Treatment of Liver Transplant Recipients Who Have Chronic Hepatitis C Virus Infection

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Abstract

Chronic hepatitis C virus infection is the most common cause of chronic liver disease and indication for liver transplant in Western countries. Viral infection may recur after transplant in most patients. The diagnosis of histologic recurrence of hepatitis C virus infection after liver transplant may be difficult and may be confused with acute cellular graft rejection. Characteristics of the recipient, donor, virus, and transplant may be associated with disease progression. Treatment of hepatitis C virus infection has a positive effect on the outcome of liver transplant. There are 3 approaches used to minimize recurrent hepatitis C virus infection after liver transplant: antiviral therapy before transplant, antiviral preventive and preemptive treatment after transplant, and treatment of established reinfection. Protease inhibitors are being evaluated in patients who have severe hepatitis C virus recurrence after liver transplant. Liver graft survival is less frequent after revision transplant. Several new drugs currently are being evaluated in clinical trials for treatment of hepatitis C virus infection.

Key words: Antiviral therapy, Cirrhosis, Diagnosis, Interferon, Ribavirin, HCV

Introduction

Chronic hepatitis C virus (HCV) infection is the most common cause of chronic liver disease and indication for liver transplant in Western countries. In Turkey, 15% liver transplants are performed for HCV infection. With increased prevalence of chronic liver disease, demand for liver transplant, and HCV-related death, health issues associated with HCV may become more prevalent in the future.

Viral infection may recur after transplant in most patients, and the rate of progression of fibrosis is faster with higher stages of fibrosis and reduced time in a given stage of fibrosis. Histopathologic changes associated with acute HCV infection appear at 4 to 12 weeks after transplant. Most patients experience HCV-related problems, and histologic features of chronic HCV infection may be demonstrated in 70% to 90% recipients at 1 year and 90% to 95% at 5 years after transplant. Cirrhosis may recur at median 8 to 10 years after transplant, and 30% patients develop cirrhosis within 5 years. After cirrhosis develops, annual decompensation occurs in 30% to 40% patients. Although 50% patients have mild to moderate inflammation on liver histology, 10% patients develop severe recurrence with cholestatic features. Patients who are not treated usually die within 6 months after transplant.

In 11,036 patients who had 11,791 liver transplants, HCV infection had a major effect on patient and graft survival. The frequency of survival of the graft and patient at 5 years is 20% to 25% lower in liver transplant recipients who do not have HCV infection.

Diagnosis

The diagnosis of histologic recurrence of HCV infection after liver transplant may be difficult and may be confused with acute cellular graft rejection. The level of HCV RNA and liver biopsy are important to confirm the diagnosis, stage the disease,
and plan treatment. Protocol biopsies are recommended annually or when clinically indicated.

Factors Associated With Hepatitis C Virus Disease Progression

Characteristics of the recipient, donor, virus, and transplant may be associated with disease progression. Factors associated with the recipient that negatively affect progression of HCV disease are older age, African American race, and coinfection with human immunodeficiency virus. The recipient and donor IL28B non-CC genotype may be a strong positive predictor of recurrence and response to therapy. After liver transplant, cytomegalovirus and human herpesvirus 6 infections are associated with rapid progression of HCV recurrence. Cytomegalovirus infection and disease are associated with more severe fibrosis in patients who have HCV infection.

Donor-related factors that may predict disease progression and risk of graft loss include older donor age, especially donor age > 40 years. The outcomes of liver transplant performed with donors that have anti-HCV antibodies are similar to liver transplant with HCV-negative organs. Previous studies reported different outcomes with living or deceased donors, but results of living- and deceased-donor liver transplant are similar at centers experienced with living-donor liver transplant. After performing 20 living-donor liver transplants, the transplant center has achieved adequate experience. The effect of donor steatosis on the outcome of graft survival is controversial. Mild steatosis may be safe, but donor steatosis > 30% may be a risk factor for early and severe recurrence of HCV infection.

There is controversy about the effect of mismatch between donor and recipient human leukocyte antigen (HLA) profile on HCV recurrence and severity of disease after liver transplant. In addition, the severity of HCV recurrence may be affected by gene polymorphisms in the allograft for cytokines such as tumor necrosis factor β, interleukin 16, transforming growth factor β, interleukin 10, and interferon γ.

