

Review Article

Liver Transplantation and Hepatitis C

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Hepatitis-C-virus- (HCV-) related end-stage cirrhosis is the primary indication for liver transplantation in many countries. Unfortunately, however, HCV is not eliminated by transplantation and graft reinfection is universal, resulting in fibrosis, cirrhosis, and finally graft decompensation. The use of poor quality organs, particularly from older donors, has a highly negative impact on the severity of recurrence and patient/graft survival. Although immunosuppressive regimens have a considerable impact on the outcome, the optimal regimen after liver transplantation for HCV-infected patients remains unclear. Disease progression monitoring with protocol biopsy and new noninvasive methods is essential for predicting patient/graft outcome and starting antiviral treatment with the appropriate timing. Antiviral treatment with pegylated interferon and ribavirin is currently considered the most promising regimen with a sustained viral response rate of around 30% to 35%, although the survival benefit of this regimen remains to be investigated. Living-donor liver transplantation is now widely accepted as an established treatment for HCV cirrhosis and the results are equivalent to those of deceased donor liver transplantation.

1. Introduction

End-stage liver disease caused by chronic hepatitis C virus (HCV) infection is the leading cause of liver transplantation in developed countries [1, 2], including Japan [3]. Unfortunately, liver transplantation does not cure HCV-infected recipients, but reinfection of HCV universally occurs and disease progression is accelerated compared with that in the nontransplant population, resulting in poor outcomes for HCV-infected recipients. Although several studies have investigated the factors affecting the natural history of recurrent HCV, many aspects remain unclear and require further investigation [4]. For patients with progressive fibrosis, it is essential to monitor disease progression and the only strategy that is known to modify the outcome is antiviral therapy at an appropriate disease stage. In this paper, we address the issues that transplant physicians face in the management of patients with recurrent hepatitis C, review the results of antiviral treatments, and discuss on living donor liver transplantation (LDLT) for HCV cirrhosis.

2. Natural History of Hepatitis C after Liver Transplantation

HCV reinfection of liver allografts is universal, occurring just after reperfusion followed by a rapid increase in HCV ribonucleic acid (RNA) levels within 4 postoperative months [5]. Diagnosis of recurrent HCV infection is based on the detection of HCV RNA in the serum and/or liver graft, but diagnosis of recurrent disease requires histologic confirmation [6]. The histologic features of liver injury usually resemble those of nontransplant HCV hepatitis typically developing after 3 months, but the clinical presentation, severity, and outcome are extremely heterogeneous and more profound compared to those in immune competent patients [7]. The pattern of recurrence is worse over time compared with chronic hepatitis, and further cirrhosis, as well-described in the nontransplant population, develops with higher viremia and faster fibrosis progression. Progression to cirrhosis usually takes 9 to 12 years after liver transplantation with a linear progression of histologic fibrosis [7, 8]. A less

common, but well-documented form of recurrence is called fibrosing cholestatic hepatitis (<10%), possibly mediated by a direct cytopathic mechanism under an extremely high viral load and immune-compromised condition. Graft failure occurs in 50% of recipients within a few months after fibrosing cholestatic hepatitis develops [9]. Some HCV-reinfected recipients, however, show no apparent disease progression for at least the first decade and their graft injury remains mild or even absent despite a high viral burden.

Overall, cirrhosis develops in approximately 25% of liver transplant recipients (range 8%–44%) after 5 to 10 years and this percentage is likely to increase with an increase in the follow-up period [7, 8]. Once cirrhosis is complete, survival time is severely decreased and decompensation is encountered with cumulative rates at 1 and 3 years of 40% and 60%, respectively, which finally results in graft failure [8, 10].

The development of decompensated cirrhosis due to recurrent hepatitis C is now the most frequent cause of graft failure, patient death, and the need for retransplantation in HCV-infected recipients [6, 8, 10–13]. As a result, survival is significantly decreased compared with other indications, an overall 10% difference at 3 years. In the most recent United Network for Organ Sharing/Organ Procurement and Transplantation Network (UNOS/OPTN) study from the United States, 3-year survival is 78% among 7459 HCV-positive recipients compared with 82% among 20734 HCV-negative recipients ($P < 0.0001$; <http://www.unos.org/>) [14].

The poor outcome of HCV-positive recipients has resulted in the divergence in transplant outcomes between HCV-positive recipients and HCV-negative recipients. Improvements in organ preservation, surgical techniques, and postoperative care have dramatically improved the survival of HCV-negative recipients over the last two decades, whereas this has not been the case in HCV-positive recipients for whom outcome has remained unchanged or even worsened over time [14–17].

This background indicates the importance of identifying the factors related to severe recurrent hepatitis C and monitoring disease progression.

