Antihepatitis C virus therapy in liver transplanted patients

Antonino Picciotto

Department of Internal Medicine, University of Genoa, Genoa, Italy

Abstract: Hepatitis C virus (HCV) management in the transplant setting is still an open issue. The therapeutic strategies being addressed include: (a) pre-transplant prophylaxis (to prevent the infection of the transplanted organ); (b) post-transplant prophylaxis (to reduce the possibility of developing acute hepatitis); (c) management once the chronic disease has already set in and stabilized. Combination therapy with peginterferon alfa-2b plus ribavirin seems to play an important role for patients with established recurrent hepatitis C.

Keywords: liver transplantation, hepatitis C, peginterferon, ribavirin

Epidemiological and clinical issues

Liver transplantation for terminal liver disease due to hepatitis C virus (HCV) infection is a considerable problem in contemporary society, both because this condition affects a high number of patients who have undergone liver transplants and because of the difficulties in managing the post-transplant stage. Over the last 20 years, a dramatic increase in the number of liver transplants due to hepatitis viruses occurred, in particular the hepatitis C virus, which is the cause of about 50% of liver transplants both in the US and in Europe (Curry 2004). This situation is confirmed by Italian data obtained from the Monotematica AISF (Italian Association for the Study of the Liver) 2000-Orthotopic Liver Transplantation (OLT)-Study Group (Fagiuoli et al 2002), which demonstrated that the most frequent indication for liver transplantation is represented by hepatitis B and C (59.4%), and particularly by hepatitis C, which is responsible for about one third of indications for liver transplantation (Figure 1).

The projections for the future are not encouraging: the impact of hepatitis C on public health seems bound to grow in the next years. A five-fold increase in the transplantation requirements due to hepatitis C has been estimated for the decade 1998–2008, on top of an almost three-fold increase in hepatic failures, a more than two-fold increase in mortality rate due to liver disease, and an increase by 68% and 61% in the cases of hepatic carcinoma and cirrhosis respectively (Davis et al 1998).

One of the main problems to solve after intervention is the prevention of HCV reinfections of the transplanted organ. Some studies over the last few years have helped understand the kinetics of the HCV during and immediately after transplantation. According to a study by Garcia-Retortillo et al (2002) involving 20 consecutive patients who had undergone liver transplantation due to HCV-related cirrhosis, in most cases a fall in viraemia occurs during the anhepatic stage and in the stages immediately after reperfusion, probably because of the scarce virion production and a clearance of the viral load. However, in the following days, viremia tends to increase quite rapidly and may even exceed the initial values and then stabilize in chronic hepatitis. Without an effective prophylaxis, the HCV infection recurrence is almost unavoidable. The reinfection of the transplanted organ usually stems from a

Correspondence: Antonino Picciotto
Department of Internal Medicine, University of Genoa, Viale Benedetto XV, n.6, 16132 Genoa, Italy
Tel +39 010 353 8992
Fax +39 010 353 8992
Email picciott@unige.it

generally asymptomatic globular hepatitis usually originated between the first and the fourth month after transplantation. This form of hepatitis clears up very rarely: more frequently it evolves into chronic hepatitis. The liver cells necrosis, with considerable increases in the aminotransferase (ALT) activity, is not a constant factor in these patients (however, there seems to be a scarce correlation between ALT serum values and the severity of the damage of the transplanted organ) (Bizollon et al 1999). In some cases, within the first months from transplantation, a sclerosing, cholestatic hepatitis (with a very serious prognosis) may occur.

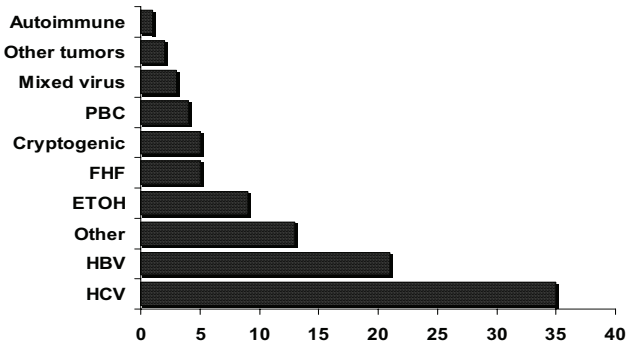

Figure 1 Indications for liver transplantation.
Abbreviations: ETOH, alcohol (ethanol); FHF, fulminant hepatic failure; HBC, hepatitis B virus; HCV, hepatitis C virus; PBC, primary biliary cirrhosis.

