



Treatment of hepatitis C before and after liver transplantation

Rosalba Moreno Alcántar¹

Liver cirrhosis secondary to chronic hepatitis C virus (HCV) infection is the primary reason for transplantations in most centers. Despite a reduction in the incidence of hepatitis C, the number of HCV-positive individuals with end-stage liver disease is expected to increase. Factors responsible for this trend include the development of cirrhosis in one third of HCV patients after 25–35 years of infection, the high prevalence of HCV in people aged 30–50 years, and the lack of an effective treatment for hepatitis C.^{1–3}

Infection or viremia recurs in all patients after transplantation, but not all patients develop significant histological lesions. The survival rates of HCV-positive liver transplant patients and grafts 5–8 years after transplantation is similar to that of transplant patients not infected with HCV.^{4,5} On the other hand, recurrence of hepatitis or disease on the graft is variable. In some patients, accelerated progression to cirrhosis results in loss of the graft; in others, recurrence is minimal and not progressive. However, two lines of evidence suggest that recurrent hepatitis C is aggressive and should be treated. Firstly, the number of cases of chronic hepatitis who progress to cirrhosis, graft failure, and retransplantation has increased. Some studies have shown that 30% of patients develop graft cirrhosis^{5–7} years after transplantation. Secondly, in HCV patients, the rate of progression to fibrosis is faster than that in immunocompetent patients, which suggests that cirrhosis develops more rapidly in HCV patients than in immunocompetent patients.⁶

There are three forms of recurrence, which differ in clinical presentation, pathophysiology, prognosis, and their treatment.

1. Chronic hepatitis C of grafts has a higher rate of progression to fibrosis than that of HCV patients who have not received transplants. Because fibrogenesis is more aggressive in transplanted patients than in immunocompetent patients, advanced fibrosis or cirrho-

sis develops faster (9–12 years *vs* 20–50 years).⁶ In 80% of patients, the degree of hepatitis 1 year after the transplantation is compatible with that of chronic hepatitis patients.

2. Fibrotic cholestatic hepatitis occurs in less than 10% of cases, but it is a serious condition. It causes graft failure within a few months in 50% of cases afflicted by it. It is characterized by biochemical cholestasis, marked jaundice, very high viremia titers, and histological inflammation.⁷
3. Hepatitis that progresses slowly during the first decade occurs in some patients. Histological damage is scarce or absent despite a high viral load. About 25% (8%–44%) of patients develop cirrhosis of the graft 5 years after transplantation. The results of recent studies indicate that the rate of graft cirrhosis is higher now than several years ago.

Cirrhosis is more aggressive in transplant patients than in patients who have not received transplants. The median of the first episode of decompensation is 8 months after diagnosis of cirrhosis of the graft. Transplant patients with decompensated cirrhosis experience episodes of ascites and, less frequently, encephalopathy. The accrued rate of decompensation in liver transplant patients with cirrhosis is 42% per year and 63% in 3 years; in patients with cirrhosis who have not received liver transplants, decompensation is only 3% per year and 18% in 5 years. The following indices are predictive of decompensation: a Child score greater than A, albumin levels less than 3.4 g/dL, and an interval of less than 1 year between transplantation and diagnosis of decompensated cirrhosis. The survival rate of HCV patients with these conditions is less than 10% in 3 years; the survival rate of HCV patients who have not undergone transplantation is 60%).^{8–11}

Factors affecting the development of hepatitis in liver transplant patients are the same as those for immunocompetent hosts:

- host factors (demography, immune status, comorbidity, liver function at the time of transplantation),
- viral factors (genotype, viral load, quasispecies), and
- factors associated with the transplant status:
- donor factors (age, extent of liver steatosis, liver volume, live donor or corpse),

¹ Departamento de Gastroenterología, IMSS Hospital de Especialidades Bernardo Sepúlveda CMN Siglo XXI, México, D.F. México.

- surgical factors (duration of ischemia), and
- environmental factors (immunosuppression, ingestion of alcohol, viral coinfections).

