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Recurrence of hepatitis C after liver transplantation

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Abstract

Recurrence of hepatitis C virus (HCV) infection following liver transplantation is a major source of morbidity and mortality. The natural history of hepatitis C in the transplant setting is shortened. Overall, one third of HCV-infected recipients have developed allograft cirrhosis due to HCV recurrence by the 5th-7th year post-transplantation. The most significant variables which determine disease progression are the use of organs from old donors, the use of an inadequate immunosuppression (too low, inducing treatment rejection episodes, too potent or too rapidly changing), and the presence of comorbid conditions that also impact the quality of the graft (biliary complications, metabolic syndrome). The only factor consistently shown to modify the natural history of recurrent disease is antiviral therapy. A sustained viral response, achieved by one third of those treated with dual therapy, is associated with improved histology, reduced liver-related complications and increased survival. Variables associated with enhanced viral response with dual therapy include an adequate genetic background (IL28B C/C of both donor and recipient), good treatment adherence (full doses of ribavirin, treatment duration), lack of graft cirrhosis at baseline, and viral genotype non-1. Data with triple therapy are encouraging. Response rates of about 60% at end-of-therapy have been described. Drug-drug interactions with calcineurin inhibitors are present but easily manageable with strict trough levels monitoring. Side effects are frequent and severe, particularly anemia, infections and acute renal insufficiency. In the future new oral antivirals will likely prevent viral reinfection. In this review, we will cover the most significant but also controversial aspects regarding recurrent HCV infection, including the natural history, retransplantation, antiviral therapy, and outcome in HIV-HCV patients.

Keywords Hepatitis C recurrence, liver retransplantation, HIV-HCV coinfection, antiviral treatment

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Introduction

Hepatitis C virus (HCV)-related end-stage cirrhosis is the most common indication for liver transplantation (LT) in western countries. (www.unos.org, www.eltr.org), and the number of HCV patients refered for transplantation will continue to increase in the next decade despite great advances in antiviral therapy. Reinfection of liver allografts is universal in patients with pre-transplantation viremia and occurs at reperfusion [1]; only a few hours after transplantation HCV RNA levels increase to peak by the fourth postoperative month. While the diagnosis of recurrent HCV infection is defined by the presence of HCV RNA in serum and/or liver [2], the diagnosis of recurrent disease requires histological confirmation. Histologic features of liver injury resemble those observed in the non-transplant graft and typically develop after 3 months post-LT; changes of chronic hepatitis C can be demonstrated in 70-90% of recipients after 1 year and in 90-95% after 5 years. Clinical course, severity of recurrent disease and outcome though are highly variable [3]. The commonest course involves a form of progressive chronic liver disease similar to that observed in the immunocompetent population, but occurring at higher viral load and fibrosis progression (which is the consequence of an early activation of stellate cells) [4]. In these patients the injury to the hepatocyte is thought to be mediated by the immune response. The median interval from transplantation to cirrhosis is 9.5 years (range 7-12) versus 30 years (range 20-50) from infection until cirrhosis in immunocompetent patients [3,5]. Due to the high speed of progression in transplanted patients, median annual rates