Natural history of HCV patients after liver transplantation

In a period of about 5 years, the chances in favour of developing cirrhosis of the transplanted organ have been estimated to vary from 15% to 45%, depending on the data observed (Gane et al 1996; Feray et al 1999; Prieto et al 1999; Berenguer 2002; Sanchez-Fueyo et al 2002; Neumann et al 2004a, 2004b) (Figure 2). The factors that seem to most affect the prognosis, in terms of survival of the patient and of the transplanted organ, include positivity to HCV virus, as demonstrated by the USA data obtained from United Network for Organ Sharing on 11 036 patients who have undergone 11 791 transplants (Forman et al 2002). Indeed, liver transplantation in HCV-positive patients has proved to be correlated to a higher mortality rate (hazard ratio [HR] 1.23; 95% confidence interval [CI], 1.12–1.35) and loss of the transplanted organ (HR 1.30; 95% CI, 1.21–1.39) as compared to HCV-negative transplanted patients. This difference seems to increase with time. These data have been confirmed by another study by Berenguer et al (2002) involving 522 patients who had undergone liver transplantation due to hepatitis C cirrhosis. After 5 years of follow up, the percentage of deceased patients in the HCV-positive group was significantly higher than in the HCV-negative group (37% vs. 22%; $p<0.001$). After 7 years of follow-up, this trend is confirmed: for the HCV-positive group, the survival rate amounted to 77% after 1 year, 61% after 5 years, and 55% after 7 years, whereas in the HCV-negative group it amounted to 87%, 76%, and 70% respectively ($p=0.0001$). The main cause of death in HCV-negative patients is the decompensated cirrhosis of the transplanted organ (22%). The natural history of cirrhosis development is different in the pre- and post-transplant stages (Berenguer 2003), as the disease progression is much faster after liver transplantation (Table 1).

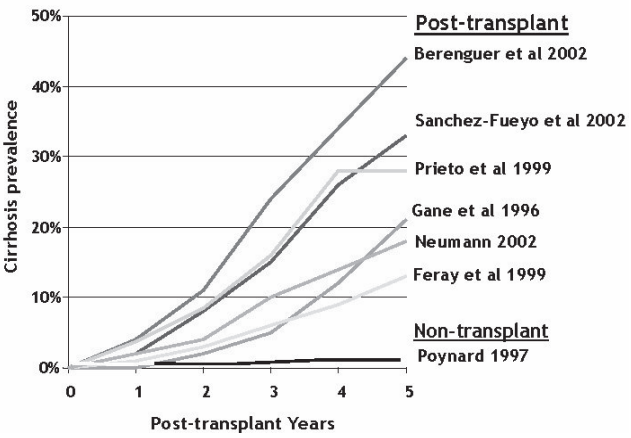

Figure 2 Cumulative probability of developing HCV–graft cirrhosis.

Table 1 Natural history of hepatitis C before and after transplantation

	Pre-OLT	Post-OLT
Fibrosis progression (units fibrosis/year)	0.2/year (0.09–0.8/year)	0.3/year (0.004–2.19/year)
Median time to cirrhosis	20–30 years	10–12 years
Decompensation rate afterdevelopment of cirrhosis	20%–25% in 10 years	50% in 1 year
Survival after decompensation	50% in 5 years	41% at 1 year
Overall patient survival	Not different in HCV vs nonHCV	Lower in HCV vs nonHCV

Abbreviations: HCV, hepatitis C virus, OLT, orthotopic liver transplantation.

