Living donor liver transplantation to patients with hepatitis C virus cirrhosis

Yasuhiko Sugawara, Masatoshi Makuuchi

Yasuhiko Sugawara, Masatoshi Makuuchi, Artificial Organ and Transplantation Division, Department of Surgery, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
Supported by Grant-in-aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan
Correspondence to: Yasuhiko Sugawara, MD, Artificial Organ and Transplantation Division, Department of Surgery, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. yasusuga-tky@umin.ac.jp
Telephone: +81-3-38155411 Fax: +81-3-56843989
Received: 2005-09-12   Accepted: 2005-11-18

Abstract

Living donor liver transplantation (LDLT) is an alternative therapeutic option for patients with end-stage hepatitis C virus (HCV) cirrhosis because of the cadaveric organ shortage. HCV infection is now a leading indication for LDLT among adults worldwide, and there is a worse prognosis with HCV recurrence. The antivirus strategy after transplantation, however, is currently under debate. Recent updates on the clinical and therapeutic aspects of living donor liver transplantation for HCV are discussed in the present review.

INTRODUCTION

The use of live donors for liver transplantation was initiated more than a decade ago as a solution to the cadaveric donor shortage for pediatric recipients[1]. After the first successful case in an adult patient in 1994[2], this procedure is now widely applied to adult recipients, especially in countries where the availability of brain-dead donors is severely restricted[3] and also in the United States and European countries, due to a critical shortage of cadaveric organs. Improved surgical techniques and the introduction of new immunosuppressive agents have enhanced the long-term results of living donor liver transplantation (LDLT), leading to an increased demand for liver transplantation that exceeds the number of potential donor organs. In initial experiences with adult LDLT in Japan, the most common indication was cholestatic liver disease, including primary biliary cirrhosis and primary sclerosing cholangitis in Japan. The number of LDLT patients indicated for hepatitis C virus (HCV) has recently increased rapidly.

A recent study[4] of deceased donor liver transplantation (DDLT) reported that HCV infection was associated with a 23% increase in mortality and a 30% increase in the rate of graft failure. The poor results might be due to the recurrence of HCV disease in the graft[5]. HCV-induced graft hepatitis and fibrosis/cirrhosis occur in 75% to 80% and 10% to 30% of recipients, respectively, at 5 years[6,7]. Once liver cirrhosis is established, the cumulative probability of developing clinical decompensation is close to 50% after 1 year and survival after decompensation is extremely short[8]. Cholestatic hepatitis occurs in approximately 10% of patients infected with HCV and leads to accelerated graft failure and death[9]. One of the hottest debates is the possibility of increased severity of recurrent HCV in LDLT patients. The benefit of LDLT might be offset if the outcome of LDLT for HCV patients is worse than that of DDLT. In this review, we describe current trends and controversies in LDLT for patients with HCV. Our results for LDLT and HCV are also reported.

CURRENT STATUS OF LDLT

According to the Japan Liver Transplantation Society[10], the number of adult patients (≥18 years old) is increasing annually, and has reached 300 in 2003. The most common indication for adults has been hepatocellular carcinoma (*n* = 311), followed by primary biliary cirrhosis (*n* = 255), and HCV-related cirrhosis without carcinoma (*n* = 113). The 1, 3, and 5 year survival rates of all the adult patients were 76%, 72%, and 69%, respectively. Those of HCV-positive patients were 76%, 73%, and 65%, respectively.

In the United States in 2000, there was a high level of enthusiasm for adult LDLT, with 49 centers performing at least one LDLT. Overall, in experienced centers, about a third of adults on the waiting list had a potential living donor and half of them had undergone LDLT; thus, LDLT might be applicable for up to 15% of individuals on the list[11]. The enthusiasm was, however, quickly tempered