3. Factors Associated with the Outcome of HCV-Infected Recipients

In the transplant setting, many factors contribute to disease progression compared with nontransplant patients [10], including, in addition to viral-related factors, donor and recipient-related factors, graft and surgical factors, and immunosuppressive agents (Table 1). Although numerous studies have examined this issue, nearly all have, unfortunately, been retrospective, conducted in limited populations and at single centers, utilized immunosuppressive therapies in an uncontrolled manner, and failed to utilize protocol biopsy to evaluate histologic progression. Yet, investigation of the prognostic factors of severe recurrent disease is important for identifying potential factors for modifying disease outcome and improving organ allocation.

TABLE 1: Factors associated with the severity of recurrent hepatitis C after liver transplantation.

| Variables | Effect on recurrent hepatitis C |
|--|---|
| Donor and graft factors | |
| Age | More severe disease (>40, >50, >65) |
| Steatosis | Few studies |
| Prolonged ischemic time | More severe disease |
| HCV+ graft | No influence |
| Reduced size versus whole liver (LDLT versus DDLT) | No difference |
| Pretransplant recipient factors | |
| Genotype 1b | Controversial |
| Pre-LT higher viral load | Unclear |
| Age | Few studies |
| Race | Few studies |
| Sex | Few studies |
| HIV coinfection | No influence |
| IL-28B gene polymorphism | More severe disease in CT and TT genotype |
| Posttransplant recipient factors | |
| Post-LT higher viral load | More severe disease |
| CMV infection | Unclear More severe disease |
| Diabetes mellitus (metabolic syndrome) | More severe disease |
| Immunosuppression | |
| Steroid bolus | More severe disease |
| OKT3 | More severe disease |
| Maintenance steroid | Severe disease when rapidly tapered |
| Steroid free regimen | No influence |
| Tacrolimus versus Cyclosporine | No difference |
| Anti-IL-2 receptor antibodies | Controversial |
| Azathioprine | Controversial |
| Mycophenolate mofetil | Controversial |
| mTOR inhibitors | Few studies |

Abbreviations: CMV: cytomegalovirus; DDLT: deceased donor liver transplantation; HCV: hepatitis C virus; HIV: human immunodeficiency virus; LDLT: living-donor liver transplantation; LT: liver transplantation; mTOR: mammalian target of rapamycin.

3.1. Donor Age. The impact of donor age on outcome has gained increased attention due to the increased use of liver grafts from older donors, which reflects the absolute shortage of available organs. Accumulating data indicates that grafts from older donors are at greater risk for severe histologic findings, disease progression, and impaired graft/patient survival compared with those from younger donors [13, 15, 18–25]. In addition, older donor age might hinder the efficacy of posttransplant antiviral treatment [26–28]. Features of older grafts, such as telomere shortening, impaired hepatocyte proliferation, increased fibrogenesis, and immunologic

problems, are thought to be the cause of the lower quality of grafts from aged donors [29]. Recently, Avolio et al. [30] reported that the model for end-stage liver disease (MELD) score adjusted by donor age (D-MELD; calculated as Donor age \times MELD) could accurately predict the outcome of HCV-infected recipients.

3.2. Graft Characteristics. The use of extended criteria for the donors is especially important for HCV-positive recipients, although studies evaluating long-term outcomes in HCV-positive recipients are lacking. Several studies revealed that grafts from HCV-positive donors could be used as safely as those from HCV-negative donors for hepatitis C cirrhosis [2, 17, 22, 31–34]. Considering superinfection and the impaired response of genotype 1 to antiviral treatment, it is recommended that HCV-positive grafts be used only in HCV genotype 1-positive recipients.

On the other hand, ischemic injury to the graft seems to have a serious impact on patient/graft survival and disease progression [35–39]. An increased risk of severe recurrence of hepatitis C is reported with cardiac death allografts [40], but the most recent analysis of the UNOS/OPTN database revealed the opposite results, and concluded that the use of liver grafts from cardiac death donors is a valuable option for HCV-positive recipients [41].

As for steatosis of graft, despite early studies associating graft steatosis with poor function [42, 43], the impact of allograft steatosis for fibrosis progression and outcome in HCV-positive recipients is unclear [33, 44]. The most recent study by Subramanian et al. [45] indicated that fatty grafts might contribute to fibrosis and poor outcome in HCV-infected recipients. Another recent study by Brandman et al. [23] associated graft steatosis with severe fibrosis at 1 year.

Additionally, several experienced centers reported that LDLT could be performed as safely as deceased donor liver transplantation (DDLT) with an equivalent outcome for HCV-positive recipients [21, 46–50].