In this stage the median time to cirrhosis is much shorter (about one third, or even half) than the time recorded when no transplant has been performed. The hepatic failure rate after the development of cirrhosis is also dramatically different: it amounts to 20%–25% in 10 years before

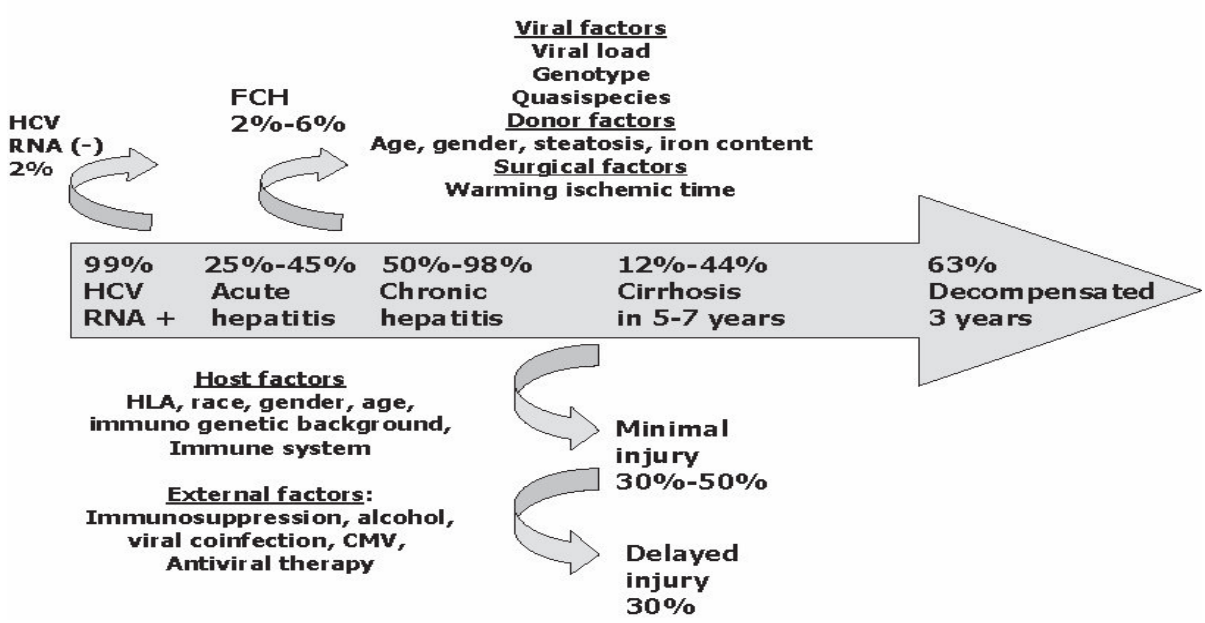

Figure 3 Factors impacting on disease progression post-OLT.

Abbreviations: CMV, cytomegalo-virus; FCH, fibrosing cholestatic hepatitis; HCV RNA, hepatitis C virus RNA; HLA, human leucocyte antigen; OLT, orthotopic liver transplantation.

transplantation and 50% in only 1 year after transplantation. Moreover, the survival rate after the onset of hepatic failure is much lower after transplantation: 50% in 5 years before transplantation and 41% in only 1 year after transplantation. After transplantation, the progression of the disease may be affected by various factors. HCV reinfection is present in almost all cases. In 25%–45% of cases a clinically patent acute hepatitis is recorded, part of which (about 6%) is in a sclerosing cholestatic form. A very high percentage of patients (up to almost 100%) develop chronic hepatitis. Furthermore, it is estimated that in 5–7 years about half of the patients develop cirrhosis and, later on, hepatic failure (Figure 3).