Of these factors, those that promote accelerated progression of fibrogenesis are a low immunosuppression status induced by antirejection treatment or HIV coinfection, elevated secondary viral load, previous liver damage, and ischemia during surgery. It is assumed that greater drug-induced immunodepression and decreased quality of transplant organs because of the increasing age of donors are responsible for the recent increase in the incidence of recurrent hepatitis C.¹²⁻¹⁶

Antiviral treatment

There are several potential strategies for management of liver transplant patients, each of which has advantages and disadvantages.

1. Antiviral treatment during the pretransplantation phase. This strategy is associated with a risk of precipitating liver failure, complications of the HCV infections, or severe cytopenias. The benefit of this practice is that it reduces the aggressiveness of the recurrence.
2. Antiviral treatment shortly after transplantation and before histological damage is incurred. In theory, this alternative is convenient but its use is limited by difficulties associated with the administration of antiviral drugs during a period of high immunosuppression and frequent cytopenias.
3. Antiviral treatment of established hepatitis, either during the acute phase or during the chronic phase.
4. Antiviral treatment of patients who received retransplants because of graft failure. This option is much debated.

Pretransplantation treatment of patients on the waiting list for donor organs should be restricted to patients with compensated cirrhosis, because treatment of patients with decompensated cirrhosis may cause serious complications. The objectives of treatment during this phase are to achieve a sustained virological response (SVR) to prevent the recurrence of cirrhosis after the transplant or to stabilize the progression of the disease. The treatment of choice for HCV patients with compensated cirrhosis is a combination of pegylated interferon and ribavirin. Despite the improvement evident after this therapy, the SVR seems to be lower in patients with compensated cirrhosis (43%–50%) than in patients without cirrhosis (57%–65%; 11% in patients with genotype 1 HCV and 50% in patients with HCV genotypes other than genotype 1). Responses of patients with severe cirrhosis are low because of a high prevalence of patients with genotype 1 HCV, an inability to maintain full treatment doses because of cytopenias, particularly neutrope-

nia, which is most frequent with pegylated interferon treatment, and the risk of complications that affect the liver function. Growth factors such as erythropoietin and the stimulating factor of neutrophils may be useful to avoid having to reduce dosages of drugs or discontinue medication. As the optimal doses have not been defined for transplant patients with HCV, the recommended doses and durations of treatment are mainly based on the genotype present. Some authors support the practice of progressive increases of an initially low dose according to the patient's tolerance and others recommend treatment with the full dose from the beginning.¹⁷⁻²¹ If the transplantation is done when viremia is negative, infection of the graft can be prevented in up to 65% of cases.

Early posttransplantation treatment refers to the first 2–6 weeks after transplantation when reinfection has already appeared but signs of hepatocyte injury are not evident. The SVR rate is 0%–11% with interferon monotherapy, 8% with pegylated interferon and 18%–33% with interferon in combination with ribavirin. Maintenance of antiviral treatment during this phase of transplantation is problematic because of comorbidities (poor resilience of recently transplanted patients, graft rejection, cytopenia, and infections) and poor tolerance of side effects.²²⁻²⁶ Because of these limitations, this treatment should be reserved for patients who have a high risk of aggressive relapse (patients coinfecting with HIV, those who have undergone retransplantation, and those who have received transplant organs from live donors), provided that there are no contraindications.

The results of treatment of recurrent hepatitis C (established disease) with interferon or ribavirin monotherapy are not encouraging. SVR rates are 18% for pegylated interferon monotherapy, 22% for standard interferon plus ribavirin and 28% for pegylated interferon plus ribavirin. The most common adverse effect of treatment of recurrent hepatitis C is anemia caused by hemolysis, which occurs mainly in patients with renal failure. In general, positive virological responses are associated with histological improvement.²⁷⁻³⁵ The results of antiviral treatment are worse in liver transplant patients than in immunocompetent patients because the former group has:

1. an elevated prevalence of HCV genotype 1,
2. high levels of viremia,
3. a high prevalence of nonresponders,
4. a high incidence of patients for whom antiviral doses are reduced because of low tolerance to treatment, mainly to ribavirin, and
5. reduced sensitivity to interferon.

Recommendations of the consensus panel

Does the course of HCV infection in transplant patients differ from that in patients who have not undergone transplants?

The progression of hepatitis C is faster in transplant patients than in patients who have not undergone transplants.

Evidence quality: 1

Should liver transplants be conducted in patients with HCV infection?

