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Retransplantation in patients with hepatitis C recurrence after liver transplantation

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Hepatitis C virus (HCV) infection recurs universally after liver transplantation (LT) and fibrosis progression is accelerated in the graft. Retransplantation (RT) is the only therapeutic option to achieve long-term survival in patients with decompensated cirrhosis after LT. Patient and graft survival rates after RT are inferior to those after primary LT. It is generally accepted that severe hepatitis C recurrence (cholestatic hepatitis) and forms with rapid fibrosis progression have a poor survival after RT. However, it is not clear whether rapid fibrosis progression in the first graft will be followed by the same rate of fibrosis progression in the second graft. The use of prognostic scores as screening tools has shown an improvement in survival in HCV-infected patients after RT, reaching similar survival rates as those obtained in non HCV-infected patients. Moreover, these scores can identify candidates with a high risk of mortality in whom the use of a new organ would be unreasonable. Prevention of severe hepatitis C recurrence could be the first step to avoid RT. Thus, antiviral treatment on the waiting list (if possible) and early identification and treatment of patients with severe hepatitis C recurrence may be a good strategy to avoid RT. In addition, active management of factors which can accelerate fibrosis progression (donor age, post-transplant diabetes, high dose of corticosteroids) might reduce the incidence of severe forms of hepatitis C recurrence.

Retransplantation in HCV-infected patients: general considerations

Hepatitis C virus (HCV) infection has become the most common cause of cirrhosis and hepatocellular carcinoma in the Western world. End-stage liver disease due to HCV-infection is the leading indication for liver transplantation (LT). Unfortunately, HCV infection recurs universally after LT in patients with detectable HCV RNA at the time of transplantation [1]. Fibrosis progression, cirrhosis development, and clinical decompensation occur more rapidly in HCV-infected liver transplant recipients than in immunocompetent patients [2]: whereas the median interval from infection to cirrhosis is around 9.5 years in LT recipients, the same interval is around 30 years in immunocompetent patients. Cirrhosis develops in around one-third of HCV-infected patients during the first 5 years after LT [3]. In addition, a small number of individuals (2–5%) develop fibrosing cholestatic hepatitis (FCH), a severe form of hepatitis C recurrence characterized by cholestatic hepatitis, hepatocyte ballooning, and perisinusoidal fibrosis leading to graft failure within a few months after LT [4]. As a consequence, hepatitis C recurrence is the primary cause of graft loss and reduction in patient survival in transplant programs in which HCV-infection is the main indication for LT [5]. The prognosis of patients once graft cirrhosis is established is poor and when graft failure occurs, retransplantation (RT) is the only therapeutic option offering a chance for long-term survival. Berenguer et al. [2] found that patients with clinically compensated cirrhosis achieved a 1-year survival rate of 74%. However, once patients developed clinical decompensation, survival decreased to 41% at 1 year and approximately 10% at 3 years.

It is generally accepted that progression to cirrhosis is faster after RT than after primary LT, particularly in patients with severe hepatitis C recurrence (cholestatic hepatitis and graft failure within the first year). Patient and graft survival rates after RT are inferior to those after primary LT and are associated with a greater cost. Pelletier et al. [6] demonstrated a 30% increase in mortality for HCV-infected RT recipients (20% for HCV-infected primary LT [7]). Table 1 shows the liver graft survival rate after LT and after RT between 1984 and 2008 in Spain. Most deaths after RT are, however, not related to hepatitis C recurrence but to post-operative complications such as bacterial infections. Patients with a more severe liver disease and poor preoperative clinical conditions have the highest mortality following RT [8]. Despite liver fibrosis progression after primary LT has been well characterized [9], studies assessing this subject after RT are insufficient to draw any solid conclusions [10,11]. Moreover, other facts may influence the evolution of HCV-infection after RT. Recent studies have suggested that the grafting of a new liver may produce significant changes in the HCV *quasispecies* and may thereby change the severity of the disease and the susceptibility to antiviral treatment [12,13].

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Abbreviations: RT, retransplantation; LT, liver transplantation; HCV, hepatitis C virus; PNF, primary non-function; HAT, hepatic artery thrombosis; UNOS, United Network for Organ Sharing; MELD, model for end-stage liver disease; ECD, extender criteria donors; HCC, hepatocellular carcinoma; SVR, sustained virological response.

Table 1. Graft survival of transplanted (LT) and retransplanted (RT) patients from 1984 to 2008 in Spain. Database from "Organización Nacional de Trasplante" (ONT) [14].

	1-month survival	3-month survival	1-year survival	3-year survival	5-year survival	10-year survival	15-year survival	20-year survival	Mortality risk: HR (95%CI), *p*
All etiologies									
LT (n = 14,223)	90.3%	86%	78.5%	69.7%	64.1%	52.7%	44.2%	35.6%	
2º graft (n = 1,239)	76.3%	67.1%	58.1%	50.9%	44.5%	35%	30.2%	24%	2nd vs. 1st graft: 1.53 (1.38 - 1.7), <0.01
3º graft (n = 127)	66.1%	58.3%	49.6%	44.2%	38.3%	27%	27%	-	3th vs. 1st graft: 1.85 (1.4 - 2.4), <0.01
HCV-infected patients									
LT (n = 4,925)	91.9%	87.5%	77.7%	65.8%	57.7%	43.8%	34.3%	-	
2º graft (n = 273)	83.5%	73.4%	63.4%	53%	42.4%	32.6%	20%	-	
3º graft (n = 13)	100%	92.3%	69.2%	43.3%	34.6%	34.6%	-	-	

LT, liver transplantation; RT, retransplantation; HR, hazard ratio; 95% CI, 95% confidence interval.

