSC patients are very sick and have decompensated liver disease and, thus, a high risk of complications such as ascites, fluid in the stomach, hepatic encephalopathy, or other complications of portal hypertension.

However, patients with PSC also have unique factors that can be considered indications. Patients may develop recurrent cholangitis or infections in the bile ducts, which can lead to hospitalizations and severe infections. Such a scenario may be an indication for transplant, especially if it requires repeated hospitalizations. The development of PSC symptoms, including weight loss and very intractable itching, can be considered an indication to transplant, particularly if it dramatically impairs the patient's quality of life.

Lastly, patients with PSC are at risk for developing cholangiocarcinoma, a type of cancer of the bile ducts, which can also be an indication for a liver transplant if the patients meet very specific criteria. The criteria for consideration of liver transplant for patients with cholangiocarcinoma, and receipt of exception points (extra waitlist priority), are based on tumor size and location, lack of spread outside of the liver, and management by a

transplant center with a specified protocol for cholangiocarcinoma in the setting of liver transplant.

**G&H** Have any studies examined the timing of liver transplant in patients with PSC?

**DG** There have been no systematic studies on this issue. Historically, repeated episodes of cholangitis were thought to be an indication for transplant and a reason to give patients extra priority. It was thought that having recurrent bouts of cholangitis, in and of itself, was associated with a higher risk of death. However, it appears that this notion is not actually true. Patients with cholangitis and repeated infections do experience impaired quality of life and repeated hospitalizations. However, data that my colleagues and I have recently published, as well as data that other groups have subsequently published, have shown that the presence of cholangitis is not associated with mortality.

**G&H** When is liver transplant contraindicated in patients with PSC?

**DG** As with patients with any condition, liver transplant is contraindicated when patients with PSC are too unstable or sick (eg, overwhelming infection, mechanical ventilation, or severe deconditioning and muscle wasting). More importantly, the main contraindication is the presence of very advanced cholangiocarcinoma that is either too large or has spread outside of the liver. This contraindication is unique to patients with PSC.

**G&H** Who is the ideal liver donor for a patient with PSC?

**DG** From the perspective of a transplant recipient, the ideal donor is a living donor. The data are convincing that people with PSC who receive a transplant from a living donor actually have much better outcomes, specifically longer survival of the graft and longer overall survival. These data include a study by my colleagues and I that looked at the national sample of all patients in the United States who had received a liver transplant either from a deceased donor or a living donor, making the cohort included in this analysis the largest cohort of patients that could have been studied for this condition.

The caveat is that the transplant should be performed by an experienced center because it has been shown that the outcomes of liver transplant differ based on center experience.

It should also be noted that using a living donor may have some disadvantages. Data from Japan, as well as recent data from the United States, suggest that receiving a living donor transplant from a first-degree relative might lead to a higher risk of recurrence of PSC. However, even though the living donor transplant may be associated with disease recurrence, this does not impact patient outcomes; it is still the patients who use a living donor who live longer.

**G&H** Are there any other advantages to using a living donor?

**DG** Another advantage of using a living liver donor is that surgery can be scheduled at a planned time. Currently, there is a shortage of organs, and patients need to be sicker and sicker before they have high enough Model for End-Stage Liver Disease (MELD) scores to receive a transplant from a deceased donor. A living donor transplant could be performed earlier than a deceased donor transplant, when a patient is more clinically stable and has not had to have many hospitalizations or become very sick. Having the transplant performed earlier also reduces the risk of a person dying on the waiting list while waiting for an organ.

In addition, there may also be benefits to performing a transplant from a donor who has not died. We know that in kidney transplants, the use of a deceased donor impacts outcomes because death is not a natural state for organs, and there is the potential that the benefits of using a living kidney donor may also be evident for using a living donor for a liver transplant.

**G&H** Are there any other disadvantages to using a living donor?

**DG** The obvious disadvantage is that the patient has to find someone who is willing to be a donor and to undertake the associated risk. Essentially, a healthy person, usually a friend or loved one, is undergoing major surgery. The risk of complications is low, but it still does exist.

In addition, when using a living donor, the patient only receives part of the liver, unlike when a deceased donor is used and the patient receives the full liver, with full-sized blood vessels and bile ducts. With a smaller liver, there is the risk that the liver may not be big enough, and patients may have complications. There is also an increased risk of bile duct complications and biliary strictures because smaller pieces are being connected.

**G&H** In terms of donor selection, are there any other factors that should be considered when selecting a liver donor for PSC patients?

**DG** In terms of donor selection, nothing else has specifically been shown to affect outcomes in PSC patients.

**G&H** Could you briefly explain how livers on the waiting list are allocated?

**DG** Livers are allocated on a "sickest first" system. Therefore, the sicker the patient, the higher the priority on the waiting list. Sickness is measured by the MELD score, which is calculated by laboratory values for kidney function, bilirubin, blood clotting, and international normalized ratio. The higher the calculated MELD score, the higher the priority on the waiting list.

As mentioned above, there is currently a shortage of organs, so there is a long wait on the waiting list. However, the wait is not based on time, it is based on how sick the patient is. Therefore, a patient could be on the list for 5 years, and another person who is sicker could come in and receive higher priority right away. We know that 20% to 25% of patients will die on the liver waiting list, and that does not even account for patients who are too sick or just cannot make it to the waiting list. Thus, waiting times can vary depending on how sick the patient is and why he or she is receiving a transplant.

**G&H** Among the various indications for liver transplant, how common is PSC?

**DG** The 3 most common indications are hepatitis C virus infection, alcoholic liver disease, and fatty liver. However, within these diseases, the indications vary and can involve end-stage liver disease, decompensated liver disease, liver cancer, and so on. PSC represents less than 5% of all liver transplants in the United States.

**G&H** How common is PSC in the United States?

**DG** It is difficult to fully estimate the prevalence of this disease. Unlike some diseases, PSC does not have an associated database or a specific International Classification of Diseases–9 code that can be checked to see how many people have the disease. Another challenge is that much of the data on PSC, including its prevalence, is derived from single centers, which are not fully representative of the larger population of the United States. According to the best estimate that is currently available, the prevalence of PSC is roughly 10 cases per 100,000 people.

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

**DG** It would be ideal to develop medications that can slow or prevent the progression of PSC. Currently, there are several ongoing clinical trials on new agents to slow disease progression prior to transplant. Ultimately, such agents may be able to prevent transplant. If any of these medications prove to be effective, it would be a logical next step to then see whether the drug prevents or treats a recurrence of PSC after transplant.

In addition, we need to identify patients who are at greater risk of becoming very sick or developing bile duct cancer so that they can be transplanted before they become ineligible for the procedure.

*Dr Goldberg has received consulting fees from Merck related to a study of patients with hepatitis C, and he is the site principal investigator for a phase 2 clinical trial of obeticholic acid for patients with PSC. However, he does not receive any direct funds from Intercept, which funds the study.*

## Suggested Reading


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