Table 1 Comparison between LDLT and DDLT for hepatitis C virus cirrhosis

Study			N		Dif[1]	Protocol biopsy	Findings
Author	Year	Institution	LDLT	DDLT			
Gaglio[23]	2003	Colombia U.	23	45	Yes	No	Cholestatic hepatitis in 17% of LDLT and 0% of DDLT (*P* = 0.001). No significant difference in incidence of Rec.
Shiffman[28]	2003	Virginia Commonwealth U.	22	53	No	Yes	79% patient survival in LDLT and 91% in DDLT during 3 year (NS). No significant difference in inflammation score in liver specimen after 3 years
Russo[29]	2004	UNOS data	279	3955	No	No	87% 1-year patient survival in both.
Thuluvath[30]	2004	UNOS data	207	408	No	No	No significant difference in patient survival (*P* = 0.6).
Van Vlierberghe[32]	2004	Ghent U.	17	26	No	No	Rec in 35% of LDLT and 38% of DDLT during 1 year (*P* = 0.1)
Bozorgzadeh[34]	2004	Rochester U.	35	65	No	No	Rec in 77% of LDLT and 72% of DDLT during 1 year (NS), 89% patient survival in LDLT and 75% in DDLT during 39 mo (NS)

[1] Difference in short-term outcomes or severity of virus recurrence between living and deceased donor liver transplantation. Abbreviations: Rec, Virus recurrence; U, University; NS, not significant; UNOS, United Network for Organ Sharing.

by the death of a donor in 2002 in the United States[12]. Since 2001, the number of patients who have undergone LDLT has declined[13]. Currently less than 5% of all adult liver recipients use living donors. By July 2005, 2734 LDLT cases had been performed. There were 1761 adult patients and HCV was the most common indication. HCV is the most common indication for LDLT[14] and the number of HCV-positive patients is stable, approximately 100 per year between 2000 and 2002.

By the end of 2003, 1743 LDLT cases were recorded in the European Liver Transplantation Registry[15]. According to the Transplant Procurement Management[16], the number of LDLT peaked in 2003 and has gradually decreased over recent years. LDLT accounts for approximately 5% of the total liver transplants performed in Europe. Among the 806 LDLT cases from October 1991 to December 2001[17], the overall 5-year graft survival rate was 75%, better for children than for adults (80% *vs* 66% at 3 years). Cirrhosis secondary to HCV infection is a leading indication for LDLT among adults in Europe[18]. The number of LDLT patients is shown in the Table 1.

INDICATIONS

In areas with low deceased donor organ availability, the indications for LDLT are similar to those for DDLT. In contrast, in Western countries, LDLT is conducted in an attempt to alleviate the shortage of donor organs and to decrease the mortality among the patients awaiting transplants. That is, a balance needs to be achieved between the candidate's liver disease severity and the adequacy of a partial graft for transplantation. The candidate's liver disease should be advanced to the extent that transplantation is justified, but the liver disease cannot be so advanced that a partial graft will not provide adequate hepatic mass.

According to Russo's report[19] a substantial proportion of patients were United Network for Organ Sharing (UNOS) status 3 at the time of LDLT (43%). The policy at their centers prior to the implementation of a model for end stage liver disease (MELD)-based allocation was not to proceed with LDLT in patients meeting UNOS status 2A criteria. Their patient survival rate was 57% with an average stay of 23 d in the intensive care unit. In comparison, 1-year patient survival was 82% in DDLT recipients who were UNOS status 2A at the time of transplant[20].

The waiting list mortality increases in patients with advanced liver disease and patients with a MELD score of 25 have a 20% 3-mo mortality[21]. In general, it is uncommon to proceed with LDLT in patients with MELD scores above 25. Thus, depending on the region of the country and the average MELD score at the time of the transplant within the area served by the organ procurement organization, LDLT might offer patients transplantation before they die waiting for a deceased donor liver. The lower MELD score limit with LDLT is more controversial and varies from center to center. Russo[19] commented that they do not proceed with LDLT in candidates with MELD scores under 11.

LDLT AS A RISK FACTOR FOR RECURRENCE OF HCV

One study from Barcelona[22] reported that LDLT patients (*n* = 22) had younger donors, less graft steatosis, more frequent biliary complications, and earlier and more severe acute hepatitis compared with DDLT (*n* = 95) patients. A report from Colombia University[23] indicates that cholestatic hepatitis or severe HCV recurrence occurs more frequently in LDLT. These reports indicate that more intensive antiviral therapy might be necessary for recipients of living donor grafts.

