
a series of fact sheets written
by experts in the field of liver
disease

HCV Disease Progression:

Liver Transplantation

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DESPITE IMPROVEMENTS IN TREATMENTS, many people with hepatitis C still develop cirrhosis and liver cancer. As disease progresses to the point where the liver is unable to carry out its important functions (end-stage liver disease, or ESLD), a liver transplant is usually the only option. In the United States and Europe, hepatitis C is the most common reason for liver transplantation. While much remains to be learned about liver transplantation, the current picture contains both good news and bad.

The good news is that liver transplant survival rates have increased steadily in recent decades with the development of improved surgical techniques, more experience with post-transplant medical management, and better immunosuppressive drugs. The one-year post-transplant survival rate has increased from about 30% in the 1970s to 85-90% today, and the five-year survival rate is about 75-80%.

The bad news is that there is a severe and worsening shortage of donor livers. There are currently more than 17,000 people on the United Network for Organ Sharing (UNOS) liver waiting list; in 2004, about 6,000 liver transplants were performed. Given this discrepancy between supply and demand, about 10% of patients die each year while on the waiting list.

MELD System (Organ Allocation)

A process is in place to ensure that the most appropriate candidates receive available cadaver livers (livers from deceased persons). In 2002, UNOS adopted a new system

called MELD (Model for End-Stage Liver Disease) that uses three lab tests – bilirubin, creatinine, and prothrombin time – to predict how likely patients are to die. Previously, candidates were assigned a status based on symptoms of decompensation such as ascites, bleeding varices, itching, blood clotting problems, or encephalopathy. The MELD system is intended to give priority to patients who need new livers most urgently, rather than to those who have been waiting the longest. According to a study in the January 2004 issue of *Liver Transplantation*, the number of liver transplants increased by 10% and the waiting list mortality rate fell by nearly 4% after MELD was adopted.

But the new allocation scheme remains controversial since it tends to prioritize patients with specific causes of liver disease (especially liver cancer) and does not take into account other factors that might make certain patients higher priority candidates. As such, researchers are studying new metrics for allocation. T.I. Huo and colleagues, for example, reported in the June 2005 *Journal of Hepatology* that the change in MELD score over time may be a more accurate predictor of mortality risk than the MELD score at a single time point.

Given the shortage of donor livers, new methods have been developed to extend the supply, including split liver and living donor transplantation.

Split Liver Transplantation

The liver is the only organ in the body that can regenerate itself. Thus, a cadaver liver may be split into two pieces and transplanted into two recipients, where each piece will grow into a fully functioning organ. Split liver transplants produce the best results when the larger right lobe is given to an adult and the smaller left lobe goes to a child. In some cases, split liver transplants may be appropriate for two adults, depending on donor and recipient size. In the future, the split liver procedure may become more widely used if researchers figure out a way to accelerate liver regeneration.

Living Donor Liver Transplantation

In a living donor transplant, a piece of liver is taken from a live person, usually a relative (although livers do not require close genetic matching like some other organs). Pioneered in the late 1980s, several thousand living donor liver transplants have been performed to date, and the procedure now accounts for about 5% of all liver transplants. While living donor

transplants have the potential to dramatically increase the supply of organs, the procedure is not without risk to the donor. A study published in the February 27, 2003 *New England Journal of Medicine* found that 65 of 449 donors (14.5%) experienced at least one complication, including bile leakage, infection, and excessive bleeding. In 2002, a living donor at Mount Sinai Hospital in New York City died of an infection after donating a section of his liver to his brother, but such deaths are very rare. Occasionally, under very specific circumstances, a “domino” procedure may be done in which one patient receives a new donor liver and that patient’s old liver is then given to a second recipient.

In the January 2006 *Journal of Hepatology*, Mylene Sebagh and colleagues compared the outcomes of split liver, living donor, and domino procedures at a single center in France. They found that the rate of acute and chronic organ rejection was similar among the groups, but acute rejection was more severe in the split liver group. The split liver group was also more likely to experience biliary complications (40% for split liver, 26% for living donor, 8% for cadaver donor), possibly because bile ducts are more heavily damaged when the liver is divided into sections. In general, the survival rate for split and living donor transplants is similar to the rate for cadaver transplants, but some evidence suggests people with hepatitis C do less well with living donor organs.