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ranging from 0.2 to 0.8 Metavir stages / year compared to 0.1-0.2 in non-transplanted patients [6]. The pattern of progression of the stage of fibrosis is not uniform: fibrosis can progress linearly [5], present an initial exponential increase followed by stabilization in the medium to long term, or alternatively, an initial benign course followed by a sudden and unexpected acceleration [7,8]. The lack of linearity was recently confirmed by a non-Markov analysis based on 901 histological fibrosis assessments in 401 patients [9]. This model showed that disease activity is variable over time and that current time at a given stage rather than prior time in earlier stages is most predictive of future progression. A small proportion of patients (<10%) develop a very severe pattern of recurrent disease termed fibrosing cholestatic hepatitis (FCH) that typically leads to graft loss within months of onset. FCH is associated with extremely high HCV RNA levels, absence of a specific HCV response and a TH2 intrahepatic cytokine response [interleukin (IL)-10 and IL-4], suggesting a direct cytopathogenic effect of HCV within the liver graft [2,3,10,11]. Histologically, it is characterized by absence of lobular inflammation and lymphoid aggregates together with severe centrizonal hepatocyte ballooning and clinically by intense cholestasis. Interestingly, in a proportion of infected recipients, progression is not apparent, at least in the first decade, and liver injury remains mild or absent despite high viral burden. Regardless of the pattern of recurrence, HCV-related allograft cirrhosis develops in approximately 25% of recipients (range: 6-44%) within 5 years after LT and this percentage is likely to increase with longer duration of follow-up [5,10] (Table 1). The course of established graft cirrhosis is also more aggressive in LT recipients than in non-transplanted HCV-cirrhotic patients; survival decreases to 41% and 10% at 1 and 3 years, respectively once cirrhosis develops. The first episode of decompensation usually occurs after a median of 8 months from diagnosis of cirrhosis with 42% and 63% cumulative rates at 1 and 3 years. Variables associated with decompensation, retransplantation (RT), and mortality include a high Child-Pugh score (>A), low levels of albumin (<3.5 mg/dL), a short interval (<1 year) between LT and post-LT cirrhosis [12], and a hepatic venous pressure gradient (HVPG) ≥10 mmHg [13].

Graft failure secondary to recurrent HCV represents the most frequent cause of death, graft failure and need for RT in HCV-transplanted recipients [14,15]. Largely as a result of recurrent HCV, the 5- and 10-year survival rates are inferior to those reported in uninfected recipients [10]. In a recent OPTN/UNOS study from the US, the 3-year survival was 78% among 7,459 anti-HCV-positive recipients compared to 82% in 20,734 anti-HCV-negative patients (P<0.0001) (www.unos.org). Similarly, in the Spanish National Registry of patients transplanted between 1991 and 2010, the 15-year survival was 50% in 4,592 non-HCV patients but only 35% in 3,461 anti-HCV-positive patients (www.ont.es). Furthermore, in some centers, the rate at which fibrosis progresses has increased in patients who have recently undergone LT [5], highlighting differences in transplant outcomes between HCV-positive and HCV-negative recipients. While survival has improved over time in the HCV-negative patients, in HCV patients, outcomes have remained stable [16-18] or even worsened, probably reflecting both the effects of changes in immunosuppression and donor quality.

Retransplantation in HCV recurrence

In patients with established graft cirrhosis, and particularly those who develop clinical decompensation, Retransplantation (RT) is the only therapeutic option. However, due to organ shortage, cost issues and worse survival reported in some series for this indication, RT for HCV recurrence remains a controversial issue.

In general, RTs account for about 10% of liver transplants [19,20], and have worse graft and patient survival than primary transplantations (approximately 20% reduction in survival). Of these, HCV recurrence accounts for about 30-40% of elective RTs [21,22]. Previous studies concerning RT in general and for HCV recurrence in particular, are conflicting, with some suggesting a poorer prognosis after RT associated with HCV recurrence, and others which have failed to demonstrate this association [22].

Among the studies that did not clearly identify HCV infection as an independent predictor of mortality after RT [23-31], other factors were found to be related to poor graft and patient outcome. These mostly include the need for pre-operative mechanical ventilation, old recipient and donor age and high pre-operative serum levels of bilirubin and creatinine

Table 1 Progression to cirrhosis in HCV-infected liver transplant recipients at 5 years

Author, yr (Ref.)	N	Outcome measure	5-yr outcome
Gane *et al,* 1996 [117]	149	Cirrhosis	20%
Prieto *et al,* 1999 [118]	81	Actuarial rate of cirrhosis	28%
Berenguer *et al,* 2002 [119]	189	Actuarial risk of cirrhosis	44%
Wali *et al,* 2003 [120]	49	Cirrhosis	24% non GT4 vs 85% GT4
Neumann *et al,* 2004 [8]	183	Cirrhosis or death	25%
Yilmaz *et al,* 2007 [121]	227	Cirrhosis	6%

yr, year; HCV, hepatitis C virus; GT4, genotype 4

Table 2 Factors other than HCV associated with poor outcome following retransplantation