3.3. Pretransplant Recipient Characteristics. Studies evaluating the association between the severity of HCV recurrence and HCV genotype are conflicting. Some studies suggest that genotype 1b is associated with a poorer outcome [21, 26, 51–53], but other recent studies have not confirmed this finding. Several studies demonstrated that pretransplant HCV RNA in the serum is associated with increased mortality and graft loss [16, 54–56]. It has been also suggested that a less complex quasispecies composition before transplantation is associated with a more severe recurrence [56–58]. Older recipient age [51, 59, 60], race (white donor/black recipient) [61–63], and sex (male [64]/female [15, 65] recipient) are also reported to be associated with impaired outcome. Recent studies suggest that polymorphisms close to the interleukin (IL)-28B gene, both in the recipient and the donor, can affect not only the course of recurrent HCV hepatitis but also the response to antiviral therapy after liver transplantation with a poorer outcome in the CT and TT genotypes than in the

CC genotype [66–69], which could be useful for selecting a suitable donor for HCV-infected recipients.

The coexistence of hepatocellular carcinoma is reported to have a negative impact on HCV-positive recipient survival [21, 51, 70–76].

Coinfection of the human immunodeficiency virus (HIV) in patients with HCV cirrhosis, once considered to be a contraindication for liver transplantation, has now gained wider acceptance for liver transplantation, with the introduction of highly active antiretroviral therapy that increases survival of HIV/HCV coinfecting patients and makes end-stage HCV cirrhosis the leading cause of death [77]. Studies suggest that liver transplantation in HIV/HCV coinfecting patients is safe and that HIV coinfection does not influence the outcome [78–83]. UNOS no longer considers HIV an absolute contraindication for liver transplantation (<http://www.hivtransplant.com/>) [84].

3.4. Posttransplant Recipient Characteristics. Early high viral loads at 7 days [7, 85], 4 months [55, 86], and 12 months posttransplantation [87, 88] are associated with lower patient and graft survival. A recent study by Shackel et al. [88] demonstrated a linear association between viral titers at 12 months and patient survival.

Postoperative infection with cytomegalovirus (CMV) is associated with more severe HCV disease, increased progression to cirrhosis, and a higher rate of graft failure compared to those without CMV infection [17, 51, 86, 89–92].

Metabolic syndrome occurs in half of HCV-infected recipients within the first 12 months after transplantation and is associated with a greater progression of fibrosis [86]. Several studies demonstrated that posttransplant diabetes in HCV-infected recipients increases the risk of fibrosis/cirrhosis [93–96], but conflicting results have been reported [97]. A causal relationship rather than an association between HCV and diabetes was strongly suggested by a study of 28,942 kidney transplant recipients [98], and accumulating evidence indicates that HCV induces insulin resistance by a variety of mechanisms, which should alert clinicians to the importance of minimizing diabetogenic drugs in the transplant population together with aggressive diabetic control [96]. A recent study by Veldt et al. [99] revealed that increased insulin resistance is associated with a higher rate of advanced fibrosis/cirrhosis in HCV-infected recipients.

4. Immunosuppression and Recurrent Hepatitis C

It is generally accepted that over-immunosuppression, such as steroid bolus and OKT3 as rejection therapy, and maintenance immunosuppression with triple-quadruple therapies at full dose are risk factors for HCV liver injury and are associated with a poorer outcome. The optimal immunosuppressive regimen for HCV-infected patients after liver transplantation remains unclear, however, despite several advances in our knowledge regarding the impact of various

medications on HCV recurrence in parallel with the development of promising new drugs.

4.1. Steroid Boluses and OKT3. Numerous early studies clearly demonstrated that steroid boluses and/or OKT3 administered for graft rejection in HCV-positive patients accelerate recurrent hepatitis C [2, 16, 17, 76, 100–103].

4.1.1. Steroid Maintenance. Based on early perceptions that a steroid bolus for acute rejection accelerates hepatitis C progression, steroids were believed to increase HCV injury. Considering liver injury and the long-term side effects of steroids, steroids were routinely discontinued by 3 months in most liver transplant programs until 2002 [104]. Another option to avoid the negative effects of steroids is to use a steroid-free immunosuppressive regimen.

In addition to early reports [53, 76], two recent retrospective studies [105, 106] revealed that slow steroid tapering (over 6 months) might be associated with less severe recurrent disease. The most compelling data supporting the beneficial effects of low-dose steroids is from Vivarelli et al. [107], who reported the results of a randomized study of rapid (3 months) versus slow (25 months) steroid tapering in conjunction with tacrolimus. The rates of histologic recurrence at the 1-year followup and of advanced fibrosis at the 2-year followup were significantly higher in the rapid tapering group. This important finding might resolve the controversy about the impact of low-dose steroids on the natural history of recurrent hepatitis C.

