ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

Section Editor: Eugene R. Schiff, MD

Controversies in Liver Transplantation

James F. Trotter, MD
Medical Director of Liver Transplantation
Baylor University Medical Center
Dallas, Texas

G&H Should hepatitis C virus–positive patients with Child-Pugh class C scores who are on the transplant waiting list be treated prior to transplantation?

JT The answer is not clear and likely varies in different parts of the country depending upon several factors. The first factor is the availability and use of hepatitis C virus (HCV)-positive livers. In areas where these organs are very prevalent, the emphasis will likely be not to treat patients for HCV infection who are on the transplant list so that they can access HCV-positive livers. In parts of the country where HCV organs are not as prevalent, there will be a greater emphasis toward treating these patients prior to transplantation. A recent study in the *American Journal of Transplantation* showed that the usage of HCV-positive livers at individual centers varies between 0% and 40%. In fact, approximately one-quarter of the centers in the country have never used an HCV-positive liver, whereas at one center as many as 40% of the organs came from donors who were infected with HCV. Therefore, there is a wide variation in the use of HCV-positive livers. The decision of whether to treat patients prior to transplantation is based in part on this issue.

Another factor involves the Model for End-Stage Liver Disease (MELD) score at transplant. In parts of the country where MELD scores are particularly low, the emphasis will again be toward treatment. These patients can be rendered virus-free with a sustained virologic response (SVR) achieved by direct-acting antiviral agents and then transplanted at relatively low MELD scores (<25). In parts of the country where MELD scores are higher (particularly >30), there is likely less of an emphasis to treat those patients because treating them and rendering them virus-free would put them into so-called "MELD purgatory." This term refers to patients who are not sufficiently sick enough to quality for transplantation, but are not well enough to function adequately. This has long been an argument about why patients should not be treated.

A final factor to consider is the patient's ability to complete a continuous course of therapy, which is typically 12 weeks. The most common reasons for failure to achieve SVR is either not completing the full treatment course or taking the medication incorrectly (missing doses). This is likely more common in patients with decompensated liver disease requiring recurrent hospitalizations. In addition, there is evidence that patients with decompensated liver disease have a lower SVR rate compared with less sick patients.

Although it is difficult to make generalized statements on this topic, most clinicians would probably say that patients with MELD scores of 20 or higher are likely not good candidates for HCV treatment. However, this will vary across the country based upon physician experience, the availability of HCV-positive organs, and the MELD score.

G&H Should HCV-positive donor kidneys be used in HCV-negative hemodialysis patients?

JT The answer is not clear. The question of whether HCV-positive organs should be used in HCV-negative patients applies not only to kidney transplants, but to liver, lung, and heart transplants as well. One issue for kidney

transplants is that not all of the HCV treatment regimens are suitable for patients with renal failure. In fact, some of the most commonly used regimens are not approved by the US Food and Drug Administration for use in patients with renal dysfunction; therefore, the choice of therapies has to be determined carefully.

Another consideration is that using an HCV-infected organ in an HCV-negative patient is potentially infecting that patient with a potentially fatal viral infection at the time of transplantation. Although almost 100% of patients can be cured, it is conceivable that infecting such a patient could lead to death because of the development of severe HCV infection after transplantation, which, in some rare instances, may not be suitably treated with the new highly effective HCV regimens.

Another concern involves the logistics of obtaining HCV treatment for these patients, as many (although not all) of the therapies are not approved for use after transplantation.

There may also be difficulties receiving approval for HCV treatment from insurance companies, and all of these treatments are quite expensive. If a patient is infected with a virus that could potentially lead to death, it is essential to definitively know that the patient can be treated afterward. Although this is a controversial issue, if costs and logistics for HCV treatment can be accounted for, I think HCV-negative patients can receive HCV-infected organs. Personally, if I was on a transplant list and I did not have HCV, I would take an organ from an HCV-infected patient without any concerns as long as I could have a guarantee that I could get treatment afterward. The biggest problems are guaranteeing treatment and assuring patients that they will receive it.

On balance, most transplant professionals would likely agree that it is in the favor of the patient to accept these organs with the aforementioned caveats of cost and logistics being resolved. Studies are currently being planned and are under institutional review board (IRB) approval for treating patients in this setting. For example, there is a study underway at the University of Pennsylvania on people receiving kidneys from HCV-positive donors. There was a meeting at the last American Association for the Study of Liver Diseases conference about putting this study through an IRB and getting multiple like-minded centers to accept use of HCV-positive organs, at least for liver transplantation, with a plan in place to give patients 100% assurance that they will be treated for HCV infection following transplantation. This is an area of active interest and investigation.