Author (reference)	Doyle [23]	Markmann [26]	Rosen [32]	Yoo [33]	Roayaie [34]	Pelletier [35]	Ghabril [15]	Andres [43]
LT (n)	2376	1097			1738		46982	2289
RT (n)	418	150	1356	4189	82	1718	2283	1422
RT-HCV (n)	?	?	323	1006	42	464	1034	1422
Time period	1987-1993	1992- 1996	1990-1996	1987-2001	1989-2001	1997-2002	1994-2005	
Variables associated with poor outcome after RT								
Donor gender	Female							
Donor age	x			x	x	x		x
Mechanical ventilation	x	x						
Bilirubin	x	x	x					
Creatinine	x	x	x	x		x		x
Prothrombin time / INR					x			x
Albumin								x
Type of primary immunosuppression	CsA							
Recipient age	x	>18 years	x	x		x	x	x
Ischemia time		CIT >12 h					WIT >75 min	
UNOS status			x	x		Admission in ICU		
Cause of graft failure			x	PNF				
Race				AA				
MELD score							x (>25)	
Time interval to RT							x	

LT, Liver transplantation; RT, retransplantation; HCV, hepatitis C virus; UNOS, United Network for Organ Sharing; MELD, Model for End Stage Liver Disease; PNF, Primary Non-function; CIT, Cold ischemia time; WIT, Warm ischemia time; ICU, Intensive care unit; AA, African-American

(Table 2). On the other hand, other studies have found HCV infection as a risk factor of poor outcome after RT [32-39]. Yoo *et al* [33] analyzed 4,189 RT patients (UNOS data, from 1987 to 2001), finding HCV as an independent risk factor for poor graft and patient survival at 1 to 5 years, along with six other factors (primary non function, donor and recipient age, creatinine, African-American race and UNOS status). Pelletier *et al* [35] evaluated 1,718 RT patients (of whom 464 HCV positive) showing a decreased survival of the HCV cohort compared to non-HCV patients (44.8% vs 56.3% at 5 years, P<0.001). RT recipients with HCV had a 30% higher covariate-adjusted risk of death than those without HCV (HR 1.3; 95% CI 1.10-1.54; P=0.002). In addition to HCV, other variables associated with significantly increased risk of death after RT included recipient age, presence in Intensive Care Unit, creatinine and donor age >60 years. More recently, Ghabril *et al* [15] evaluated 1,034 HCV RT patients and 1,249 non-HCV RT patients, and showed again that survival was significantly lower in the HCV group. Nevertheless, in the multivariate analysis, the only factors associated with an increased mortality were recipient age, Model for End Stage Liver Disease (MELD) >25, RT following the first year after primary LT, donor age >60 years and a warm ischemia time >75 min.

Predictive models / scores for RT

Even though results from previous studies are controversial, many of them suggest that an adequate candidate selection can result in acceptable patient and graft survival rates after RT. Due to the number of variables that should be taken into account when indicating RT for HCV recurrence and to the lack of a clear consensus, several predictive scores have been developed in order to help decision making and patient selection. Most of these scores were developed based on data from patients retransplanted for any etiology, including urgent and elective RT, and, therefore, are not specifically designed to evaluate the convenience of retransplanting in HCV recurrence.

Markmann *et al* developed a score [26], including recipient age (>18 years), need for mechanical ventilation, cold ischemia time (>12 h), creatinine and bilirubin levels, which identifies a subgroup of patients with a score >2.3 with an expected 1-year survival <40% in whom RT should therefore be avoided.

One of the best known and validated scores for elective RT is the Rosen score [40], which includes recipient age, bilirubin, creatinine, UNOS status, and the cause of graft failure. A Rosen score >20.5 is associated with a survival of 42% and 38%, at 1 and 3 years, respectively.

The MELD score is also used to evaluate patients in the RT setting. A MELD score >25 has shown to be a clear risk factor of short-term survival after RT [41]. Furthermore, some authors have suggested that RT should be avoided with MELD score >28 [42].