Several studies, including a meta-analysis, have demonstrated that steroid-free protocols are not significantly different from other protocols with regard to viremia, patient survival, or fibrosis progression [108–114]. Manousou et al. [115] reported significantly more severe fibrosis in a group receiving tacrolimus monotherapy compared to those receiving triple immunosuppression with azathioprine and short-term steroids, but a recent randomized multicenter study reported that although steroid-free immunosuppression is safe and effective for liver transplant recipients with hepatitis C, steroid-free protocols have no advantage over traditional immunosuppression [116]. Considering the well-known diabetogenic complications of steroids, especially when tacrolimus is the primary immunosuppressive agent, the role of long-term steroid administration remains an important and difficult problem that requires further investigation. Current opinion regarding steroid use in HCV-positive recipients is that steroid boluses should be avoided in cases of mild rejection, steroid-free regimens are safe, and, when steroids are used, withdrawal should be extended with complete discontinuation not before 6 months.

4.2. Calcineurin Inhibitors. In vitro series revealed that cyclosporine inhibits HCV replication in a cell-based replicon model [117–119]. Several studies with small populations have confirmed this in vivo series [26, 120–123]. Recently, Spanish groups performing a multicenter retrospective analysis reported that the use of cyclosporine-based

immunosuppression regimens and longer treatment duration may protect patients against viral relapse after antiviral treatment [124]. Larger studies reported comparable, even improved results, in a tacrolimus group. Martin et al. [125] found a significantly increased viral load in patients receiving cyclosporine, without any difference in fibrosis or patient/graft survival. In two large prospective studies comparing cyclosporine and tacrolimus, no difference was observed in HCV-positive patients [126, 127]. Berenguer et al. [128] studied the relationship between calcineurin inhibitors and the development of acute hepatitis, fibrosing cholestatic hepatitis, and severe recurrence by protocol biopsies among 136 cyclosporine and 117 tacrolimus patients, which revealed no difference in any of the evaluated variables or in survival. The same authors performed a meta-analysis comprising 366 HCV-positive recipients (183 with tacrolimus, and 183 with cyclosporine) from 5 studies, which revealed no difference in patient or graft survival [129]. The most recent large retrospective study based on the UNOS/OPTN database by Irish et al. [130] analyzed patient death, graft failure, failure due to recurrent disease, and acute cellular rejection among 8092 tacrolimus patients and 717 cyclosporine patients. The findings revealed an increased risk of patient death, graft failure, and acute rejection in the cyclosporine group while the 3-year unadjusted patient and graft survival were comparable, and concluded that the targeted administration of cyclosporine in HCV-infected recipients should be reconsidered. To date, the use of specific calcineurin inhibitors cannot be recommended based on existing data indicating there are no differences in graft/patient survival nor in the progression of recurrent hepatitis C.

4.3. Role of Other Immunosuppressive Agents: Antithymocyte Globulin, IL-2 Receptor Antibodies, Mycophenolate, Azathioprine, and Mammalian Target of Rapamycin (mTOR) Inhibitors. Because induction with OKT3 and alemtuzumab is strongly associated with severe recurrent HCV [131, 132], several alternative regimens have been proposed for induction. Among these regimens, the use of rabbit antithymocyte globulin (ATG) as part of a steroid-free protocol gained popularity because an early randomized controlled trial showed a reduced incidence of recurrent HCV in the ATG group compared with a steroid bolus group [109]. Subsequent studies, however, failed to show a positive impact of ATG induction [133, 134], and at present, there are no data that conclusively show that ATG has a positive impact on HCV recurrence compared with steroid induction. Only a few studies have evaluated the impact of the anti-IL-2-receptor monoclonal antibodies baxiliximab and daclizumab for induction in HCV-positive recipients [113, 116, 135–137]. Three prospective studies [116, 136, 137] evaluating induction with IL-2 receptor antibodies failed to show a positive impact on recurrent disease and patient/graft survival. On the other hand, a retrospective study by Nelson et al. [138] reported more severe hepatitis C recurrence in patients with anti-IL-2 receptor antibody induction with mycophenolate mofetil (MMF) when compared to standard therapy based on tacrolimus and steroids. Until adequately powered

randomized controlled trials are performed, the use of monoclonal antibodies in HCV-positive liver transplant should be applied with caution and under the rigor of clinical trials.