Viral factors that may be predictors of recurrence include high viral load in the recipient before transplant and status of genotype 1b. Several reports suggested that viral load before or after transplant did not correlate with the severity of liver disease or predict the timing of HCV recurrence after transplant, but another study showed an association between increased viral titers and worse histologic activity, increased risk of fibrosis, and decreased survival. Transplant-related factors that may be associated with progression of HCV disease include immunosuppressive treatment. Steroid maintenance therapy has no detrimental effect on graft or patient survival. However, some treatments against rejection are associated with HCV disease severity and progression, such as corticosteroid boluses, rapid corticosteroid tapering, and antilymphocyte preparations. Therefore, mild rejection is treated with increased maintenance immunosuppression and not corticosteroid boluses. In 2 randomized, prospective, multicenter trials with liver transplant patients who had chronic HCV infection, the steroid-free regimen was safe and effective, but there was no advantage between immunosuppressive regimens with respect to HCV recurrence. The use of steroids in HCV-infected recipients is not contraindicated.

No single drug or combination immunosuppressive regimen that may minimize histologic progression of HCV disease. Cyclosporine may inhibit HCV replication in vitro, but tacrolimus does not inhibit HCV replication in vitro. A meta-analysis that compared immunosuppression with tacrolimus or cyclosporine in HCV-infected recipients included 5 randomized, controlled trials and 366 patients, and there were no significant differences between regimens in mortality, graft survival, biopsy-proven acute rejection, steroid-resistant rejection, or fibrosing cholestatic hepatitis. Nevertheless, some authors suggest that immunosuppression with tacrolimus may be better than cyclosporine or sirolimus, but there is controversy about the effect of sirolimus in minimizing fibrosis progression in patients who have HCV infection.

Treatment

Treatment of HCV infection has a positive effect on the outcome of liver transplant. After patients
achieve sustained viral response, 97% to 100% patients have negative tests for HCV RNA at long-term follow-up. When recipient HCV RNA levels are negative during transplant, the frequency of HCV recurrence is lower. The best strategy to prevent the recurrence of HCV is to eradicate HCV infection before liver transplant. There are 3 approaches used to minimize recurrent HCV infection after liver transplant: antiviral therapy before transplant, antiviral preventive and preemptive treatment after transplant, and treatment of established reinfection.

Antiviral therapy before transplant

Treatment to suppress HCV viremia before transplant in patients on the transplant waiting list may reduce the risk of graft reinfection. The aim of antiviral therapy before transplant is to achieve negative serum HCV RNA levels during transplant. Suppression of HCV RNA in patients who have advanced disease is achievable in 10% to 50% patients, and 20% to 30% treated patients may remain without HCV infection after transplant.²⁵,²⁶

Factors that predict virologic response in patients who have advanced stages of chronic HCV infection have been recognized. Factors predictive of sustained viral response in 124 patients with advanced HCV infection include (1) infection with HCV genotype 2 or 3 (in contrast with genotypes 1, 4, or 6), (2) Child-Pugh class A cirrhosis (in contrast with Child-Pugh class B or C), and (3) dose and duration of interferon or pegylated interferon and ribavirin treatment.²⁷ A randomized, controlled trial evaluated treatment of chronic HCV using pegylated interferon plus ribavirin before transplant to prevent recurrent HCV infection after transplant.²⁸ In 30 patients who had genotype 1, 4, or 6 and who were treated for HCV infection, 23 patients had liver transplant, and 22% who had transplant achieved a virologic response after transplant. Major adverse events were similar in the treated and untreated groups, and patients who had ≥ 16 weeks treatment before transplant achieved the highest frequency of virologic response after transplant.²⁸ However, treatment was associated with an increased frequency of major adverse events including infections. In this trial, virologic response after transplant was only possible in patients who had negative levels of HCV RNA by week 12. Predictors of viral clearance included genotypes other than genotype 1 and an early virological response.