The first score specifically designed for HCV-positive patients was recently published by Andres *et al* (n=1422 HCV-RT) [43], including variables from the first transplant (recipient age) and second transplant (donor age, creatinine, INR, serum albumin). This score presented an area under the time-dependent ROC (receiver operating characteristic) curve of 0.643 (95% CI, 0.629-0.657) at 3 years post-RT.

In conclusion, many conditions can influence the decision to indicate RT in HCV recurrence, some of them dependent on patient characteristics and disease severity, and others on transplant center policies, experience, and geographic donor organ availability. In the future, new antiviral therapies with direct antiviral agents will likely modify the course of graft reinfection, as previously described in HBV-infected patients, significantly decreasing the need for RT.

Antiviral treatment in the liver transplant setting

Rationale to use antiviral therapy in the transplant setting

Successful antiviral therapy is the strongest factor that has conclusively shown to modify the course of recurrent HCV-graft disease [44-49]. Sustained virologic response (SVR) is long-lasting and results in histologic improvement [6,45,49,50]. In the only randomized study published to date where patients with mild disease were randomized to either receive dual therapy with peg-interferon (pIFN) and ribavirin (RBV) (n=27) or placebo (n=27), antiviral therapy was the only variable independently associated with histologic response (OR 5, 95%CI 1.5-17; P=0.01) [49]. Changes in histology though are not immediate after therapy and initially consist of improvement in the degree of necroinflammation [50]; with time, 20-60% of patients also show an improvement in the stage of fibrosis [6,49-51]. Histological changes translate in the short-medium term in reduction of portal pressure [49], reduced rate of clinical decompensation and increased survival [44-49]. In one study, in patients with cirrhosis at baseline, the 5-year risk of graft decompensation was higher in non-responders compared to those achieving an SVR (33% vs. 16%) [45]. Interesting recent data have shown that the impact of therapy on survival is significantly greater if therapy is started at milder stages of fibrosis (i.e., Metavir 0-2) [49-52]. In one study, survival since LT was significantly better in SVRs (100% at 3, 5 and 10 years) compared to non-responders (90%, 76% and 76% at 3, 5 and 10 years; P=0.024) solely in patients with F0-1 (n=50). In patients with advanced fibrosis at baseline (F3-4, n=64), the difference was present but did not reach statistical significance with 1, 3, 5 and 7 year survival rates of 96%, 91%, 85% and 85%, respectively vs 97%, 92%, 75% and 72% (P=0.38) [53]. These differences in transplant benefit probably reflect the high mortality observed when treating patients with graft cirrhosis due to the varied and frequent complications that develop in association with antiviral therapy [52-53]. Furthermore, lower SVR rates have been documented when treatment is initiated at advanced stages of fibrosis [44,46,49,52]. Monitoring disease progression is hence essential to initiate therapy at mild stage of fibrosis where greater transplant benefit is achieved. While the gold standard to monitor progression has classically been the liver biopsy, newer tools are being increasingly used, including models based on transient elastography [54,55] or on simple laboratory parameters [56-58].

In the immune competent population, treatment of chronic hepatitis C depends on viral genotype. While patients with HCV genotype 1 are treated with triple therapy based on protease inhibitors (telaprevir or boceprevir) + pIFN + RBV, those with HCV genotypes 2-6 are treated with dual therapy of pIFN + RBV [59]. Unfortunately, there is almost no data on the safety and efficacy of these drugs in special populations, particularly those in whom the need for antiviral therapy is more urgent such as cirrhotic patients in the waiting list for LT or LT recipients with aggressive recurrent disease. In these cohorts, most of the experience is with dual therapy; data are however emerging from single-center experiences on the efficacy and tolerability of triple therapy. Since current licensed oral antivirals are used with IFN and RBV, the efficacy will likely increase in these difficult-to-treat patients but issues regarding tolerability and safety will remain the same if not increased when using triple therapy [60,61].