Azathioprine and MMF are other immunosuppression maintenance drugs associated with disease progression in HCV-infected recipients. An early prospective study showed no effect of MMF in HCV-infected recipients [139]. Recently, however, several studies have reported favorable results for either adding MMF or substituting MMF for azathioprine for graft/patient survival and fibrosis progression [140–145], while other authors found improved or equal effects of azathioprine on disease progression and patient outcome when compared with MMF [64, 115, 146, 147]. A recent review also advocated reappraisal of azathioprine based on several studies that obtained better results with azathioprine [147]. Thus, the overall intensity of immunosuppression rather than the independent action of either drug may have greater impact on HCV recurrence, as shown in recent randomized studies of triple agents [115, 116].

Although mTOR inhibitors have gained widespread use in selected transplant programs as maintenance agents because of their renal-sparing properties, few studies have evaluated the effect of those drugs on the course of recurrent hepatitis C [148–150]. While findings of a few retrospective studies [149, 150] suggested a beneficial effect, there is little evidence to support its widespread use in recurrent HCV patients until results from well-designed, randomized trials are available.

5. Posttransplant Followup and Monitoring of HCV Hepatitis Disease Progression

The risk of progression to cirrhosis can be predicted by the biochemical and histologic recurrence pattern. Aminotransferase peak, bilirubin level, and the presence of biochemical cholestasis are associated with a higher rate of progression to graft cirrhosis [151–153]. Histologic findings from liver biopsies performed in the first 12 months after transplantation are useful for predicting the risk of developing cirrhosis, severity of fibrosis, and graft loss [14, 21, 60, 76, 103, 151, 154, 155]. The presence of histologic recurrence, including cholestasis and hepatocellular ballooning, at an early stage is associated with higher rates of progression to cirrhosis [151]. Moderate-to-severe inflammation in liver biopsies performed within the first 12 months is also predictive of progression to cirrhosis and graft loss [21, 60, 103, 154].

In this background, posttransplant monitoring with reliable methods is crucial for predicting patient/graft outcome, to make an early diagnosis of disease progression, and to start antiviral treatment at the appropriate time. There are two types of prevalent diagnostic methods for monitoring recurrent hepatitis C after liver transplantation; invasive (liver biopsy and measurement of hepatic venous pressure gradient) and noninvasive (elastography, biochemical serum, and fibrogenesis markers, and predictive mathematical models of fibrosis).

Liver biopsy remains the gold standard and the key diagnostic criterion with which other tests are compared in assessing fibrosis. As discussed above, early studies demonstrated the prognostic value of liver biopsy at the time of recurrence and for monitoring disease progression within the first 12 months. With respect to antiviral treatment, a biopsy is essential not only to assess the severity of hepatitis but also to rule out rejection, and initiating treatment in earlier stages of fibrosis results in improved sustained viral response (SVR) rates [26–28]. Consequently, consecutive follow-up protocol biopsies are now widely accepted and recommended by different transplant teams and societies [1, 2, 17, 156, 157]. In contrast, some clinicians object to sequential protocol biopsy given the known limitations of treatment and difficulty in predicting the future of this unpredictable disease [104]. Recently, measuring hepatic venous pressure gradients during transjugular liver biopsies was reported to have a good correlation with fibrosis progression obtained from liver biopsies [158–160]. Hepatic venous pressure gradients greater than 6 mmHg at 12 months are even better for predicting the future development of hepatic decompensation than liver biopsy (sensitivity/specificity; 92%/88% versus 69%/88%) [158].

The estimation of liver stiffness (measured in kilopascals, kPa) with transient elastography (Fibroscan) has been aggressively investigated and is reported to correlate well with the fibrosis progression of HCV-infected grafts after liver transplantation [161–166]. The best cut-off values for detecting patients with graft fibrosis (stage ≥ 2 for METAVIR or Scheuer scores and ≥ 3 for Ishak score) vary among studies between 7.9 and 10.1 kPa, with high positive predictive values (65%–85%), negative predictive values (88%–94%), and good discrimination for significant fibrosis (area under the receiver operating characteristics [ROC] curve: 0.81–0.94). For diagnosis of graft cirrhosis, the cut-off values range from 10.5 to 12.5 kPa with 50% to 74% positive predictive values, 99% to 100% negative predictive values, and 0.87 to 0.99 area under the ROC curve [162–166]. Recently, further evaluation by Carrion et al. [167] indicated that repeated measurements of HCV-infected graft stiffness allow for discrimination between slow and rapid fibrosis progression, and that simple scores, including bilirubin and elastography, or donor age and elastography at 6 months, can accurately predict the risk to develop significant fibrosis or portal hypertension in these patients. Elastography using magnetic resonance imaging was also recently reported to be effective [168].