Many factors may affect this progression of the disease and the development of short- and long-term outcomes. These factors may be associated with the host (human leucocyte antigen [HLA], race, gender, age, immune genetic background, immune system) or may be external such as immunosuppression, alcohol, viral coinfections, the presence of cytomegalovirus, and antiviral therapy. An important role in the progression of the disease is also played by viral factors (ie, viral load, genotype 1 and 4, quasispecies), factors associated with the donor (ie, age, sex, steatosis, iron content) and the surgical operation (warming ischemic time) (Shuhart et al 1997; Charlton et al 1998; Ghobrial et al 2001; Berenguer et al 2002; Burak et al 2002; Wali et al 2002; Zekry et al 2003; Machicao et al 2004; Neumann et al 2004a). A faster progression is generally recorded when other factors are present at the time of transplantation, such as a high viral load, genotype 1b (most transplanted patients have this genotype which responds with more difficulty to the antiviral therapy), the donor's age > 50 years and a long ischemic time. The use of antirejection treatments with cortisone or monoclonal antibodies, an intense immunosuppressive therapy, and the onset of a cytomegalovirus infection contribute to determining a worse prognosis.

Therapeutic options

In summary, the problem of HCV infections after liver transplantation is extremely complex and has a strong impact, not only because HCV is the first indication for liver transplantation (and estimates show a further increase), but also because a relapse of the infection occurs in almost all cases and the onset of chronic hepatitis in the great majority of these patients. The patients' survival rate is reduced as the disease is more aggressive after transplantation. Effective management strategies are therefore required. From a therapeutic point of view, the problem may be tackled in three ways: through pre-transplant prophylaxis (to prevent the infection of the transplanted organ); post-transplant prophylaxis (to reduce the possibility of developing acute hepatitis); and through a stage to be considered once the chronic disease has already

set in and stabilized. The pre-transplant stage is scarcely applicable because of the frequent intolerance to the therapy and the high incidence of side effects that limit its use in these high risk patients with a serious clinical situation (Saab and Wang 2003). However, this approach is supported by evidence suggesting that pre-transplant interferon therapy may delay/prevent post-transplant reinfection if associated to a virologic response (Forns et al 2003; Thomas et al 2003), but the matter needs to be analysed more thoroughly.

It is not yet clear whether the severity of recurrent hepatitis is reduced after the pre-transplant therapy. Little information is available so far on the early post-transplant stage, and results are not clear, depending widely on when the therapy is started and on the kind of patient (who ought to be treated at a very early stage after transplant, at a time that cannot be critical yet with reference to specific complications). The studies currently available in this respect have assessed the treatment of interferon alfa begun 2 weeks to 1 month after the operation (Sheiner et al 1998; Singh et al 1998; Mazzaferro et al 2001; Chalasani et al 2005).

These trials have demonstrated that an early antiviral treatment with interferon after transplant seems to offer some benefits in terms of reduction in hepatitis recurrences, suggesting further elaborations. The sustained virologic response, when assessed, has yielded very different results: 33% in the study by Mazzaferro et al (2001) and much lower (8%) in the study by Chalasani et al (2005). The main doubts on this approach include the appropriate time for the beginning of therapy after transplant, as the available interval of time for treatment is practically inexistent since the virus can already be detected few hours after transplant. Treatment should therefore be started at an even earlier stage. However, starting therapy too early after transplant may cause rejection. Most studies and attempts to treat hepatitis C relapses after transplant have involved patients with stabilized chronic infection. Some data in this respect regarding interferon-alfa have not yielded the expected results, especially in terms of sustained virologic response, which is always very low (< 3%) ((Wright et al 1994; Feray et al 1995; Gane et al 1998; Ahmad et al 2001; Colter et al 2001) (Figure 4).

Some progress was made through the introduction of ribavirin in addition to interferon alfa, but most data stem from uncontrolled studies. A study by Bizollon et al (1997) on 21 patients who had undergone liver transplant and had been treated with interferon alfa-2b (3 MU three times a week) plus ribavirin 1000–1200 mg/day for 6 months, followed by 6 months of therapy with ribavirin alone, has

