ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Hepatitis C Virus–Viremic Liver Transplantation

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G&H For a patient with active hepatitis C virus infection, how do outcomes compare when receiving a liver also infected with active hepatitis C virus vs a liver without the virus?

DG First, it is important to note that a consensus paper published last year by the American Society of Transplantation recommended that the terminology historically used in this setting, hepatitis C virus (HCV)-positive, be replaced with HCV-viremic or -infected to signify active virus in the blood that can be detected. Approximately one-third of donors who would have been labeled HCV-positive in the past no longer should be, as they have a positive HCV antibody but no detectable virus in the blood. The vast majority of these people were previously infected with HCV but cleared the infection spontaneously on their own and have a normal immune system. Thus, they do not have active infection, which means that there is no risk of transmitting the virus unless they develop a secondary HCV infection.

In terms of outcomes, the transplantation of HCV-viremic livers to HCV-viremic patients is comparable to the transplantation of non–HCV-viremic livers to HCV-viremic patients as long as the donor liver is good (ie, does not have much scarring). This can be determined by performing a simple visual inspection and looking at laboratory findings, or by obtaining a biopsy at the time of procurement to look at how much scar tissue is present. Currently, it is considered standard of care to transplant a HCV-viremic liver into a HCV-viremic patient, and, with the new, highly effective direct-acting antiviral (DAA) agents, there is no reason to expect that the outcomes for graft and patient survival would be any different from the outcomes associated with transplanting a donor liver without active HCV infection into that HCV-viremic patient.

G&H According to the most recent literature, how safe and effective are DAA agents in HCV-viremic patients pre- or posttransplantation?

DG DAA agents have been well studied in various patient populations and are all thought to be safe. Data have shown that cure rates posttransplantation appear to be the same as pretransplantation (98%-99%), and recurrence is no longer an issue (unlike in the past).

However, protease inhibitor–based therapies may not be as safe if patients have liver dysfunction (eg, if patients have posttransplant complications and high bilirubin levels), and sofosbuvir-based regimens are to be used with caution if patients have renal dysfunction (particularly if it is very severe). Potential therapies are more limited in these patients, although by and large, doctors can still find a DAA regimen that can be used safely before or after transplantation.

In the past, some HCV drugs did not work well for certain genotypes, so doctors would try to avoid giving a patient with an easy-to-treat genotype a liver from a donor with active HCV infection because of the risk of transmitting a hard-to-treat genotype. However, with the current DAA therapies, genotypes are a nonissue.

G&H What is the optimal timing for HCV treatment in these patients—before or after liver transplantation?

DG This issue is still being debated within the community. It is clear that if a HCV-viremic patient is going to receive a living donor transplant, the HCV should be treated first to maximize the patient's outcomes. However, the vast majority of people who need a liver transplant do not have living donors. Thus, the question becomes whether or not treating the patient's HCV may allow him or her to recover liver function to the point that a liver transplant could be delayed or perhaps even avoided. If a patient has mild liver dysfunction (ie, he or she has a Model for End-Stage Liver Disease [MELD] score of 15 but is otherwise fairly stable), it is possible that HCV treatment might allow him or her to get better and avoid transplantation.

Once it has been determined that transplantation is needed, there are different thresholds at which point patients may be treated. Modeling studies have tried to determine the optimal MELD score for treating patients, but are only as good as the data that are inputted. The optimal timing likely depends on how sick the patient is and where in the United States he or she is located. There is a large geographic variability in the supply of HCV-viremic donor livers. For example, the donor supply is larger in the Northeast, Southeast, and Ohio Valley, partially due to the increasing number of people with HCV dying of opiate overdoses. Thus, at my transplant center, which is located in Philadelphia, and others in the Mid-Atlantic, HCV-viremic patients may be transplanted with a HCV-viremic liver when having a MELD score 10 points lower than in other areas of the United States. Therefore, my threshold to treat HCV is much higher. In areas where there are fewer donors, the risks and benefits of treating before vs after liver transplantation may differ.

However, because there are many HCV-viremic donors and fewer patients being listed with active HCV infection, and because HCV treatment is now so effective, it often works in the patient's favor to leave the virus active and not receive HCV treatment until after liver transplantation.

G&H Has there been any research on the use of HCV-viremic livers for transplantation in non–HCV-viremic patients?

DG A recent Markov model found that such transplantation is cost-effective. There have also been several case reports or case series on the transplantation of HCV-viremic livers in non–HCV-viremic patients with excellent posttransplant outcomes and HCV cure rates.

Thus, one of the biggest questions is whether HCV-viremic to non–HCV-viremic liver transplantation should be offered to all patients, or whether it should be kept to clinical trials. Currently, only some transplant centers are performing this type of transplantation, although the exact number is not known because there is no mandatory reporting of this practice. No databank is tracking this information, even transplant registries such as the United Network for Organ Sharing database. When a patient is placed on an organ waiting list, transplant centers ask if the patient has a HCV antibody but do not ask whether the virus is active. Thus, if a patient with active HCV infection was treated and cured several years ago but then has a complication requiring liver transplantation, the patient would still be recorded as HCV-positive even though his or her infection is no longer active. If that patient is given a HCV-viremic liver, the transplant would not be recorded as HCV-viremic to HCV-negative even though it essentially is.