Other noninvasive methods utilizing biochemical markers and predictive mathematical models of fibrosis have also been investigated [161, 169–175]. These include alanine aminotransferase/aspartate aminotransferase ratio index, aspartate aminotransferase/platelets ratio index, Forns index, Fibrotest, hyaluronic acid, procollagen type IV, YKL-40, and mathematical predictive models utilizing some of aforementioned biomarkers with other serum markers [165, 166, 170–175]. The diagnostic accuracies of these studies are reported to have 40% to 75% positive predictive values, 42% to 93% negative predictive values, and 0.56 to 0.82 area under the

ROC curve, none of which seems to improve nor surpass the diagnostic efficacy of elastography.

6. Antiviral Treatment

Strategies to improve the outcomes of liver transplantation in HCV-infected recipients include eradication of the HCV virus before transplantation with the use of pretransplant antiviral treatment, eradication of HCV virus early after transplantation preemptively to prevent graft damage, and treatment for established recurrent hepatitis C in the acute, or more commonly, chronic phase. Regardless of the antiviral treatment timing, interferon (INF), especially pegylated-INF (PEG-INF), in conjunction with ribavirin (RBV) are currently accepted as a standard key drugs according to the perspectives obtained in nontransplant populations.

6.1. Pretransplantation Antiviral Therapy. Antiviral treatment before transplantation is aimed at suppressing HCV viremia in liver transplant candidates, which may reduce or eliminate the risk of recurrent infection and disease progression, but this approach is severely limited by poor liver function, a high prevalence of nonresponders, severe cytopenia, and complications, including life-threatening infections [176]. To date, only five studies [177–181] have been published in this phase with differences in the treatment duration (6–14 months versus 2–3 months) and in regimens used (INF only, INF/RBV, or PEG-INF/RBV). Regardless of the approach used, the results are similar, resulting in the prevention of HCV reinfection in about 20% of treated patients with high discontinuation rate and high-dose reduction rate [176]. Based on these five studies, the best candidates for pretransplant antiviral therapy remain Child-Pugh class A whose virologic response rate is high and in whom the risk of side effects is almost identical to controls. Antiviral therapy is contraindicated for Child-Pugh class C patients considering the high risk of severe infections and low SVR rate. In Child-Pugh class B patients, treatment should be discussed on a case-by-case basis considering factors for a potential response. The combination of PEG-INF and RBV at a standard dose in conjunction with growth factors is recommended, and can be discontinued after 1 to 3 months if there is no response.

6.2. Posttransplantation Prophylactic and Preemptive Therapy. Viral kinetic studies demonstrated that viremia is minimal in the anheptic phase and immediately after surgery, but the viral load increases as early as the second posttransplant week, reaching its maximal level between the first and third posttransplant month, with even higher levels than those observed at pretransplant period [5]. Therefore, several studies have reported that “prophylactic” or “preemptive” antiviral treatment should be started during this time to suppress viral replication and disease progression, but the results seem less effective [182, 183]. Studies of hepatitis C antibody therapy in the form of hepatitis C immune globulin or monoclonal antibodies against the E2 region motivated by the success of antihepatitis B immune globulins have

been disappointing, with only a transient decrease in liver HCV RNA and serum aminotransferase levels [176, 184, 185]. Thus, prophylactic or preemptive antiviral treatment generally means antiviral treatment with INF/PEG-INF and RBV started at early posttransplant period, without requiring evidence of recurrent hepatitis C. The main drawbacks of this therapy are low applicability due to the existence of cytopenia, renal dysfunction, rejection, or extrahepatic complications, high levels of immunosuppression in this time window, and subsequent high frequency of dose reduction and drug discontinuation. In published studies [186–191] of preemptive antiviral therapy, SVR rates are reported to range from 8% to 34% (5% to 43% for genotype 1 and 14% to 100% for genotypes 2 or 3). The rates of dose reduction and drug discontinuation are approximately 70% and 30%, respectively. The most recently published prospective, multicenter, randomized study (PHOENIX study) by Bzowej et al. [192] was designed to compare the efficacy, tolerability, and safety of an escalating dose regimen of PEG-INF alpha 2a/RBV for 48 weeks for preemptive antiviral treatment versus no treatment; 55 received preemptive treatment and 60 patients underwent observation only. The primary endpoint was the proportion of patients with significant histologic recurrence 120 weeks postrandomization. Enrollment into the study ended early because of the slow inclusion of patients, indicating the difficulties of initiating antiviral treatment in the early posttransplant period. The median delay from transplantation to initiation of therapy was 111 and 121 days in the prophylaxis and observation arms, respectively, which was significantly longer than in other preemptive antiviral studies. SVR was achieved in 22% of the prophylaxis patients. The rate of marked HCV recurrence at 120 weeks (62% in prophylaxis patients versus 65% in observation patients), the time until the first recurrence of HCV, histologic recurrence grades, and the progression of fibrosis at 120 weeks, as well as patient/graft survival were similar in both study arms in this intention-to-treat analysis. Dose reduction and discontinuation were required in 70% and 28%, respectively, in the preemptive antiviral treatment group. Based on these results, European and United States transplant societies do not support the routine use of preemptive antiviral therapy.