Pretransplantation antiviral therapy

The past: Data on treatment with pIFN and RBV in advanced cirrhotic patients, mainly those awaiting LT, come from few studies [62-65]. Two approaches have been proposed: a low accelerated dose regimen used during the standard full duration (6-12 months depending on the infecting genotype) aimed at achieving an SVR before LT [62], and a full dose regime administered for a short period of time aimed at achieving viral undetectability up to the time of transplantation [66]. Regardless of the approach used, prevention of graft reinfection by HCV is achieved by 2 of 10 treated patients (in the 2 most important studies, 13% in genotype 1 vs 56% in non-1 genotypes). The duration of therapy before LT has a significant impact on the rate of patients who are HCV RNA negative at transplantation and the rate of patients achieving post-transplant virologic response. In a recent multicenter randomized US study, two thirds of patients treated for 10

weeks or more, were RNA negative at time of LT. However, relapse was high in patients treated for less than 15 weeks. Post-transplant virologic response was highest for those with the greatest duration of treatment (>15 week) – 44% overall – 25% for genotype 1/4/6 and 63% for genotype 2/3 [63].

Besides its low efficacy, there are two major limitations to pretransplantation antiviral therapy. These include its low applicability and its poor tolerability. It is applicable in only a minority of transplant candidates, generally those with preserved hepatic function. Overall, only half or less of patients in a typical waiting list are potential candidates to receive antiviral therapy, and these are patients with hepatocellular carcinoma (HCC) arising on a compensated cirrhotic liver [62, 63, 66]. Furthermore, it is poorly tolerated and can precipitate worsening hepatic function and severe infections [64-66]. In one study where the outcome of treated patients (n=51) was compared to a controlled group of non-treated cirrhotics in the waiting list for transplantation (n=51), infections, particularly bacteriemias and spontaneous bacterial peritonitis occurred significantly more frequently in the former than in the latter group (23% vs 5%), but only if they were Child B or C, with no differences observed among Child A patients [66]. Factors associated with infectious complications in treated patients were high Child-Pugh score, low baseline albumin, ascites or MELD ≥14. All infections occurred in those with a Child-Pugh score >8. In the multicenter US study where the median Child Pugh score of those treated was 7 and the median Meld score 11, a greater percentage of treated patients experienced adverse (98% vs 70%) and serious adverse events (75% vs 50%), but mortality rates between treated and untreated patients were similar (14% vs 15%) [63].

In summary, with dual therapy, patients with decompensated cirrhosis and preserved hepatic function (MELD <15, Child <B9) can be treated, but the decision should be individualized and possibly targeted to those with good virologic profile (genotypes non-1, genotype 1 and low viremia). Infection, particularly spontaneous bacterial peritonitis, is a potentially severe complication in these patients. In one study, prophylactic norfloxacin was associated with a lower risk of developing infection [66]. Treatment should be stopped in those who do not achieve an early viral response 3 months after starting therapy [62-64, 66].

The present: Data on triple therapy with either telaprevir or boceprevir in combination with pIFN-RBV in patients with cirrhosis is very limited. In phase III studies, the proportion of cirrhotic patients was very low, around 7% [67-70]. These studies demonstrated high efficacy rates among some subgroups, particularly naïve (71-92% with telaprevir, 42% with boceprevir) or relapsers (84% with telaprevir, 50-83% with boceprevir) but significantly less in experienced patients (34% and 14% for partial and null responders retreated with telaprevir-based triple therapy, 30-46% for partial responders retreated with boceprevir-based triple therapy). Furthermore, tolerability was significantly poorer in these patients; as expected, side-effects were those previously reported with dual therapy, including anemia that frequently required the use of erythropoietin or transfusions as well as liver decompensation. These results though, come from trials where selected F4 patients were evaluated. Real-life data are accumulating, and show that indeed these regimes can be effective in cirrhotic patients, that the inclusion of the protease inhibitor in the treatment regimen is associated with an enhanced rate of early serum HCV RNA negativity, but that their use is associated with high rates of serious adverse events and treatment discontinuations [70-75]. In a large cohort of experienced cirrhotic patients treated in France (n=485) (median MELD score 8 ranging from 6 to 28, a third of patients with phase III trials exclusion criteria), 40% of 295 telaprevir patients and 41% of 190 boceprevir treated patients achieved an SVR [71]. Importantly, 77-81% of telaprevir patients and 51-65% of boceprevir patients were HCV RNA negative after only 8 to 16 weeks of therapy, a relevant end-point when trying to prevent HCV recurrence. Serious adverse events were very common (about half of treated patients) resulting in treatment discontinuation in 14-21% of patients. Factors independently associated with poor outcome (defined as severe infections, liver decompensation and deaths) were platelet count <100.000/u^3 and albumin levels <3.5 g/dL [71].