There is no formal contraindication against the eligibility of patients with chronic HCV infection for transplantation.

Evidence quality: 1

Do immunosuppressive regimens have an influence on the post-transplantation progression of hepatitis C?

Yes.

Evidence quality: 2

What is the ideal time to initiate posttransplantation antiviral treatment?

Most panelists recommended that treatment be initiated after liver damage is proven; 62% were in favor of initiating treatment after the presence of lobular hepatitis is established, and 38% suggested initiating treatment when the presence of chronic hepatitis with fibrosis is established.

Evidence quality: 3

What is the treatment of choice for posttransplantation treatment of HCV?

Pegylated interferon and ribavirin.

Evidence quality: 2

References

- Berenguer M, Lopez-Labrador FX, Wright TL. Hepatitis C and liver transplantation. *J Hepatol* 2001; 35: 666-78.
- Wiesner RH, Sorrell M, Villamil F. Report of the first international liver transplant society consensus conference on liver transplantation and hepatitis C. *Liver Transpl* 2003; 9(Suppl.3): S1-S9.
- Gane E. The natural history and outcome of liver transplantation in hepatitis C virus-infected recipients. *Liver Transpl* 2003; 9(Suppl.3): S28-S34.
- Charlton M. Liver biopsy, viral kinetics, and the impact of viremia on severity of hepatitis C virus recurrence. *Liver Transpl* 2003; 9(Suppl.3): S58-S62.
- Garcia-Retortillo M, Forns X, Feliu A, et al. Hepatitis C virus kinetics during and immediately after liver transplantation. *Hepatology* 2002; 35: 680-7.
- Berenguer M, Ferrell L, Watson J, et al. HCV-related fibrosis progression following liver transplantation: increase in recent years. *J Hepatol* 2000; 32: 673-84.
- McCaughan GW, Zekry A. Mechanisms of HCV reinfection and allograft damage after liver transplantation. *J Hepatol* 2004; 40: 368-74.
- Berenguer M, Prieto M, San Juan F, et al. Contribution of donor age to the recent decrease in patient survival among HCV-infected liver transplant recipients. *Hepatology* 2002; 36: 202-10.
- Forman LM, Lewis JD, Berlin JA, et al. The association between hepatitis C infection and survival after orthotopic liver transplantation. *Gastroenterology* 2002; 122: 889-96.
- Berenguer M, Crippin J, Gish R, et al. A model to predict severe HCV-related disease following liver transplantation. *Hepatology* 2003; 38: 34-41.
- Berenguer M, Prieto M, Rayón JM, et al. Natural history of clinically compensated HCV-related graft cirrhosis following liver transplantation. *Hepatology* 2000; 32: 852-8.
- Berenguer M. What determines the natural history of recurrent hepatitis C after liver transplantation? *J Hepatol* 2005; 42: 448-56.
- Berenguer M. Host and donor pre- and post-liver transplant risk factors impacting on HCV recurrence. *Liver Transpl* 2003; 9(Suppl.3): S44-S47.
- Charlton M. Liver biopsy, viral kinetics, and the impact of viremia on severity of hepatitis C virus recurrence. *Liver Transpl* 2003; 9(Suppl.3): S58-S62.
- McCaughan GW, Zekry A. Impact of immunosuppression on immunopathogenesis of liver damage in hepatitis C virus-infected recipients following liver transplantation. *Liver Transpl* 2003; 9(Suppl.3): S21-S27.
- Lake JR. The role of immunosuppression in recurrence of hepatitis C. *Liver Transpl* 2003; 9: S63-S66.
- Everson GT. Should we treat patients with chronic hepatitis C on the waiting list? *J Hepatol* 2005; 42: 456-62.
- Crippin JS, Sheiner P, Terrault NA, Sheiner P, Charlton MR. A pilot study of the tolerability and efficacy of antiviral therapy in patients awaiting liver transplantation for hepatitis C. *Liver Transpl* 2002; 8: 350-5.
- Everson GT. Treatment of patients with hepatitis C virus on the waiting list. *Liver Transpl* 2003; 9(Suppl.3): S90-S94.
- Thomas RM, Brenns JJ, Guzmán-Hartman G, Yong S, Cavaliere P, Van Thiel DH. Infection with chronic hepatitis C virus and liver transplantation: a role for interferon therapy before transplantation. *Liver Transpl* 2003; 9: 905-15.
- Forns X, Garcia-Retortillo M, Serrano T, et al. Antiviral therapy of patients with decompensated cirrhosis to prevent recurrence of hepatitis C after liver transplantation. *J Hepatol* 2003; 39: 389-96.
- Terrault NA. Prophylactic and preemptive therapies for hepatitis C virus infected patients undergoing liver transplantation. *Liver Transpl* 2003; 9: S95-S100.
- Sheiner P, Boros P, Klion FM, Thung SN, Schluger LK, Lau JY, et al. The efficacy of prophylactic interferon alfa-2b in preventing recurrent hepatitis C after liver transplantation. *Hepatology* 1998; 28: 831-38.
- Singh N, Gayowski T, Wannstedt C, Shakil O, Wagener M, Fung J, et al. Interferon- α for prophylaxis of recurrent viral hepatitis C in liver transplant recipients. *Transplantation* 1998; 65: 82-6.
- Mazzaferro V, Tagger A, Schiavo M, Regalia A, Pulvirenti M, Ribero J, et al. Prevention of recurrent hepatitis C after liver transplantation with early interferon and ribavirin treatment. *Transpl Proc* 2001; 33: 1355-7.
- Shergill AK, Khalili M, Straley S, Bollinger K, Roberts JP, Ascher N, Terrault NA. Applicability, tolerability and efficacy of preemptive antiviral therapy in hepatitis C infected patients undergoing liver transplantation. *Am J Transpl* 2005; 5: 118-124.
- Berenguer M, Prieto M, Palau A, Carrasco D, Rayon JM, Calvo F, Berenguer J. Recurrent hepatitis C genotype 1b following liver transplantation: treatment with combination interferon-ribavirin therapy. *Eur J Gastroenterol Hepatol* 2004; 16(11): 1207-12.
- Ross AS, Bhan AK, Pascual M, Thiim M, Cosimi AB, Chung RT. Pegylated interferon alfa-2b plus ribavirin in the treatment of post-liver transplant recurrent hepatitis C. *Clin Transplant* 2004; 18: 166-73.
- Dumortier J, Scoaxec JY, Chevallier P, Boillot O. Treatment of recurrent hepatitis C after liver transplantation: a pilot study of peginterferon alfa 2b and ribavirin combination. *J Hepatol* 2004; 40: 669-74.