The possible causes of HCV recurrence include HLA matching between donor and recipient. Because cellular immune reactions restricted by both HLA class I and II antigens are involved in the recognition of HCV peptides[24], HLA matching between donor and recipient could potentially increase damage to the graft from recurrent viral infections by facilitating host recognition of viral antigens[6]. Recently, a beneficial effect of a complete HLA-DQ mismatch was reported in 14 patients after transplantation for HCV cirrhosis[25]. Another possible cause might be related to liver regeneration[26], although recent data[27] did not support this hypothesis. *In vitro*, HCV internal ribosome entry site activity and replication are higher in actively dividing cells, and it is possible that

viral translation is enhanced by factors that stimulate the regeneration of hepatocytes. Moreover, there are experimental data suggesting that liver regeneration induces low density lipoprotein receptor expression, which might facilitate HCV entrance into the hepatocytes.

In contrast, comparable data between LDLT and DDLT for HCV was recently reported[28]. Russo and colleagues[29] compared patient and graft survival in recipients transplanted for chronic HCV who received a living donor organ (*n* = 279) and deceased donor organ (*n* = 3955) using the UNOS liver transplant database. One-year patient survival was 87% in both groups and 2-year patient survival was 83% and 81% in the living donor group and deceased donor group (*P* = 0.68), respectively. Similar results (DDLT, *n* = 480 *vs* LDLT, *n* = 207) were obtained from another analysis using the UNOS data base[30]. Analyses from the Mayo Clinic[31] and Gent University[32] also demonstrated no negative impacts of LDLT on the results of liver transplantation for HCV-related cirrhosis.

These data should be interpreted with caution, however, because of the important clinical distinction between LDLT and DDLT recipients. At the time of transplantation, the LDLT group recipients are far less sick than their DDLT group counterparts[33]. The LDLT (*n* = 35) and DDLT (*n* = 65) data from a single institution, Rochester University, were examined[34]. Patient survival, graft survival, rate of HCV recurrence, severity of HCV recurrence, graft loss from HCV, and interval for HCV recurrence in DDLT and LDLT were similar. It remains unclear, however, whether LDLT is truly disadvantageous compared to DDLT for HCV-positive patients because the number of cases or follow-up duration is not yet sufficient.

According to the data from Russo[29], from 1999 to 2000, the 1-year patient survival in the LDLT group increased from 69% to 90% (*P* = 0.04), and 1-year graft survival increased from 63% to 79% (*P* = 0.16). In contrast, in the DDLT group, 1-year patient and graft survival did not substantially change from 1999 to 2000. As a result, 1-year survival rates became similar between the LDLT and DDLT groups in 2000. The results indicated an experience effect and learning curve on outcomes after LDLT for HCV. Therefore, the initial reports indicating poorer results of LDLT might be due to technical problems from a lack of experience. Recent data indicating similar results between LDLT and DDLT might be due to the increased experience with LDLT. The multicenter adult to adult LDLT cohort study (A2ALL) might soon provide some answers to the questions about recurrent HCV after LDLT and DDLT[35].

MANAGEMENT OF HCV

Therapy for reccurrence in DDLT
If HCV recurs earlier and more severely after LDLT, a specific strategy for preventing the detrimental effects of HCV on living donor grafts must be developed. One strategy might be aggressive treatment for HCV. Treatment of recurrent HCV disease with interferon and ribavirin after DDLT is used in some centers[36-38]. One standard regimen includes interferon-alpha2b (3 MU × 3

per week) and ribavirin (1000 mg/d) for 6 mo. In a recent trial, polyethylene glycol-conjugated interferon therapy was used[35,38-43], with a sustained viral response rate ranging from 13% to 47%.

Preemptive therapy for HCV after DDLT
Preemptive therapy in the early post-transplantation period with interferon either alone or in combination with ribavirin has been attempted in DDLT, although its effectiveness is controversial. In one study, HCV-positive recipients were randomized within 2 wk of transplantation to receive either interferon alone (3 MU × 3 per wk, *n* = 30) or placebo (*n* = 41) for 1 year[39]. Only 17 patients could complete 1 year of interferon therapy. Eight patients (27%) in the interferon group and 22 (54%) of the untreated patients had recurrent hepatitis (*P* = 0.02). Patient and graft survival at 2 years did not differ between the groups, however, and the rate of viral persistence was not affected by treatment.

