

Hepatitis C

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Long-Term HCV Persistence

Sustained virological response (SVR), the gold standard for judging the effectiveness of hepatitis C therapy, means that HCV RNA is still undetectable in the serum six months after the end of treatment. But achieving SVR does not necessarily mean HCV is completely and permanently eradicated from the body. In the June 2004 issue of the *Journal of Virology*, T.N. Pham and colleagues reported that HCV genetic material persists in certain immune system white blood cells. Using a highly sensitive PCR assay, the researchers detected HCV RNA in the peripheral blood mononuclear cells (PBMCs) of all 16 tested patients up to five years after spontaneous or treat-

ment-induced HCV clearance. The virus was also detected in monocyte-derived dendritic cells in 6 out of 7 patients tested. "These results imply that HCV RNA can persist at very low levels in the serum and peripheral lymphoid cells and that an intermediate replicative form of the HCV genome can persist in PBMC for many years after apparently complete spontaneous or antiviral therapy-induced resolution of chronic hepatitis C," the authors concluded.

Post-Transplant HCV Therapy

This long-term persistence helps explain why HCV almost always reinfects the new liver after patients with chronic hepatitis C receive transplants. In the July 2004 issue of the *Journal of Hepatology*, Montserrat

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Garcia-Retortillo and Xavier Forno reviewed the current state of knowledge about HCV prevention and treatment in liver transplant recipients. HCV replication in the new liver typically occurs within a few weeks after transplantation, following a sharp decrease in viral load. Unlike hepatitis B, therapeutic immunoglobulins (antibodies) do not appear to prevent infection of the new liver, although studies are underway with new types of antibody preparations.

Although anti-HCV therapy can be risky in people with decompensated cirrhosis, interferon plus ribavirin are increasingly used in HCV patients awaiting a liver transplant. While adverse events are common and these patients often must discontinue therapy or decrease their dosage, some do achieve SVR—although the rates are lower than those seen in HCV patients with less advanced liver disease. Other researchers have tried treating patients with interferon-based therapy soon after liver transplantation, while their HCV viral load is still low. Although adverse events and treatment discontinuation are again common, studies

show that a small number of patients can benefit from therapy started within the weeks following transplant. More commonly, however, HCV treatment may be started months or years after liver transplantation. Because liver damage tends to progress more rapidly in people with compromised immune systems—and transplant recipients must take immunosuppressive drugs to prevent organ rejection—frequent biopsies of the new liver are indicated to monitor disease progression.

In the July 2004 issue of *Liver Transplantation*, Todd Stravitz and colleagues reported on a retrospective evaluation of interferon therapy in 23 post-transplant patients with recurrent hepatitis C and histological evidence of fibrosis progression. The patients completed at least six months of interferon therapy (83% with pegylated-interferon), but only four were able to tolerate ribavirin. After six months of treatment, 11 patients (48%) had undetectable HCV RNA; of these, eight (35% of the total) achieved SVR. Liver biopsies performed two years after HCV became undetectable showed decreased necroinflammatory activity, and 6

of 11 patients showed histological improvement on follow-up liver biopsies. Eight (35%) of the 23 patients treated with interferon showed evidence of liver rejection and two required retransplantation. These results are consistent with those of other studies showing that post-transplant SVR rates are lower than those seen in non-transplant HCV patients, but that patients who do respond often show improved necroinflammatory activity and decreased fibrosis progression.

Interferon and Liver Rejection

Because of its immunomodulatory activity, interferon may increase the risk of organ rejection. This is known to occur in kidney transplant recipients, but data regarding liver recipients has been inconsistent. In the same issue of *Liver Transplantation*, Sammy Saab and colleagues examined acute rejection in 44 new liver recipients treated with interferon for recurrent HCV. Five (11.4%) developed acute liver rejection during interferon therapy, a rate higher than that seen in liver transplant patients not receiving interferon. These five started interferon an average of 42 months (and

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up to 83 months) after transplantation, and were treated an average of three months before rejection set in. Rejection was successfully treated with steroids and increased immunosuppressive drugs in three patients, although two of these rapidly developed cirrhosis. One other patient required a second liver transplant, and the final patient died due to sepsis. “Interferon-based therapy may lead to acute rejection and subsequent graft loss and should therefore be used with caution,” the authors concluded. Because it stays in the body longer, pegylated interferon may be more likely to cause rejection than standard interferon. (In this study, four of the five patients who experienced rejection were receiving pegylated interferon.) Conversely, ribavirin may reduce the risk of rejection, but many post-transplant patients cannot tolerate the drug.

Interferon-induced organ rejection may be related to increased HLA mismatches between the recipient and the donor liver. HLA antigens are cell markers that allow the immune system to distinguish “self” from “non-self.” Interferon may enhance the expression of

HLA antigens in the donor liver and bile ducts, triggering an attack by the recipient’s immune system. Some laboratory studies have shown HLA expression is enhanced in response to interferon.

However, in the August 2004 issue of the *American Journal of Transplantation*, Francesca Cardarelli and colleagues reported that among 44 liver transplant recipients tested, anti-HLA antibodies were detected in about 8% of HCV patients receiving interferon, 20% HCV patients not on interferon, and 10% of HCV-negative patient—not a statistically significant difference. Among this group of patients, none experienced acute rejection after starting interferon.

In an editorial in the *July Liver Transplantation* Didier Samuel noted that, “[A]ntiviral treatment is now fully part of the overall therapeutic strategy post-transplantation.” But caution is warranted, and more research is needed. “[F]rom these [Stravitz’s and Saab’s] reports, we can conclude that while there is a risk of rejection during interferon-based treatment for hepatitis C recurrence after liver transplantation, the prevalence and the severity of rejection remains matters for debate.”