30. Rodríguez-Luna H, Khatib A, Sharma P, De Petris G, Williams JW, Ortiz J, et al. Treatment of recurrent hepatitis C infection after liver transplantation with a combination of pegylated interferon alfa 2b and ribavirin: an open label series. *Transplantation* 2004; 77: 190-4.
31. Neff GW, Montalbano M, O'Brien C, Nishida S, Dafdar K, Bejarano PA, et al. Treatment of established recurrent hepatitis C in liver transplant recipients with pegylated interferon alfa-2b and ribavirin therapy. *Transplantation* 2004; 78: 1303-7.
32. Todd-Stravitz R, Shiffman ML, Sanyal AJ, Luketic VA, Sterling RK, Heuman DM, et al. Effects of interferon treatment on liver histology and allograft rejection in patients with recurrent hepatitis C following liver transplantation. *Liver Transpl* 2004; 10: 850-8.
33. Saab S, Kalmaz D, Gajjar NA, Hiatt J, Durazo F, Han S, et al. Outcomes of acute rejection after interferon therapy in liver transplant recipients. *Liver Transpl* 2004; 10: 859-67.
34. Bizollon T, Admed SNS, Radenne S, Chevallier M, Chevallier P, Paraz P, et al. Long-term histologic improvement and clearance of intrahepatic hepatitis C virus RNA following sustained response to interferon-ribavirin combination therapy in liver transplant patients with hepatitis C recurrence. *Gut* 2003; 52: 283-7.
35. Abdelmalek MF, Firpi RJ, Soldevila-Pico C, Reed AI, Hemming AW, Liu C, et al. Sustained viral response to interferon and ribavirin in liver transplant recipients with recurrent hepatitis C. *Liver Transpl* 2004; 10: 199-207.