In another controlled trial[43], 24 recipients were randomized at 2 weeks post-transplantation to receive interferon (3 MU × 3 per wk) or placebo for 6 mo. There were no differences in graft or patient survival. There were no differences between groups in the incidence of histological recurrence or its severity differed between groups. Recurrent HCV was delayed 408 d in treated patients versus 193 d in the control cohort.

In a case series by Mazzaferro[44], 36 recipients were treated with interferon-alpha 2b (3 MU × 3 per wk) and ribavirin (10 mg/kg per d). They started treatment at a median of 18 d after the operation and treatment continued for 11 mo. After a median follow-up of 52 mo, the 5-year patient survival was 88%. Serum HCV RNA clearance was obtained in 12 patients (33%). They did not require further antiviral treatment because of negative HCV RNA in serum and normal liver histology for a median of an additional 36 mo. The former two randomized trials on preemptive interferon monotherapy demonstrated minimal benefits of the drug. In contrast, Mazzaferro reported more encouraging results, although their protocol brings into question how long therapy is needed once embarking on a preemptive strategy.

Re-transplantation
The approach to retransplantation for recurrent HCV varies widely among the transplant centers of DDLT[11]. The results after retransplantation for HCV (45% at 5 years) are poorer than that for other causes[45] (56%, *P* < 0.001). The patients with recurrent HCV in the early timing and graft failure within the first year have poor outcomes after retransplantation. These individuals should be considered contraindicated for retransplantation. The experience of retransplantation for HCV in LDLT has not been well accumulated.

OUR EXPERIENCE
We performed preemptive therapy for LDLT patients with HCV infection[38]. From 1996 to 2004, 67 patients underwent LDLT for HCV cirrhosis at the Tokyo University Hospital. The patients were 51 men and 16

women and their ages ranged from 23 to 63 years (median 55). The HCV genotype was 1b in 53 patients (79%). Forty-one patients (61%) had hepatocellular carcinoma. All the patients received the same immunosuppressive regimens with tacrolimus and methylprednisolone.

All the patients preemptively received antiviral therapy consisting of interferon α-2b and ribavirin, which was started approximately 1 mo after the operation. The therapy was continued for 12 mo after the first negative HCV RNA test. The standard regimen included interferon α-2b (3 MU × 3 per wk) and ribavirin (800 mg/d) for 6 mo. The patients were then observed without the therapy for 6 mo. The therapy was continued for at least 12 mo even if the HCV RNA test remained positive.

Therapy was discontinued when there was significant leukopenia (< 1500 /mL), thrombocytopenia (< 50 000 /mL) despite application of granulocyte colony stimulating factor (Gran®, Sankyo, Co. Ltd., Tokyo, Japan), hemolytic anemia (hemoglobin < 8 g/L), renal dysfunction (serum creatinine > 20 mg/L), depressive psychological status, or general fatigue. The subjects were removed from the protocol if they did not continue the therapy for 12 mo due to adverse effects or could not start the therapy due to early death.

Blood counts and liver function tests were checked every 2 wk for the first month, and at 4 wk intervals thereafter. Serum samples were collected once a month for quantitative HCV RNA detection. Protocol liver biopsy was not performed. The log-rank test was used to compare the survival rate of the HCV-positive patients with the HCV-negative patients who underwent transplantation during the same period ($n = 168$).

A total of 28 patients were excluded from the analysis; 12 patients were removed from the protocol because of early death ($n = 9$) or because of drug cessation ($n = 3$). Another 16 patients are currently on the protocol and were therefore excluded from the analysis. Of the remaining 39 patients, 16 (16/39; 41%) obtained a sustained virologic response. The cumulative 5-year survival of the HCV-positive patients was 84%, comparable with that of patients negative for HCV ($n = 168$, 86%).