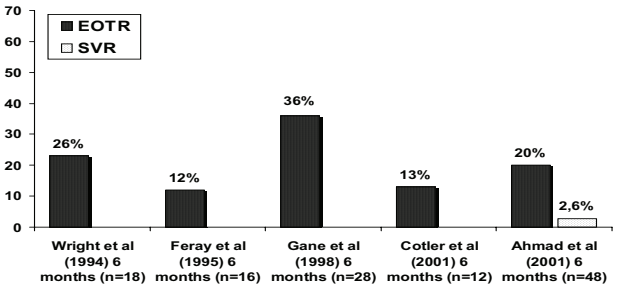

Figure 4 Interferon alfa monotherapy for established recurrent hepatitis C

shown that 100% of patients had ALT normalization at the end of the treatment with interferon, while 48% had undetectable HCV RNA. At the end of the follow-up, 94% of patients still had normalized serum ALT levels, while HCV RNA reappeared in 28% of treated patients. Other studies have produced uneven results. Gopal et al (2001) have reported (in a total of 12 patients) an early virologic response in 50% of patients treated with the combined therapy of interferon plus ribavirin, and a sustained virologic response in 8% of cases. Another study by Alberti et al (2001) involving 18 patients has recorded an early virologic response in 44% of cases and sustained virologic response in 27% of them, while in a study by Narayanan et al (2002) involving 26 patients, percentages amounted to 35% and 23% respectively. Similar values were obtained by a study by Lavezzo et al (2002). The only controlled study is a trial by Samuel et al (2003) on 52 patients who had undergone liver transplant with recurrent chronic hepatitis C randomized to receive a combination of interferon alfa-2b (3 MU three times a week) and ribavirin 1000–1200 mg/day for one year, or no treatment. The trial showed that the HCV RNA serum levels had become undetectable in 32% of patients at the end of the treatment, and in 21.4% of cases at the end of the follow-up period (6 months after the end of treatment). Adverse events caused 43% of patients to discontinue treatment.

The introduction of interferon, whose possible efficacy in patients with a hepatitis C relapse after liver transplant was revealed in a recent study by Chalasani et al (2005), has opened a new scenario. The study consists of two

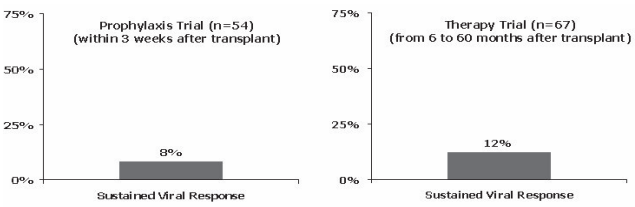

Figure 5 Peginterferon alfa-2a monotherapy after liver transplant

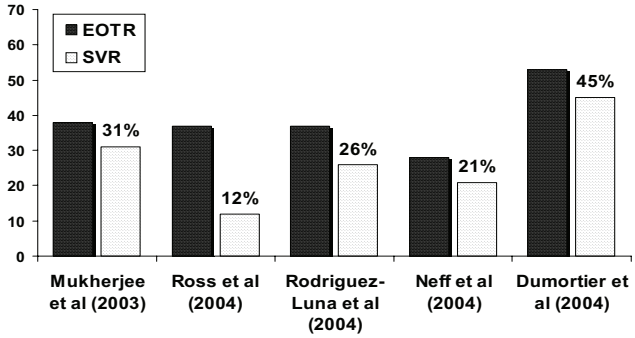

Figure 6 Peginterferon alfa-2b plus ribavirin for established recurrent hepatitis C.
Abbreviations: EOTR, end of treatment response; SVR: sustained virologic response.

controlled trials: prophylaxis and treatment. The purpose was to assess the efficacy and safety of the treatment with peginterferon alfa-2a in patients who had undergone liver transplantation. The prophylaxis trial enrolled 54 patients within 3 weeks from the transplant and the treatment trial involved 67 patients. In this case the treatment began 6–60 months after transplantation. Patients were randomly assigned to monotherapy with peginterferon alfa-2a 180 mcg once a week, or to no treatment for 48 weeks and were followed-up for 24 additional weeks. The results were not satisfactory. In the prophylaxis trial, the sustained virologic response amounted to 8% and was null in the nontreated control group. In the treatment trial, the sustained virologic response amounted to 12% of treated patients (Figure 5).