6.3. Antiviral Treatment for Established Recurrent Hepatitis C. The most widely accepted and used strategy is initiating antiviral therapy once recurrent hepatitis C in the graft is established by liver biopsies. Initial studies of monotherapy with IFN-alpha yielded poor results, with SVR rates lower than 5% [193]. With the addition of RBV to IFN-alpha treatment, there is a noticeable improvement in treatment outcomes with an SVR rate of 17% to 30% [194]. More recently, several centers reported that PEG-INF/RBV treatment with an improved SVR rate which has now become an established treatment for recurrent hepatitis in HCV-positive recipients [194–198].

The recent reports of PEG-INF/RBV treatment are summarized in Table 2 [26–28, 199–223]. Most of the data come from uncontrolled studies with different designs regarding

TABLE 2: Studies of antiviral treatment with pegylated interferon alpha and ribavirin for established recurrent hepatitis C after liver transplantation.

| Author | Year | Included patients (n) | Genotype 1 (%) | FCH | PEG-INF alpha (dose) | RBV dose (mg/day) | Time since LT | Treatment duration (months) | Growth factor | SVR, n (%) | Discontinuation n (%) | Dose reductions n (%) |
|-----------------------------|------|-----------------------|----------------|-----|---|--|------------------|-----------------------------|---------------|------------|-----------------------|--------------------------|
| Rodriguez-Luna et al. [199] | 2004 | 19 | 63 | NA | 2b: 0.5–1.5 µg/kg per week (n = 19) | 400 then escalated to 800–1000 | 4.2 (1–16.2) | 12 | Yes | 5 (26) | 7 (38) | NA |
| Neff et al. [200] | 2004 | 57 | 98 | NA | 2b: 1.5 µg/kg per week (n = 57) | 400–600 | 23.5 (1.6–84.7) | 12 | Yes | 8 (14) | 18 (32) | INF 38 (67), RBV 22 (39) |
| Ross et al. [201] | 2004 | 16 | 69 | 2 | 2b: 1.5 µg/kg per week (n = 16) | 800–1200 | 9.5 | 12 | Yes | 0 (0) | 8 (50) | INF 12 (75), RBV 13 (81) |
| Dumortier et al. [202] | 2004 | 20 | 80 | 0 | 2b: 0.5–1 µg/kg per week (n = 20) | 400 | 28 (3–103) | 12 | No | 9 (45) | 4 (20) | INF 13 (65), RBV 6 (30) |
| Babatin et al. [203] | 2005 | 13 | 46 | 0 | 2b: 0.9 µg/kg per week (n = 13) | 600 | 24 (6–73) | 12 | Yes | 4 (31) | 7 (54) | 9 (72) |
| Toniutto et al. [204] | 2005 | 12 | 100 | 0 | 2b: 0.5 µg/kg per week (n = 12) | 600–800 | 14 (0.6–60.8) | 12 | No | 1 (8) | 7 (58) | 11 (92) |
| Castells et al. [205] | 2005 | 24 | 10 | 0 | 2b: 1.5 µg/kg per week (n = 24) | 600 | 3.8 ± 2.2 | 12 | Yes | 8 (35) | 3 (13) | INF 6 (25), RBV 14 (58) |
| Biselli et al. [206] | 2006 | 20 | 80 | 0 | 2b: 1 µg/kg per week (n = 20) 2b: 1.5 µg/kg per week (n = 13), 2a: 180 µg/week (n = 23) | 600 | 56.5 (13–157) | 12 | Yes | 9 (45) | 1 (5) | RBV 7 (35) |
| Berenguer et al. [207] | 2006 | 36 | 89 | NA | 2b: 1.5 µg/kg per week (n = 13), 2a: 180 µg/week (n = 23) | 600–1200 | 16.6 (2.7–132.6) | 12 | Yes | 18 (50) | 17 (47) | 19 (53) |
| Oton et al. [208] | 2006 | 55 | 91 | 0 | 2b: 1.5 µg/kg per week (n = 51), 2a: 180 µg/week (n = 4) | 800–1200 | 63.3 ± 45.5 | G1/4: 12, G2/3: 6 | Yes | 24 (44) | 16 (29) | INF 17 (31), RBV 17 (31) |
| Mukherjee and Lyden [209] | 2006 | 32 | 75 | NA | 2a: 180 µg/week (n = 32) | 800 then escalated to 1000–1200 | 16 (2–70) | G1/4: 12, G2/3: 6 | Yes | 11 (34) | 5 (16) | NA |
| Mukherjee and Lyden [210] | 2006 | 39 | 79 | NA | 2b: 1.5 µg/kg per week (n = 39) | 800 | 20 (2–168) | G1/4: 12, G2/3: 6 | No | 13 (33) | 17 (44) | NA |
| Fernández et al. [211] | 2006 | 47 | 94 | 10 | 2b: 1.5 µg/kg per week (n = 47) | 600–800 | 32 ± 25 | 12 | Yes | 11 (23) | 10 (21) | RBV 15 (32) |
| Neumann et al. [212] | 2006 | 25 | 80 | 0 | 2b: 1 µg/kg per week (n = 25) | 600 | 38 (2–108) | 12 | Yes | 9 (36) | 1 (4) | INF 15 (52), RBV 9 (36) |
| Neumann et al. [212] | 2006 | 61 | 87 | 0 | 2b: 1 µg/kg per week (n = 61) | 600–800 | 25 (3–131) | G1/4: 12, G2/3: 6 | No | 17 (28) | 9 (15) | 48 (79) |
| Angelico et al. [214] | 2007 | 42 | 81 | 0 | 2a: 180 µg/week (n = 21) | 200 then escalated to 1200 until tolerated | 48 ± 29 | 12 | No | 7 (33) | 7 (33) | INF 8 (38), RBV 21 (100) |