CONCLUSIONS

LDLT will remain an indispensable therapeutic tool for HCV related end stage liver disease and an alternative to DDLT. The association between LDLT and early HCV recurrence remains to be determined, although most of the recent papers suggest that live donor graft has no effect on short-term outcome or severity of virus recurrence. If living donor graft is associated with early HCV recurrence and consequently poorer graft survival, an aggressive antiviral protocol might improve the outcome of LDLT for HCV.

ACKNOWLEDGMENTS

REFERENCES

1 **Strong RW**, Lynch SV, Ong TH, Matsunami H, Koido Y, Balderson GA. Successful liver transplantation from a living donor to her son. *N Engl J Med* 1990; **322**: 1505-1507

2 **Hashikura Y**, Makuuchi M, Kawasaki S, Matsunami H, Ikegami T, Nakazawa Y, Kiyosawa K, Ichida T. Successful living-related partial liver transplantation to an adult patient. *Lancet* 1994; **343**: 1233-1234

3 **Sugawara Y**, Makuuchi M. Technical advances in living-related liver transplantation. *J Hepatobiliary Pancreat Surg* 1999; **6**: 245-253

4 **Forman LM**, Lewis JD, Berlin JA, Feldman HI, Lucey MR. The association between hepatitis C infection and survival after orthotopic liver transplantation. *Gastroenterology* 2002; **122**: 889-896

5 **Berenguer M**, Lopez-Labrador FX, Wright TL. Hepatitis C and liver transplantation. *J Hepatol* 2001; **35**: 666-678

6 **Gane EJ**, Portmann BC, Naoumov NV, Smith HM, Underhill JA, Donaldson PT, Maertens G, Williams R. Long-term outcome of hepatitis C infection after liver transplantation. *N Engl J Med* 1996; **334**: 815-820

7 **Prieto M**, Berenguer M, Rayon JM, Cordoba J, Arguello L, Carrasco D, Garcia-Herola A, Olaso V, De Juan M, Gobernado M, Mir J, Berenguer J. High incidence of allograft cirrhosis in hepatitis C virus genotype 1b infection following transplantation: relationship with rejection episodes. *Hepatology* 1999; **29**: 250-256

8 **Berenguer M**, Prieto M, Rayon JM, Mora J, Pastor M, Ortiz V, Carrasco D, San Juan F, Burgueno MD, Mir J, Berenguer J. Natural history of clinically compensated hepatitis C virus-related graft cirrhosis after liver transplantation. *Hepatology* 2000; **32**: 852-858

9 **Dickson RC**, Caldwell SH, Ishitani MB, Lau JY, Driscoll CJ, Stevenson WC, McCullough CS, Pruett TL. Clinical and histologic patterns of early graft failure due to recurrnet hepatitis C in four patients after liver transplantation. *Transplantation* 1996; **61**: 701-705

10 **The Japanese Liver Transplantation Society**. Liver Transplantation in Japan. Registry by the Japanese Liver Transplantation Society. *Jpn J Transplant* 2004; **38**: 401-408 (in Japanese)

11 **Brown RS**. Hepatitis C and liver transplantation. *Nature* 2005; **436**: 973-978

12 **Miller C**, Florman S, Kim-Schluger L, Lento P, De La Garza J, Wu J, Xie B, Zhang W, Bottone E, Zhang D, Schwartz M. Fulminant and fatal gas gangrene of the stomach in a healthy live liver donor. *Liver Transpl* 2004; **10**: 1315-1319

13 Data from the United Network for Organ Sharing. http://www.optn.org/latestData/rptData.asp

14 **Strader DB**, Wright T, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C. *Hepatology* 2004; **39**: 1147-1171

15 Data from European Liver Transplant Registry. http://www.eltr.org/publi/index_rv.php3

16 Data base from Transpalnt Procure Management http://www.tpm.org/presentation.htm

17 **Adam R**, McMaster P, O'Grady JG, Castaing D, Klempnauer JL, Jamieson N, Neuhaus P, Lerut J, Salizzoni M, Pollard S, Muhlbacher F, Rogiers X, Garcia Valdecasas JC, Berenguer J, Jaeck D, Moreno Gonzalez E. Evolution of liver transplantation in Europe: report of the European Liver Transplant Registry. *Liver Transpl* 2003; **9**: 1231-1243