In the prophylaxis trial, 31% of treated patients and 32% of nontreated patients discontinued therapy, whereas in the treatment trial these percentages amounted to 30% and 19% respectively. With regard to the combination of peginterferon and ribavirin, the only data currently available relate to peginterferon alfa-2b and in a limited range of patients. Results vary; the sustained virologic response varies from 31% to 12% (Mukherjee et al 2003; Neff et al 2004; Rodriguez-Luna et al 2004; Ross et al 2004). In one case, high sustained virologic response rates (45%) were recorded (Dumortier et al 2004) (Figure 6). The most recent data in this respect derive from a study involving well defined patient profiles presented at the last FIMAD Congress (Genoa; 12–16 Mar 2005) by Saettone et al (2005). THIS involved 45 naïve patients with relapsing post-transplant HCV accompanied by high ALT values, histologic inflammation of grade >4/18 (Ishak score), HbA1c >9 g/dL; leucocytes (white blood cell count [WBC]) >2500/mmc, and platelets >50 000/mmc. The therapy consisted in peginterferon alfa-2b 1.0 mcg/kg/week plus ribavirin for 12 months. The analysis of baseline characteristics of patients revealed that the average age was 53 years (range 32–63), 35 were male and 73% had genotype 1 or 4. Mean HCV RNA levels amounted to $1.5x10^4$ UI/ml and mean ALT values to 170 UI ±131. The treatment began from 2 to 114 months after transplantation. The results have shown an early virologic response in 30% of patients with genotype 1 or 4 and in 100% of cases among patients with genotype 2 or 3. The sustained virologic response was of 15% and 83% respectively. Eighty-five percent of patients asked for the dose to be reduced and 51% discontinued therapy.

The available studies so far indicate, therefore, that today the combination of peginterferon plus ribavirin plays a potentially important role in patients who have undergone a liver transplant with hepatitis C relapse, as it enables an increase in the virologic response, which is still lower than the one recorded in nontransplanted patients. There are still some unresolved questions as to when the treatment ought to be started and the exact target of patients.

Conclusions

Liver transplantation for end-stage liver disease due to HCV infection is a world wide social and medical problem.

Epidemiological data suggest that the increase in request for liver transplantation over the next few years will not be supported by an adequate increase in the number of donors.

The clinical outcome of the transplanted patients in most cases is characterised by HCV reinfection and development of chronic hepatitis. Management of HCV in the transplant setting is still an open issue. The therapeutic strategies being addressed include: pre-transplant prophylaxis (to prevent the infection of the transplanted organ); post- transplant prophylaxis (to reduce the possibility of developing acute hepatitis); and management once the chronic disease has already set in and stabilized.

Combination therapy with Peginterferon alfa-2b plus Ribavirin seems to play an important role for patients with established recurrent hepatitis C.

References

Alberti AB, Belli LS, Airoldi A, et al. 2001. Combined therapy with interferon and low-dose ribavirin in posttransplantation recurrent hepatitis C: a pragmatic study. *Liver Transpl*, 7:870–6.

Ahmad J, Dodson SF, Demetris AJ, et al. 2001. Recurrent hepatitis C after liver transplantation: a nonrandomized trial of interferon alfa alone versus interferon alfa and ribavirin. *Liver Transpl*, 7:863–9.

Berenguer M. 2002. Natural history of recurrent hepatitis C. *Liver Transpl*, 8(Suppl 1):S14-8.

Berenguer M. 2003. Host and donor risk factors before and after liver transplantation that impact HCV recurrence. *Liver Transpl*, 9:S44–7.

Berenguer M, Prieto M, San Juan F, et al. 2002. Contribution of donor age to the recent decrease in patient survival among HCV-infected liver transplant recipients. *Hepatology*, 36:202–10.

Bizollon T, Ducerf C, Trepo C, et al. 1999. Hepatitis C virus recurrence after liver transplantation. *Gut*, 44:575–8.

Bizollon T, Palazzo U, Ducerf C, et al. 1997. Pilot study of the combination of interferon alfa and ribavirin as therapy of recurrent hepatitis C after liver transplantation. *Hepatology*, 26:500–4.