In addition, it should be noted that the probability of HCV-viremic livers being used is the same as for non–HCV-viremic livers. Therefore, the decision to perform HCV-viremic to non–HCV-viremic transplantation is not necessarily going to increase the number of livers being used; it is just shifting to which patients the livers are being given.

G&H What are the main benefits and concerns associated with HCV-viremic to non–HCV-viremic liver transplantation?

DG The main benefit is that people who are sick can potentially be transplanted faster, which may help to minimize deaths on the waiting list and improve patient outcomes. For example, depending on where a patient is located in the United States, a MELD score in the 30s might be necessary for a patient in blood group O to obtain a non–HCV-viremic liver. In contrast, obtaining a liver from a HCV-viremic donor might require a MELD score only in the 20s for a patient in blood group O.

One of the potential concerns of HCV-viremic to non–HCV-viremic liver transplantation is the fact that it actively infects the patient with HCV. Because the liver is one of the main sources of problems associated with HCV infection, it is thought that such transplantation should be safe. However, I would argue that until we have sufficient data, we do not know for sure because HCV is being introduced to the patient and could affect other parts of the body, such as the kidneys.

Nevertheless, the biggest concern associated with this transplantation involves HCV treatment and insurance. If a patient has active chronic HCV infection and obtains a transplant from a HCV-viremic donor, the patient still

has active chronic HCV infection. Obtaining insurance approval for HCV treatment should not be an issue in this scenario (although there may be some delays for approval, potentially up to several weeks, and an appeal may be required). In contrast, if a non–HCV-viremic patient receives a liver from a HCV-viremic donor, although the HCV in that liver is chronic, the patient would arguably have acute HCV infection following transplantation. However, none of the HCV drugs currently available are approved by the US Food and Drug Administration for acute HCV infection, and few are approved for use after liver transplantation (even though they are often used in this setting). Therefore, it is possible that an insurer could refuse to approve HCV therapy for the patient. In addition, I have heard that some insurers still consider actively infecting someone with HCV to be experimental and, therefore, will not approve HCV therapy. In my opinion, the most significant barrier preventing this type of transplantation from becoming more widespread is the question of whether it is ethical to give a non–HCV-viremic patient a liver from a HCV-viremic donor if HCV therapy cannot be guaranteed after transplantation. Some transplant centers have tried to obtain guarantees from their health care system that if insurance does not approve HCV treatment, the health care system will cover the cost of therapy, but this is not universally done. Other health care systems, such as Kaiser Permanente, are closed systems that act as both the provider and the insurer. In such cases, therapy can be guaranteed. Despite the probable overall safety of HCV-viremic to non–HCV-viremic liver transplantation, if HCV treatment cannot be guaranteed posttransplantation, I would argue that it is unethical to perform.

G&H If HCV treatment can be guaranteed posttransplantation, should HCV-viremic livers be transplanted in non–HCV-viremic patients?

DG I think that this type of transplantation should be performed only in specific circumstances. The most important caveat, as mentioned above, is that HCV therapy must be guaranteed posttransplantation. I do not think that this transplantation should be performed in a setting where the plan is to apply to insurance and if insurance refuses, there is no way to guarantee therapy.

In addition, HCV-viremic to non–HCV-viremic liver transplantation should be performed under a regulated protocol in terms of obtaining consent because there are still unknowns about this type of transplantation (such as the risks of infecting the patient with HCV). It is important to make sure that patients understand the potential risks and unknowns. Thus, I would argue that this type of transplantation can be performed, but it has to be done only under specific circumstances, and I do not think that it is ready for standard of care.

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

DG Research is needed to determine whether there are any extrahepatic complications (eg, involving the kidneys or other organs) associated with infecting the patient with active HCV. In addition, we need research demonstrating that DAA agents work in the setting of posttransplant acute HCV as well as they do in the nontransplant setting. As previously discussed, we believe that this is the case, but research is needed for definitive proof.

One of the challenges of research in this area involves the debate of whether formal studies are needed, and if so, whether studies have to be registered at Clinicaltrials.gov or can be performed at transplant centers using their own internal approval process. One of the reasons we do not know how commonly HCV-viremic to non–HCV-viremic liver transplantation is being performed is that, unlike with new drug trials, the procedure may be performed without being registered at Clinicaltrials.gov. There have been gray areas as to what defines a trial.

Dr Goldberg has received research grant support from Merck through investigator-initiated grants to conduct trials of transplanting kidneys and hearts from HCV-viremic donors into patients without active HCV infection.

Suggested Reading

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