Patients who previously did not respond to interferon and ribavirin are not suitable for HCV treatment before transplant because the likelihood of achieving undetectable HCV RNA level is very low (< 10%). Patients who had previous relapse may be suitable for treatment because their predicted response may be high. The patients on the waiting list who are ideal for antiviral treatment are patients who had no previous treatment, patients who previously responded to treatment, and patients who have low Model for End-stage Liver Disease or Child-Turcotte-Pugh scores. Therapy is discontinued in patients who have no virologic response after 12 weeks. Estimated duration of treatment is 6 months for patients who have genotype 2 or 3 or 12 months for patients who have genotype 1. However, the treatment may be difficult and has limitations in patients who have decompensated cirrhosis, because of frequent and severe treatment-related complications. In addition to the limited efficacy, pegylated interferon may have limited safety in patients who have decompensated cirrhosis. Therapy may be discontinued in 43% patients, and complications during therapy may include decompensation in 29% patients and death in 8% patients.²⁹

Phase 3 trials of triple therapy based on telaprevir and boceprevir have shown higher frequencies of sustained viral response than pegylated interferon and ribavirin therapy in patients who have advanced fibrosis and cirrhosis. However, the frequency of severe adverse events are higher in patients who receive triple therapy. The frequency of sustained viral response in cirrhotic patients was 62% in the ADVANCE trial, 38% in the ILLUMINATE trial, and 42% in the SPRINT-2 trial. Patients who had compassionate use of protease inhibitors in HCV cirrhosis had higher frequency of major adverse events (30% to 51%) and discontinuation (7% to 12%) in cirrhotic nonresponders than patients in the phase 3 trials.³⁰

Preventive and preemptive treatment after transplant

In contrast with hepatitis B, there is no effective immunoglobulin prophylaxis available for HCV. The HCV immunoglobulin or monoclonal antibody may cause only a transient decrease of liver HCV RNA levels in liver transplant recipients.³¹,³² Therefore, prophylactic HCV antibody treatment is not
recommended currently because of the lack of clinical benefit and the potential for adverse events.

Antiviral therapy that is preemptive or early after transplant may prevent the rapid development of chronic hepatitis. It usually is started within 1 to 6 months after liver transplant. Antiviral therapy response is less frequent after transplant in recipients who are positive for HCV than immunocompetent subjects because of the high level of immunosuppression. In 4 studies, different regimens (2 each that used interferon or pegylated interferon monotherapy) had poor efficacy (< 20% sustained viral response) and high frequency of treatment discontinuation and graft rejection. When preemptive therapy is feasible, sustained viral response is obtained in 8% to 39% patients (5% to 33% patients who have genotype 1; 14% to 100% patients who have genotype 2 or 3). The PHOENIX trial showed that preemptive pegylated interferon and ribavirin therapy caused sustained viral response in 12 of 54 patients (22%), and recurrence of HCV at 120 weeks was similar in the prophylaxis (62%) and observation groups. In addition, the frequency of patient and graft survival and biopsy-proven acute cellular rejection were similar in the 2 study groups. Most patients (70%) required dose reductions and many patients (30%) discontinued treatment because of adverse events such as bacterial infection, hematologic toxicity, and rejection.

A meta-analysis of 11 randomized trials (477 patients) of preemptive treatment in liver transplant recipients who were positive for HCV showed no differences in patient survival, graft rejection, revision transplant, or HCV recurrence between patients who received or did not receive antiviral therapy. Most patients were treated within 26 weeks after liver transplant. Therefore, preemptive treatment currently is not recommended.

Treatment of established reinfection
Liver transplant recipients who have reinfection with HCV may be difficult to treat and cure. Viral recurrence after transplant is characterized by high viral load, accelerated fibrosis, concomitant immunosuppressive treatment, and resistance to interferon. The most effective current treatment protocol includes beginning therapy after the presence of infection is proven by biopsy. Antiviral therapy is started before advanced fibrosis develops because tolerance to therapy decreases markedly in patients who have fibrosis stage > 3. Interferon or ribavirin monotherapy has disappointing results and currently is not advised. In a systematic review of data about 689 patients (27 studies), therapy based on interferon or pegylated interferon caused low mean sustained viral response (24% to 27%) and frequent discontinuation (24% to 26%). However, sustained viral response may be better with therapy based on pegylated interferon than interferon. In patients who have recurrent HCV infection after liver transplant, sustained viral response after therapy based on pegylated interferon is 20% to 40% in patients who have genotype 1, and 50% to 100% in patients who have genotype 2 or 3.