Burak KW, Kremers WK, Batts KP, et al. 2002. Impact of cytomegalovirus infection, year of transplantation, and donor age on outcomes after liver transplantation for hepatitis C. *Liver Transpl*, 8:362–9.

Chalasani N, Manzarbeitia C, Ferenci P, et al. 2005. Peginterferon alfa-2a for hepatitis C after liver transplantation: two randomized, controlled trials. *Hepatology*, 41:289–98.

Charlton M, Seaberg E, Wiesner R, et al. 1998. Predictors of patient and graft survival following liver transplantation for hepatitis C. *Hepatology*, 28:823–30.

Cotler SJ, Ganger DR, Kaur S, et al. 2001. Daily interferon therapy for hepatitis C virus infection in liver transplant recipients. *Transplantation*, 71:261–6.

Curry MP. 2004. Hepatitis B and hepatitis C viruses in liver transplantation. *Transplantation*, 78:955–63.

Davis GL, Albright JE, Cook S, et al. 1998. Projecting the future healthcare burden from hepatitis C in the United States. *Hepatology*, 28:390A.

Dumortier J, Scoazec JY, Chevallier P, et al. 2004. Treatment of recurrent hepatitis C after liver transplantation: a pilot study of peginterferon alfa-2b and ribavirin combination. *J Hepatol*, 40:669–74.

Fagiuoli S, Mirante VG, Pompili M, et al. 2002. Liver transplantation: the Italian experience. *Dig Liver Dis*, 34:640–8.

Feray C, Caccamo L, Alexander GJ, et al. 1999. European collaborative study on factors influencing outcome after liver transplantation for hepatitis C. European Concerted Action on Viral Hepatitis (EUROHEP) Group. *Gastroenterology*, 117:619–25.

Feray C, Samuel D, Gigou M, et al. 1995. An open trial of interferon alfa recombinant for hepatitis C after liver transplantation: antiviral effects and risk of rejection. *Hepatology*, 22:1084–9.

Forman LM, Lewis JD, Berlin JA, et al. 2002. The association between hepatitis C infection and survival after orthotopic liver transplantation. *Gastroenterology*, 122:889–96.

Forns X, Garcia-Retortillo M, Serrano T, et al. 2003. Antiviral therapy of patients with decompensated cirrhosis to prevent recurrence of hepatitis C after liver transplantation. *J Hepatol*, 39:389–96.

Gane EJ, Lo SK, Riordan SM, et al. 1998. A randomized study comparing ribavirin and interferon alfa monotherapy for hepatitis C recurrence after liver transplantation. *Hepatology*, 27:1403–7.

Gane EJ, Portmann BC, Naoumov NV, et al. 1996. Long-term outcome of hepatitis C infection after liver transplantation. *NEJM*, 334:815–20.

Garcia-Retortillo M, Forns X, Feliu A, et al. 2002. Hepatitis C virus kinetics during and immediately after liver transplantation. *Hepatology*, 35:680–7.

Ghobrial RM, Steadman R, Gornbein J, et al. 2001. A 10-year experience of liver transplantation for hepatitis C: analysis of factors determining outcome in over 500 patients. *Ann Surg*, 234:384–93.

Gopal DV, Rabkin JM, Berk BS, et al. 2001. Treatment of progressive hepatitis C recurrence after liver transplantation with combination interferon plus ribavirin. *Liver Transpl*, 7:181–90.

Lavezzo B, Franchello A, Smedile A, et al. 2002. Treatment of recurrent hepatitis C in liver transplants: efficacy of a six versus a twelve month course of interferon alfa 2b with ribavirin. *J Hepatol*, 37:247–52.

Machicao VI, Bonatti H, Krishna M, et al. 2004. Donor age affects fibrosis progression and graft survival after liver transplantation for hepatitis C. *Transplantation*, 77:84–92.

Mazzaferro V, Tagger A, Schiavo M et al. 2001. Prevention of recurrent hepatitis C after liver transplantation with early interferon and ribavirin treatment. *Transplant Proc*, 33:1355.