In summary, in cirrhotic patients in the waiting list for LT, the expected benefits associated with triple therapy need to be balanced with the risks of severe adverse events, particularly in prior null responders, or those with platelet count below 100,000/u^3 and albumin levels below 3.5 g/dL. For genotype 1 patients with cancer as the main indication for LT and compensated cirrhosis, triple therapy with either telaprevir or boceprevir, pIFN and RBV can achieve serum HCV RNA undetectability in a higher proportion of patients and at an earlier stage of treatment than dual therapy. This seems a very attractive option when performing live-donor liver transplantation. For genotype 1 patients with liver insufficiency as the primary indication for LT, triple therapy should be restricted to those who are considered at an acceptable risk of developing severe complications.

Post-transplantation antiviral therapy

The past: Post-transplantation therapy may be started preemptively during the first 3 weeks before histologic damage has occurred [76-79] or in the setting of recurrent disease [44-50,51-53,80-82]. The first strategy is seldom applicable due to the frequent development of side effects and low proportion of patients in whom therapy can be started due to preexisting conditions such as anemia, neutropenia and thrombocytopenia [76-79]. Most studies have focused on treatment of established disease. Dual therapy results in SVR rates in the range of 25-40% in patients with HCV genotype 1 and 45-65% in non-1 HCV genotypes [80-82]. In *post hoc* analyses, several variables have been found to be associated with SVR. The strongest of these variables, as in the immune competent patient is viral kinetics so that if an early viral response evaluated at 12 weeks post-treatment initiation is not achieved, it is highly unlikely that the patient will achieve an SVR with the standard 12-month dual therapy [59-64, 66,

43-45] and, in contrast, those who are rapid viral responders after only 1 month of treatment are likely to achieve a good treatment response. In addition, higher response rates are achieved in those who can tolerate the complete course with full dose IFN and particularly full-dose RBV [53,80-83]. Pretreatment variables associated with higher viral response rates include low baseline viremia, absence of cirrhosis or FCH, young donor age and IL28B CC polymorphism of both the donor and the recipient [44-50,80-88]. Indeed, the increasing donor age as well as a greater number of cirrhotic patients being treated may explain poor results in some centers [52], improved results have been described when patients with less advanced disease are treated [49,53,83]. Optimal graft/recipient matching depending on IL28B alleles may improve the sensitivity to antiviral therapy posttransplantation. A donor with an IL28B CC genotype may in fact restore partially the sensitivity to IFNα in an unfavorable IL28B genotype recipient [84-88]. This could explain the observation of change in response to therapy after transplantation occurring in a subset of patients. Unfortunately, side effects occur very frequently leading to a constrained follow-up, frequent dose reductions or discontinuations, use of granulocyte colony stimulating factor and erythropoietin, hospital admissions and blood transfusions. Most side effects are of hematologic (anemia, neutropenia, thrombocytopenia), or psychiatric nature (depression) [44-50,50-53,79-83]. In addition, rejection and "*de novo* autoimmune – plasma cell hepatitis" can be triggered by the use of IFN-based therapies [88,89].