Other Transplant Options

There have also been proposals to use “less than optimal” livers to expand the supply, including organs from older donors. But this is a risky option. As reported in the March 2005 *Archives of Surgery*, Derek Moore and colleagues found that the three most important factors affecting post-transplant survival and quality of life were donor age, recipient’s UNOS urgency status, and cold ischemic time (the amount of time liver is kept on ice, without a supply of oxygen, after removal from the donor). The five-year graft survival rate was 72% when the liver came from a donor younger than 60 years, compared with 35% when the donor was age 60 years or older. In another study, 14% of HCV positive patients who received livers from donors younger than 30 years experienced recurrent post-transplant cirrhosis, compared with 45% of those who received livers from donors age 31-59, and 52% who received organs from donors older than 59.

An exception to the optimal liver rule may apply for people with HIV and/or HCV. Today, livers from HCV positive people, HIV positive people – and even groups considered “high risk,” including HIV negative gay men – are not accepted for trans-

plants. Studies suggest that HCV positive patients who receive HCV-infected livers fare no worse than those who receive HCV-free organs. Since the advent of highly active antiretroviral therapy (HAART), numerous studies have shown that HIV positive people with well-controlled HIV disease (i.e., undetectable or low HIV viral load, CD4 cell count of at least 200 cells/mm³, no opportunistic infections) have post-transplant survival rates similar to those seen in HIV negative individuals. Dozens of HIV positive liver transplants have been performed to date, and lawsuits have forced insurers to cover them. HIV/HCV coinfecting people tend to experience faster liver disease progression than HIV negative people, and (as reported in the November 2005 issue of *Liver Transplantation*) HIV positive individuals are more likely to die on the liver waiting list – even if they do not initially have more severe HIV disease or liver disease. Some experts believe coinfecting patients should be given higher priority for transplants, but this is difficult due to the scarce liver supply. Use of livers from HIV positive or at-risk donors may be a partial solution for this population.

The 17,000 people on the liver waiting list today is up from about 3,000 in 1993. The number is only expected to grow as people infected with HCV decades ago begin to develop end-stage disease or liver cancer. From a social standpoint, the severe organ shortage has prompted calls for policy changes, such as the “presumed consent” system – already in place in some European countries – under which people are automatically considered potential organ donors unless they explicitly opt out. In terms of living donor transplants, it is crucial to ensure that prospective donors are truly making an informed, voluntary decision without financial or other types of pressure.

HCV and Liver Transplantation

Liver transplant patients with hepatitis C face an additional challenge: HCV almost always infects the donated liver and may cause a new round of fibrosis progression.

Liver Transplantation and HCV Recurrence

A large body of research has shown that in untreated liver transplant recipients with chronic hepatitis C, HCV almost always infects the new liver within weeks, and sometimes in as little as 24 hours. Some – but not all – studies suggest that patients with hepatitis C fare less well after liver transplantation than HCV negative individuals. As reported in the June 27, 2004 issue of *Transplantation*, for example, Ergun Velidedeoglu, MD, and colleagues analyzed more than 13,000 patients in the UNOS database, 57% of whom had hepatitis C. They found that the five-year survival rate was 74.6% for HCV positive patients, compared with 83.5% for HCV negative

individuals. Indeed, liver failure due to recurrent hepatitis C is a leading cause of death among liver transplant recipients.

Some experts have gone so far as to describe post-transplant HCV recurrence as “universal,” but here again, data are mixed. It is evident that many patients who achieve sustained virological response (SVR) with interferon-based therapy prior to transplantation still experience viral recurrence. This indicates that a low level of HCV genetic material remains in the body waiting to “seed” the new liver, even if it is undetectable using standard tests. As reported in the January 2006 *Journal of Hepatology*, for example, Martina Gerotto and colleagues found that 26 of 208 hepatitis C patients (12.5%) who had repeatedly undetectable HCV viral load at the end of treatment using common polymerase chain reaction (PCR) technology still had residual detectable HCV RNA using a more sensitive transcription-mediated amplification (TMA) assay.

Based on research to date, the natural history and prognosis for post-transplant HCV recurrence remain uncertain, as studies have yielded conflicting data. In a forum on liver transplantation and hepatitis C in the April 2005 *Journal of Hepatology*, Greg Everson, MD, described three patterns of recurrence. While a small proportion of patients experience severe cholestatic hepatitis, recurrent HCV infection most often becomes chronic and evolves in a manner similar to that seen in nontransplant patients – but typically more rapidly and with a higher viral load set point. Everson estimated that approximately 25% of transplant recipients develop cirrhosis in the grafted liver within 5-10 years (compared with 10-40 years in nontransplant patients). Various studies have revealed a number of factors associated with rapid fibrosis progression, including genotype 1 (especially 1b) or 4 HCV, non-Caucasian race/ethnicity, donor and recipient age, and ischemia time; female gender has also been linked to worse progression, which is surprising since among nontransplant patients, women usually fare better than men.