18   **Berenguer M**. What determines the natural history of recurrent hepatitis C after liver transplantation? *J Hepatol* 2005; **42**: 448-456

19   **Russo MW**, Brown RS Jr. Adult living donor liver transplantation. *Am J Transplant* 2004; **4**: 458-465

20   **Testa G**, Malago M, Nadalin S, Hertl M, Lang H, Frilling A, Broelsch CE. Right-liver living donor transplantation for decompensated end-stage liver disease. *Liver Transpl* 2002; **8**: 340-346

21   **Wiesner R**, Edwards E, Freeman R, Harper A, Kim R, Kamath P, Kremers W, Lake J, Howard T, Merion RM, Wolfe RA, Krom R. Model for end-stage liver disease (MELD) and allocation of donor livers. *Gastroenterology* 2003; **124**: 91-96

22   **Garcia-Retortillo M**, Forns X, Llovet JM, Navasa M, Feliu A, Massaguer A, Bruguera M, Fuster J, Garcia-Valdecasas JC, Rimola A. Hepatitis C recurrence is more severe after living donor compared to cadaveric liver transplantation. *Hepatology* 2004; **40**: 699-707

23   **Gaglio PJ**, Malireddy S, Levitt BS, Lapointe-Rudow D, Lefkowitch J, Kinkhabwala M, Russo MW, Emond JC, Brown RS Jr. Increased risk of cholestatic hepatitis C in recipients of grafts from living versus cadaveric liver donors. *Liver Transpl* 2003; **9**: 1028-1035

24   **Manez R**, Mateo R, Tabasco J, Kusne S, Starzl TE, Duquesnoy RJ. The influence of HLA donor-recipient compatibility on the recurrence of HBV and HCV hepatitis after liver transplantation. *Transplantation* 1995; **59**: 640-642

25   **Gretch D**, Wile M, Gaur L. Donor-recipient match at the HLA-DQB locus is associated with recrudescence of chronic hepatitis following liver transplantation for end stage hepatitis C. *Hepatology* 1993; **18** Suppl: 108A

26   **Olthoff KM**. Hepatic regeneration in living donor liver transplantation. *Liver Transpl* 2003; **9**: S35-41

27   **Humar A**, Horn K, Kalis A, Glessing B, Payne WD, Lake J. Living donor and split-liver transplants in hepatitis C recipients: does liver regeneration increase the risk for recurrence? *Am J Transplant* 2005; **5**: 399-405

28   **Shiffman ML**, Stravitz RT, Contos MJ, Mills AS, Sterling RK, Luketic VA, Sanyal AJ, Cotterell A, Maluf D, Posner MP, Fisher RA. Histologic recurrence of chronic hepatitis C virus in patients after living donor and deceased donor liver transplantation. *Liver Transpl* 2004; **10**: 1248-1255

29   **Russo MW**, Galanko J, Beavers K, Fried MW, Shrestha R. Patient and graft survival in hepatitis C recipients after adult living donor liver transplantation in the United States. *Liver Transpl* 2004; **10**: 340-346

30   **Thuluvath PJ**, Yoo HY. Graft and patient survival after adult live donor liver transplantation compared to a matched cohort who received a deceased donor transplantation. *Liver Transpl* 2004; **10**: 1263-1268

31   **Rodriguez-Luna H**, Vargas HE, Sharma P, Ortiz J, De Petris G, Balan V, Byrne T, Moss A, Mulligan D, Rakela J, Douglas DD. Hepatitis C virus recurrence in living donor liver transplant recipients. *Dig Dis Sci* 2004; **49**: 38-41

32   **Van Vlierberghe H**, Troisi R, Colle I, Ricciardi S, Praet M, de Hemptinne B. Hepatitis C infection-related liver disease: patterns of recurrence and outcome in cadaveric and living-donor liver transplantation in adults. *Transplantation* 2004; **77**: 210-214

33   **Forman LM**, Trotter JF, Emond J. Living donor liver transplantation and hepatitis C. *Liver Transpl* 2004; **10**: 347-348