Among patients with multiple RTs, a recent analysis of the Spanish Transplant Organization showed a worse outcome in individuals with more than one RT [14] (Table 1). Multivariate analysis demonstrated a significantly higher risk of mortality in patients who received a second [HR: 1.53 (95% IC: 1.38–1.7) p <0.01] or third graft [HR: 1.85 (95% IC: 1.4–2.4) p <0.01] as compared to the first transplant [15]. However, Akpinar et al. [16], evaluated 2527 LT between 1987 and 2008. Two hundred and thirty-five (9%) patients received two grafts; 32 (1.2%) three; five (0.2%) four; and two (0.01%) five grafts. Patients who underwent more than one RT had a survival rate of 72%, 56%, and 50% at 1, 5, and 10 years, respectively. There were no statistically significant differences in survival between these patients and those who underwent one RT, concluding that multiple RT can be safely performed.

Is HCV-infection an independent risk factor for mortality after retransplantation?

The main causes of liver graft failure are primary non-function (PNF), hepatic artery thrombosis (HAT), chronic rejection, and recurrence of viral or autoimmune disease. RT is performed at different times depending on the etiology of graft failure: PNF requires RT during the first days, whereas HAT may result in urgent or delayed RT (the latter when secondary ischemic cholangitis is the main complication). Chronic rejection and recurrence of viral or autoimmune disease are indications of elective RT. In general, there are no concerns regarding the use of a liver graft for RT in emergency situations (such as PNF or HAT) but elective RT (particularly for HCV recurrence) is much more controversial. Whereas some studies do not clearly identify HCV recurrence as an independent predictive factor of mortality after RT [17–22], other recent studies [6,23–26] seem to indicate a poorer prognosis in RT of HCV-infected patients (Tables 2 and 3).

Studies evaluating early post-transplant variables did not find HCV-infection to be an independent predictor of mortality after RT [17–22]. The University of Pittsburgh [17] analyzed 418 (17.6%) patients who underwent RT out of 2376 LT performed from 1987 to 1993. The 1- and 5-year graft survival after RT was significantly lower than that of primary LT (50% and 35%, respectively). The leading causes of graft failure after RT were sepsis (44%) and ischemic injury-PNF (12%). The variables associated with graft failure after RT were donor and recipient age, female donor sex, the need for mechanical ventilation, renal failure, high levels of bilirubin and immunosuppression with cyclosporine.

Some studies have suggested HCV-infection as a risk factor of mortality [25–28]. Rosen et al. [27] analyzed 1356 patients who underwent RT from the United Network for Organ Sharing (UNOS) from 1990 to 1996. Recipient age, bilirubin and creatinine levels, etiology of graft failure and UNOS status (intensive care, hospitalization, medical care or stable at home) were independent predictors of poor outcome after RT. Hepatitis C and donor age were associated with a poor prognosis on univariate analysis, but neither had enough power to be included in a predictive model. Similarly, Ghabril et al. [28] have recently evaluated 1034 HCV-infected patients and 1249 non-HCV-infected patients who underwent RT between 1994 and 2005. Patient and graft survival were significantly lower for HCV-infected compared to non-HCV-infected patients who underwent RT at least 90 days after primary LT. However, based on multivariate analysis, the only independent predictors of mortality were recipient age, model for end-stage liver disease (MELD) >25, RT during the first year after LT, donor age >60 and, a warm ischemia time $\geqslant$75 min.

Other studies, have clearly identified HCV-infection as a risk factor of mortality not only after primary LT but also after RT [6,23,24]. One of the largest clinical UNOS series with more than 4000 patients who underwent RT from 1988 to 2001 [23] showed seven risk factors for death after RT: PNF, HCV-infection, donor, and recipient age, creatinine -serum levels before RT, African-American race, and UNOS status. Patients with HCV recurrence were 20% and 30% more likely to lose their graft between 1 and 3 years compared with non-HCV-infected patients. Roayaie et al. [24] showed that HCV-infected patients undergoing RT had a significantly shorter median survival than those undergoing RT for other chronic reasons of graft loss. However, most deaths occurred during the first 6 months after RT and were due to sepsis by peritonitis or pneumonia. Similarly, Pelletier et al. [6] analyzed 1718 RT patients (27% with HCV-infection) from 1997 to 2002 in the Scientific Registry of Transplant Recipients database. HCV-infected recipients had a 30% higher risk of mortality than those without HCV-infection (HR: 1.30; CI 95%: 1.10–1.54; p = 0.002). Most deaths occurred between 3 and 12 months after RT and variables associated with a worse outcome were donor and recipient age, serum-creatinine level, presence in the intensive care unit, and HCV-infection.