Accelerated HCV-related disease progression is thought to be the result of impaired immunity due to immunosuppressive drugs used to prevent organ rejection. Some studies have shown that administration of a large dose (bolus) of corticosteroids to treat acute rejection can worsen HCV disease severity. Conversely, other research suggests that avoiding corticosteroids altogether may be beneficial. On the other hand, there is also evidence that rapid reduction of corticosteroid dosages may exacerbate HCV disease progression. Data on the risks and benefits of other types of immunosuppressive therapy, including mycophenolate mofetil and azathioprine,

has also been inconsistent. Thus, for now, the best approach remains open to debate. According to Everson, it is likely that “the interplay between the immune system and the virus,” along with recipient genetic factors and the quality of the liver graft, influences post-transplant outcomes. Recent experience has shown that HIV positive transplant recipients have survival rates similar to those seen among HIV negative recipients, as long as they have well-controlled (ideally undetectable) HIV and relatively intact immune systems (e.g., CD4 cell counts of at least 200 cells/mm³); however, HIV/HCV coinfecting patients fare more poorly than HIV positive people receiving liver transplants for other reasons.

The good news is that some patients experience minimal liver disease progression several years after transplantation. Certain individuals show no evidence of HCV recurrence or damage to the new liver even after 10 years. Because hepatitis C normally progresses so slowly, even if fibrosis advances at a similar or moderately accelerated rate in original and newly transplanted livers, this can buy recipients 10-20 or more years of good liver function and the associated improvement in quality of life.

Pretransplant HCV Therapy

While data on the ubiquity of post-transplant HCV recurrence may appear grim, there is ample evidence that the lower one's HCV viral load at the time of transplantation, the less chance of recurrence – and the less chance of severe disease and rapid progression if the virus does come back. In some studies, more than half of patients achieving SVR with pretransplant interferon-based therapy did not experience HCV recurrence. Yet individuals awaiting transplants typically are quite ill and often have difficulty tolerating the side effects of interferon and/or ribavirin. Looking at the debate over whether to treat hepatitis C patients on the liver waiting list, Everson noted that while tolerability of therapy remains a serious concern, it is often worth pursuing since pretransplant treatment currently prevents post-transplant recurrence in as many as 25% of cases. And even therapy that does not eradicate the virus may still help prevent fibrosis progression.

Post-Transplant HCV Therapy

If pretransplant treatment is the first line of defense, commencing hepatitis C therapy immediately after transplantation – a sort of post-exposure prophylaxis – may also help prevent recurrence by inhibiting the rapid viral replication that typically occurs in the hours and days following the operation. Though post-transplant SVR rates are lower than those seen in nontransplant patients – largely due to the inability to

tolerate therapy – roughly 25% achieve long-term undetectable HCV RNA. Here, too, interferon may help stave off liver damage even if viral load remains detectable. But, as Isabelle Morard and Francesco Negro, MD, explained in the *Journal of Hepatology* forum, post-transplant disease progression varies widely among patients, and it is not clear whether immediate preemptive therapy – which would subject some patients unnecessarily to adverse side effects – is preferable to waiting until evidence of damage to the new liver becomes apparent.

Other Factors for HCV Recurrence

In addition to hepatitis C therapy, liver selection and transplant procedures can also make a difference. Since HCV patients are at greater risk for poor post-transplant outcomes, they may derive more benefit from receiving livers from younger donors. As Yasuhiko Sugawara, MD, and Masatoshi Makuuchi, MD, discussed in the *Journal of Hepatology* forum, some research indicates that HCV patients experience faster viral recurrence and more severe and rapid liver disease progression after living donor, compared with cadaver donor, transplants. The reasons for this phenomenon are not yet known, but may be related to heightened HCV replication as the liver section from a living donor regenerates in the recipient. On the other hand, success rates for living donor transplants have increased in recent years, and the apparent detriment seen in earlier studies may have been attributable to lack of experience with the procedure.

As treatment for hepatitis C improves – ideally becoming both easier to tolerate and more effective at suppressing the virus – more HCV positive individuals may truly eradicate the virus before or immediately after transplantation, thus minimizing the risk that HCV will invade their new livers.

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