In patients diagnosed with fibrosing cholestatic hepatitis, antiviral therapy must be given as early as possible because of the poor short-term prognosis and rapid progression of fibrosis. However, fibrosing cholestatic hepatitis usually is incurable with interferon treatment and prognosis is poor.

In 389 liver transplant patients (11 clinical trials) who had HCV recurrence, tolerance to therapy was poor, and there was frequent dose reduction (88%) or discontinuation (43%) because of adverse events or patient preference. There was no difference between treated and control patients in frequency of death, graft rejection, or revision transplant. Patients who were treated with pegylated interferon and ribavirin had higher sustained viral response (48%) than control patients (0%), and improvement in fibrosis was greater in treated patients. The higher sustained viral response may decrease mortality, and this may justify therapy.

Triple therapy
Protease inhibitors for treatment of HCV may provide better results, but experience after liver transplant is limited. Triple therapy based on telaprevir and boceprevir is approved only for infection in patients who have genotype 1; for other patients, recommended treatment includes only pegylated interferon and ribavirin. Telaprevir and boceprevir are potent inhibitors of cytochrome P450, family 3, subfamily A, a key hepatic enzyme that metabolizes many drugs including cyclosporine, sirolimus, and tacrolimus. Therefore, before beginning triple therapy, immunosuppressive doses are decreased and patients are monitored closely for rejection for 4 weeks; after therapy with pegylated interferon and ribavirin for 4 weeks, telaprevir is added for 12 weeks or boceprevir
is added for 32 weeks. After telaprevir or boceprevir are discontinued, the regular immunosuppressive regimen is resumed.

Early reports with few patients have suggested early viral responses, but adverse events are common and potentially life-threatening. In 1 study, early virologic response to triple therapy was 35% with telaprevir (11 patients) and 36% with boceprevir (17 patients), and undetectable HCV RNA levels after 8 weeks were noted in 56% patients who had boceprevir and 70% patients who had telaprevir.\(^4\) The combined results of the ADVANCE and SPRINT-2 trials suggest that sustained viral response may increase from 30% to 45% with triple therapy.\(^4\)

In 37 patients who had HCV recurrence after liver transplant and treated with triple therapy (12 weeks) based on boceprevir (18 patients) or telaprevir (19 patients), some patients had complete viral response (boceprevir, 89%; telaprevir, 58%), end-of-treatment response (boceprevir, 72%; telaprevir, 40%), and sustained viral response (boceprevir, 71%; telaprevir, 20%) (differences not significant).\(^4\) However, treatment failure occurred in 11 patients (30%); 5 patients discontinued therapy because of major adverse events; and 3 patients died.

Protease inhibitors are being evaluated in patients who have severe HCV recurrence after liver transplant.\(^4\) At present, triple therapy is used with caution by experienced clinicians at liver transplant centers that may provide very close monitoring for adverse events.

Revision transplant
Liver graft survival is less frequent after revision transplant. Survival is markedly worse for patients who have revision transplant for cirrhosis caused by recurrent HCV infection than other causes.\(^4\) Poor outcomes are associated with high HCV viral load, genotype 1, prior absence of response to treatment, high Model for End-stage Liver Disease score, high serum bilirubin, or high creatinine level.\(^4\) Therefore, revision transplant is not performed in some transplant centers because of organ shortage and probable recurrence in the revised graft.

Future Directions
Several new drugs currently are being evaluated in clinical trials for treatment of HCV infection, including new types of interferons, second and third generation protease inhibitors, HCV nonstructural 5A protein inhibitors, and polymerase inhibitors. Interferon-free regimens also are being investigated.

New drugs under evaluation include the HCV nonstructural 3/4A protease inhibitor simeprevir, HCV nonstructural protein 5B polymerase inhibitor sofosbuvir, and HCV nonstructural 5A protein inhibitor daclatasvir. These drugs may have increased potency and fewer adverse events, and they target unique nonoverlapping components of the HCV replication cycle. The goals of new drug therapy include improved outcomes, decreased adverse events, shortened treatment duration, simplified treatment regimens, and decreased drug-drug interactions.

References