In a US multicenter trial, the overall incidence of IFN-induced immunological complications was 7.2%. Risk factors included absence of prior pIFN therapy and the presence of immune features (mainly plasma cell hepatitis) on pre-treatment liver biopsy [89]. Despite the application of different management strategies, such as discontinuation of pIFN together with an amplification of immunosuppression, graft survival is seriously impaired. In the US study, survival was lower in treated patients with versus without immune-mediated complications (38.5% vs. 85.6%) [90]. In order to minimize the risk, close monitoring of immunosuppressive drug levels is essential, especially at the time of HCV RNA clearance [91].

The present: Triple therapy with either telaprevir or boceprevir is now being evaluated for post-transplant recurrence [60,61,91]. While challenging, because targeting "difficult-to-treat" patient population (prior non-responders, advanced fibrosis or FCH, high baseline HCV RNA), improved SVR rates are expected based on preliminary virologic data. Indeed, high rates of viral response of about 80% at week 12 (68-100%) and 60% at weeks 24-48 (50-65%) have been reported in the first weeks of therapy, with no significant differences between boceprevir and telaprevir-based therapy [92-101]. As in the cirrhotic population, high rate of adverse events, particularly infections (9-18%), hematologic toxicity and renal dysfunction, likely reflecting drug-drug interactions are being reported. In particular, anemia occurs almost invariably and results in an extremely frequent use of erythropoietin and RBV dose reductions as well as frequent transfusions. In one study, factors associated with anemia among 164 liver transplant recipients treated with dual therapy were renal insufficiency, longer time from LT to therapy, high baseline viremia, cyclosporine-based immunosuppression and use of mycophenolate mofetil [101]. In studies based on triple therapy, anemia is more frequently reported, with frequent need for dose reduction of RBV despite high use of erythropoietin and even blood transfusions [92-101]. Factors associated with anemia when using triple therapy have not been reported yet. Whether RBV dose reduction will impact SVR in the transplant setting is not known. In non-transplanted patients, RBV dose reductions do not seem to impact viral response as long as 60% of the expected dose is taken [102]. Another limitation when using protease inhibitors in transplant recipients are drug-drug interactions with calcineurin inhibitors. Boceprevir and Telaprevir are metabolized via the Cytochrome P450 3a system and compete with Cyclosporine, Tacrolimus, Everolimus and Rapamycine for metabolism [103,104]. Emerging data suggest that the area under the curve for these immunosuppressive agents is increased when given with Telaprevir or Boceprevir, particularly that of Tacrolimus when using Telaprevir [103,104]. Clinical data show however that these interactions can be managed successfully with strict and frequent monitoring of immunosuppressive levels [60,61,91]. When starting protease inhibitors, calcineurin inhibitors doses need to be reduced to avoid toxicity while increase in the doses to pre-treatment or even higher doses are required once protease inhibitors are discontinued in order to avoid rejection episodes.

In summary, based on preliminary findings, it is expected that triple therapy will result in a 30%-increase in SVR in LT recipients. As expected and given that pIFN-RBV are still needed, concerns remain regarding safety and toxicity issues. Finally, drug-drug interactions need to be acknowledged but can be easily managed through strict immunosuppressive trough level monitoring. Future studies should focus on identifying predictors for non-response to avoid unnecessary treatment and associated toxicities. As in the non-transplant setting, there is great hope for non-interferon based therapies, which might result in greater efficacy [60,61], but mostly lesser toxicity and lesser significant drug-drug interactions. Two examples of the use of these newer agents have already been published; one with Daclatasvir in combination with pIFN and RBV [105] and another with Daclatasvir and Sofosbuvir, without IFN or RBV [106], both resulting in SVR in very difficult to treat patients. Trials are currently underway to evaluate IFN-free regimes in LT patients.

HCV recurrence in Human Immunodeficiency Virus (HIV) LT recipients

Life expectancy in HIV-positive patients has improved dramatically with the introduction of combined antiretroviral treatment (cART) in 1996, and nowadays liver related diseases, mainly due to HCV, are one of the first causes of mortality [107,108]. For this reason, LT is increasingly necessary in this population. Before cART, LT in HIV patients was a formal contraindication due to high mortality rates. Currently, patients with controlled HIV infection with undetectable viral load

under cART, with CD4 count greater than 100 cells/μL and without a history of acquired immunodeficiency syndrome (AIDS-defining events, except esophageal candidiasis, tuberculosis or *Pneumocystis jirovecii* pneumonia) are considered candidates for LT.