Mukherjee S, Rogge J, Weaver L, et al. 2003. Pilot study of pegylated interferon alfa-2b and ribavirin for recurrent hepatitis C after liver transplantation. *Transplant Proc*, 35:3042–4.

Narayanan Menon KV, Poterucha JJ, El-Amin OM, et al. 2002. Treatment of posttransplantation recurrence of hepatitis C with interferon and ribavirin: lessons on tolerability and efficacy. *Liver Transpl*, 8: 623–9.

Neff GW, Montalbano M, O'Brien CB, et al. 2004. Treatment of established recurrent hepatitis C in liver-transplant recipients with pegylated interferon-alfa-2b and ribavirin therapy. *Transplantation*, 78: 1303–7.

Neumann UP, Berg T, Bahra M, et al. 2004. Fibrosis progression after liver transplantation in patients with recurrent hepatitis C. *J Hepatol*, 41:830–6.

Prieto M, Berenguer M, Rayon JM, et al. 1999. High incidence of allograft cirrhosis in hepatitis C virus genotype 1b infection following transplantation: relationship with rejection episodes. *Hepatology*, 29:250–6.

Rodriguez-Luna H, Khatib A, Sharma P, et al. 2004. Treatment of recurrent hepatitis C infection after liver transplantation with combination of pegylated interferon alpha2b and ribavirin: an open-label series. *Transplantation*, 77:190–4.

Ross AS, Bhan AK, Pascual M, et al. 2004. Pegylated interferon alpha-2b plus ribavirin in the treatment of post-liver transplant recurrent hepatitis C. *Clin Transplant*, 18:166–73.

Saab S, Wang V. 2003. Recurrent hepatitis C following liver transplant: diagnosis, natural history, and therapeutic options. *J Clin Gastroenterol*, 37:155–63.

Saettone S, Martini S, Lavezzo B, et al. 2005. PEG-IFN alfa-2b + ribavirin in the treatment of post-liver transplant recurrent hepatitis C. FIMAD, Genoa, Italy 12–16 Mar 2005.

Samuel D, Bizollon T, Feray C, et al. 2003. Interferon-alpha 2b plus ribavirin in patients with chronic hepatitis C after liver transplantation: a randomized study. *Gastroenterology*, 124:642–50.

Sanchez-Fueyo A, Restrepo JC, Quinto L, et al. 2003. Impact of the recurrence of hepatitis C virus infection after liver transplantation on the long-term viability of the graft. *Transplantation*, 73:56–63.

Sheiner PA, Boros P, Klion FM, et al. 1998. The efficacy of prophylactic interferon alfa-2b in preventing recurrent hepatitis C after liver transplantation. *Hepatology*, 28:831–8.

Shuhart MC, Bronner MP, Gretch DR, et al. 1997. Histological and clinical outcome after liver transplantation for hepatitis C. *Hepatology*, 26:1646–52.

Singh N, Gayowski T, Wannstedt CF, et al. 1998. Interferon-alpha for prophylaxis of recurrent viral hepatitis C in liver transplant recipients: a prospective, randomized, controlled trial. *Transplantation*,65:82–6.

Thomas RM, Brems JJ, Guzman-Hartman G, et al. 2003. Infection with chronic hepatitis C virus and liver transplantation: a role for interferon therapy before transplantation. *Liver Transpl*, 9:905–15.

Wali M, Harrison RF, Gow PJ, et al. 2002. Advancing donor liver age and rapid fibrosis progression following transplantation for hepatitis C. *Gut*, 51:248–52.

Wright TL, Combs C, Kim M, et al. 1994. Interferon-alpha therapy for hepatitis C virus infection after liver transplantation. *Hepatology*, 20:773–9.

Zekry A, Whiting P, Crawford DH, et al. 2003. Liver transplantation for HCV-associated liver cirrhosis: predictors of outcomes in a population with significant genotype 3 and 4 distribution. *Liver Transpl*, 9:339–47.