A recent review article made this statement: “… the management of recurrent hepatitis C virus (HCV) disease after orthotopic liver transplantation is among the most pressing issues facing transplant physicians and surgeons today”. We agree, but would add that the patients themselves, along with their local physicians who take care of them, are equally important.

HCV is the most common indication for liver transplantation, but, strikingly, liver transplantation does not cure the disease. HCV infects the new graft in the operating room. The clinical course of recurrent HCV is variable, with some patients experiencing only viremia with no liver injury, and others developing aggressive HCV within one year. Recurrence of HCV following liver transplantation can lead to significant morbidity and mortality. A large retrospective review revealed that recurrent HCV infection was associated with a 30% higher graft failure rate and a 23% higher death rate than in patients transplanted without HCV. Several factors have been examined in an effort to learn what determines the course of recurrent HCV. The most influential factor is thought to be post-transplantation immunosuppressive therapy. There has been no definitive study comparing whether tacrolimus or cyclosporine is more effective in preventing the recurrence of HCV. Likewise, the use of azathioprine, mycophenolate mofetil, and/or antilymphocyte antibodies will need randomized controlled studies to determine their effect on recurrent HCV. The data suggesting that avoidance of corticosteroids may be beneficial for patients with recurrent HCV following liver transplantation has prompted the University of Washington Medical Center, along with several other centers, to avoid steroids in patients transplanted for HCV. However, if treatment with steroids is required, we avoid rapid withdrawal of steroids due to reports of possible harm from rapid tapering.

Other than avoiding corticosteroids, or at least avoiding rapid steroid withdrawal, how can patients with HCV be managed after transplantation? Three treatment strategies are available, based on the timing of the treatment. These are prophylactic, preemptive, and post-transplantation therapies.

**Prophylactic** therapy with hepatitis C immune globulin is given at the time of transplantation. Preclinical studies with hepatitis C immune globulin in nonhuman primates showed promise, but in 15 human study patients, administration of hepatitis C immune globulin did not change serum hepatitis C viral levels, and infection occurred in all patients. This therapy remains experimental.

**Preemptive** therapy involves administering antiviral agents following liver transplantation before evidence of HCV recurrence. Unfortunately, antiviral therapy is poorly tolerated in the immediate post-operative period when patients are recovering from surgery and adjusting to their immunosuppressive medication. The antiviral treatment regimen may also lead to a higher incidence of rejection. The largest trial of preemptive therapy compared interferon (IFN) (3 million units thrice weekly) or pegylated IFN (peg-IFN) (1.5μg/kg per week) alone or in combination with ribavirin (RBV) (600mg increased to 1000 to 1,200 mg/day). The success rate was only 9.1%, with 85% of the patients requiring dose reduction, 37% requiring discontinuation, and 27% experiencing a serious event, including rejection. Preemptive therapy remains poorly tolerated, requires constant assessment and careful monitoring, and may be associated with serious side effects and adverse events.

In **post-transplantation** therapy, physicians wait until stabilization after transplantation before starting complicated treatment regimens for patients who develop histological evidence of HCV recurrence in the graft. Combination peg-IFN and RBV seem to achieve the best results, yet a large randomized controlled study is lacking. In one study, peg-IFN (1.5μg/kg/week) plus RBV (600mg/day for 24-48 weeks) lowered viral titers in 34.7% of the study patients, with 12.5% requiring drug discontinuation. Whether progression of fibrosis is slowed with this therapy is unknown. The main complications are anemia and leukopenia. For post-liver transplant patients who develop recurrent HCV
as shown by the histological signs of progressive fibrosis on follow-up liver biopsies, the University of Washington Liver Transplant Program is available to provide guidance on the most effective therapy.

The need for newer and more efficacious drugs is obvious. What does the future hold? Protease inhibitors, new interferons, polymerase inhibitors, and other drugs will be the next wave of therapy for recurrent HCV.

—James D. Perkins, M.D.

References