34   **Bozorgzadeh A**, Jain A, Ryan C, Ornt D, Zand M, Mantry P, Lansing K, Orloff M. Impact of hepatitis C viral infection in primary cadaveric liver allograft versus primary living-donor allograft in 100 consecutive liver transplant recipients receiving tacrolimus. *Transplantation* 2004; **77**: 1066-1070

35   **Russo MW**, Shrestha R. Is severe recurrent hepatitis C more common after adult living donor liver transplantation? *Hepatology* 2004; **40**: 524-526

36   **Bizollon T**, Ahmed SN, Radenne S, Chevallier M, Chevallier P, Parvaz P, Guichard S, Ducerf C, Baulieux J, Zoulim F, Trepo C. Long term histological improvement and clearance of intrahepatic hepatitis C virus RNA following sustained response to interferon-ribavirin combination therapy in liver transplanted patients with hepatitis C virus recurrence. *Gut* 2003; **52**: 283-287

37   **Giostra E**, Kullak-Ublick GA, Keller W, Fried R, Vanlemmens C, Kraehenbuhl S, Locher S, Egger HP, Clavien PA, Hadengue A, Mentha G, Morel P, Negro F. Ribavirin/interferon-alpha sequential treatment of recurrent hepatitis C after liver transplantation. *Transpl Int* 2004; **17**: 169-176

38   **Abdelmalek MF**, Firpi RJ, Soldevila-Pico C, Reed AI, Hemming AW, Liu C, Crawford JM, Davis GL, Nelson DR. Sustained viral response to interferon and ribavirin in liver transplant recipients with recurrent hepatitis C. *Liver Transpl* 2004; **10**: 199-207

39   **Sheiner PA**, Boros P, Klion FM, Thung SN, Schluger LK, Lau JY, Mor E, Bodian C, Guy SR, Schwartz ME, Emre S, Bodenheimer HC Jr, Miller CM. The efficacy of prophylactic interferon alfa-2b in preventing recurrent hepatitis C after liver transplantation. *Hepatology* 1998; **28**: 831-838

40   **Neff GW**, Montalbano M, O'Brien CB, Nishida S, Safdar K, Bejarano PA, Khaled AS, Ruiz P, Slapak-Green G, Lee M, Nery J, De Medina M, Tzakis A, Schiff ER. Treatment of established recurrent hepatitis C in liver-transplant recipients with pegylated interferon-alfa-2b and ribavirin therapy. *Transplantation* 2004; **78**: 1303-1307

41   **Castells L**, Vargas V, Allende H, Bilbao I, Luis Lazaro J, Margarit C, Esteban R, Guardia J. Combined treatment with pegylated interferon (alpha-2b) and ribavirin in the acute phase of hepatitis C virus recurrence after liver transplantation. *J Hepatol* 2005; **43**: 53-59

42   **Moreno Planas JM**, Rubio Gonzalez E, Boullosa Grana E, Garrido Botella A, Barrios Peinado C, Lucena Poza JL, Jimenez Garrido M, Sanchez Turrion V, Cuervas-Mons Martinez V. Peginterferon and ribavirin in patients with HCV cirrhosis after liver transplantation. *Transplant Proc* 2005; **37**: 2207-2208

43   **Yedibela S**, Schuppan D, Muller V, Schellerer V, Tannapfel A, Hohenberger W, Meyer T. Successful treatment of hepatitis C reinfection with interferon-alpha2b and ribavirin after liver transplantation. *Liver Int* 2005; **25**: 717-722

44   **Mazzaferro V**, Tagger A, Schiavo M, Regalia E, Pulvirenti A, Ribero ML, Coppa J, Romito R, Burgoa L, Zucchini N, Urbanek T, Bonino F. Prevention of recurrent hepatitis C after liver transplantation with early interferon and ribavirin treatment. *Transplant Proc* 2001; **33**: 1355-1357

45   **Pelletier SJ**, Schaubel DE, Punch JD, Wolfe RA, Port FK, Merion RM. Hepatitis C is a risk factor for death after liver retransplantation. *Liver Transpl* 2005; **11**: 434-440