G&H When should cirrhotic patients with portal vein thrombosis who are awaiting transplantation receive anticoagulation?

JT Historically, treating portal vein thrombosis in patients listed for transplantation has not been undertaken. However, in recent years there have been data demonstrating the efficacy of this treatment. Thus, more and more centers are treating patients with portal vein thrombosis who are listed for transplantation. One potential advantage is improved outcomes, which have been shown in randomized trials. In addition, reestablishing blood flow in the portal vein will likely improve patient outcomes after liver transplantation.

However, although centers are increasingly changing their practice and treating patients with portal vein thrombosis before transplantation, it is important that patients be carefully selected for being compliant, regimens also be carefully selected, and patients be carefully monitored.

G&H Should cachectic patients awaiting liver transplantation receive nutritional treatment?

JT Frailty and sarcopenia are emerging issues in liver transplantation. These concepts provide an objective measure for the subjective appearance of deconditioned and physically wasted patients. Frailty is objectively assessed through performance metrics such as grip strength and measured walking, whereas sarcopenia is formally assessed by measurement of the psoas muscle area on cross-sectional imaging. Cirrhotic patients with sarcopenia have increased mortality before and after liver transplantation. Thus, there is ongoing investigation to better characterize these patients and evaluate them for potential therapies. However, to my knowledge, there is no known therapy that has been shown to predictably reduce mortality for these physically ill patients.

G&H What is the status of transplanting patients with alcoholic hepatitis?

JT A landmark study from France several years ago in *The New England Journal of Medicine* indicated that very carefully selected patients with acute alcoholic hepatitis who were refractory to standard therapy had favorable outcomes after liver transplantation. However, these patients were only a small proportion (7%) of all patients who presented with this disorder. Nevertheless, the study findings led to the reexamination of transplantation for acute alcoholic hepatitis. Most centers in the United States are not transplanting these patients. In a recent survey of the approximately 100 liver transplant centers in the United States, only 12 of the 45 centers that responded had listed a patient with acute alcoholic hepatitis, and 11 performed a transplant for such a patient, representing only 1.4% of all transplants at these centers.

Two small case series of liver transplantation for acute alcoholic hepatitis have shown generally favorable results for this indication. However, experienced clinicians have concerns about this application of liver transplantation, most of which involve parity and likelihood of recidivism after transplantation. In addition, the high priority given to critically ill patients with MELD scores over 35 may allow an increased proportion of acute alcoholic hepatitis patients to be transplanted because these patients are typically younger and less debilitated than similar patients with chronic liver disease.

G&H Should the current allocation system for liver transplantation be adjusted?

JT The most effective means to allocate and distribute livers for transplantation has been evolving since inception of the procedure. Essentially, the problem is that there are more patients than there are livers, and there will never be an adequate system to rectify this problem to the satisfaction of all of the stakeholders in the immediate future. Recently, the proper allocation and distribution of livers across the United States has been revisited.

In 1999, the Institute of Medicine issued a mandate called the Final Rule, which stated that geography of residence should be irrelevant to a patient's ability to receive a liver transplant and that patients should be prioritized based upon an objective scoring system. This led to MELD-based liver allocation, which was implemented in 2002. However, the issues of geography were never effectively dealt with at that time. As noted above, there remain vast differences in the severity of illness at the time of transplantation and access to livers across the United States based upon a person's residence.

In response to growing pressure to equalize access across the country, the United Network for Organ Sharing (UNOS) Liver Committee proposed "redistricting," whereby areas of organ allocation would be increased to include wider geography via 4 or 8 districts across the United States. The vast expansion of geographic distribution would effectively normalize MELD scores at transplantation by moving organs from areas of relative excess to areas of organ scarcity. However, as with any change in liver allocation, controversy ensued with this proposed change. There have been 2 national meetings sponsored by UNOS in the past several years. Proposals have been sent out for public review, and there was a recent ballot initiative through UNOS about the redistricting proposal. However, it was surprisingly voted down by a wide margin. In general, transplant centers voted based upon their own interest. Centers at risk for losing donor organs voted against the proposal, and those who stood to benefit voted in favor. Thus, at the current time, although the Institute of Medicine, the Secretary of Health and Human Services, and UNOS are in support of widening geographic areas of organ distribution, the liver transplant community as a whole has not supported this. Nevertheless, most physicians feel as though eventually some type of system will be developed that will widen geographic areas of liver allocation, although no one knows what it will look like or what the process will be. At this time, this issue is very much in flux.

Dr Trotter has no relevant conflicts of interest to disclose.

Suggested Reading

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