Results after LT in HIV patients without HCV co-infection seem to be similar to non HIV patients, especially in HIV-HBV co-infection, drug-induced liver failure, fulminant liver failure and alcohol cirrhosis. In HCV-HIV co-infected patients, preliminary short-term results in small series and with short follow up show higher mortality rates due to aggressive HCV recurrence [109,110]. Large series published in recent years have compared patient and graft survival of HIV-HCV co-infected to that of mono-infected patients. The Spanish series included 83 HIV-HCV coinfected patients and was compared to 252 HCV mono-infected matched controls. Survival at 1st, 3rd and 5th years post-LT was 88% vs 90%, 62% vs 76% and 54% vs 71% in co-infected vs controls, respectively [110]. In the US cohort, 89 HIV-HCV co-infected were compared to 235 HCV-monoinfected. The 3rd year survival was 60% vs 79% [111]. The French cohort included 35 coinfected patients compared to 44 mono-infected. Patient survival at 2 and 5 years were 73% and 51% vs 91 and 81%, respectively [112].

All series have tried to identify factors associated with poor outcome in co-infected patients. In the US series older donor age, combined kidney-liver transplantation, anti-HCV donor and BMI <21 were associated with poor outcome [113]. In the Spanish and French series, MELD at LT was the most potent independent variable associated with outcome. Moreover, HCV genotype 1 and centers with less than 1 co-infected LT per year were associated with poor outcome in the Spanish group [110]. Main cause of mortality in all series was aggressive HCV recurrence. The French group showed that the number of patients without F2 to F4 at 3 years after LT was only 20% in co-infected compared to 80% in mono-infected [112]. Treated rejection and recipient female were factors identified with severe HCV recurrence. In contrast, older recipient age was associated with less severe HCV recurrence [111].

Results with regards to response to antiviral treatment with pIFN and RBV regimens are poor with SVR rates of only 20% [113]. Results with protease inhibitors after LT in HIV-HCV co-infected post-LT are still lacking. In patients developing cholestatic hepatitis C recurrence, a form of recurrence more frequently described in co-infected patients (19% vs 2.6%), response to antiviral treatment is even poorer and mortality is above 80% [114].

HCC is the cause of death in about a quarter of patients co-infected with HCV and HBV and LT for HCC has emerged as a frequent indication. Pathological features of HCC are similar to non HIV patients but HIV patients have higher α-fetoprotein levels before LT and dropout from the waiting list because of tumor progression is more frequent in these patients. Regardless, overall survival appears to be similar in HIV as opposed to non-HIV patients [115].

Immunosuppressive agents in patients with cART require careful consideration because of possible interactions, especially during the first month after LT. Most series describe a higher incidence of acute rejection in the coinfected than monoinfected population, probably related to drug-drug interactions with calcineurin inhibitors. Currently, raltegravir (a novel HIV-1 integrase inhibitor) in combination with another nucleoside analogue reverse-transcriptase inhibitor is the safest approach due to the lack of interactions with calcineurin inhibitors.

HIV-associated events are not an issue after LT. Most patients have high CD4+ cells levels and the majority negative plasma HIV viral load. Infections are similar to those described in mono-infected patients; only 11% of the patients developed an opportunistic infection post-LT in one study. When these infections occur, mortality is high (44%) [116].

In conclusion, results of LT in HIV-HCV coinfected patients compared to mono-infected can be summarized as follows: a) patients are younger; b) HCV recurrence is more aggressive with greater incidence of cholestatic forms; c) HCV recurrence is the main cause of death; d) results with antiviral treatments with pIFN-RBV are poor; e) problems related to HIV post LT are not typically seen; and f) survival is poorer in the coinfected than mono-infected population. Importantly, outcome is good when a proper selection of patients is done. New antiviral agents against HCV, given pre- or post-transplantation will yield better results in these patients.

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