TABLE 2: Continued.

| Author | Year | Included patients (n) | Genotype 1 (%) | FCH | PEG-INF alpha (dose) | RBV dose (mg/day) | Time since LT (months) | Growth factor | SVR, n (%) | Discontinuation n (%) | Dose reductions n (%) |
|-------------------------|------|-----------------------|----------------|-----|---|--------------------------------------|------------------------|---------------|------------|-----------------------|--------------------------|
| Carrión et al. [215] | 2007 | 81 | 93 | 4 | 2b: 1.5 µg/kg per week (n = 54) 2b: 1.5 µg/kg per week, | 400–1200 adjusted for renal function | 14.5 (2–38) | Yes | 18 (33) | 21 (39) | INF 13 (24), RBV 36 (67) |
| Sharma et al. [216] | 2007 | 35 | 77 | 1 | 2a: 180 µg/week, (no of patients not stated) 2a: 90 µg/week for 4 weeks then | 800 | 16 (1.5–129) | Yes | 13 (37) | 15 (43) | NA |
| Zimmermann et al. [217] | 2007 | 26 | 88 | 0 | 2a: 180 µg/week (n = 26) | 600 then escalated to 800–1200 | 9.4 ± 3.6 | Yes | 5 (19) | 3 (12) | 17 (65) |
| Dinges et al. [218] | 2009 | 19 | 68 | NA | 2a: 180 µg/week (n = 19) | 10 mg/kg/day | 23 (6–162) | Yes | 9 (47) | 5 (26) | INF 8 (50), RBV 7 (37) |
| Lodato et al. [219] | 2008 | 53 | 100 | 0 | 2b: 1.0 µg/kg per week (n = 53) | 8–10 mg/kg/day | 14 (3–151) | Yes | 14 (26) | 24 (45) | INF 3 (6), RBV 21 (40) |
| Roche et al. [27] | 2008 | 133 (29; INF) | 75 | NA | 2b: 0.6–1.5 µg/kg per week (n = 55), 2a: 90–180 µg/week (n = 49) | 1.8–16.9 mg/kg/day | 86 (5–231) | Yes | 58 (44) | 41 (38) | INF 41 (38), RBV 80 (60) |
| Hanouneh et al. [220] | 2008 | 53 | 79 | 0 | 2b: 1.5 µg/kg per week, 2a: 180 µg/week, (no. of patients not stated) | 1000–1200 | 15 (7–39) | Yes | 19 (35) | 14 (26) | 31 (58) |
| Berenguer et al. [28] | 2009 | 107 | 86 | 11 | 2b: 1.5 µg/kg per week (n = 41), 2a: 180 µg/week (n = 66) | 600–1200 | 21 (2–133) | Yes | 39 (37) | | INF 37 (35), RBV 43 (40) |
| Selzner et al. [26] | 2009 | 172 (36; INF) | 68 | 6 | 2b: 1.5 µg/kg per week, 2a: 180 µg/week, (no. of patients not stated) | 800–1000 | 19 (1–149) | Yes | 86 (50) | 29 (17) | 80 (47%) |

TABLE 2: Continued.

| Author | Year | Included patients (n) | Genotype 1 (%) | FCH | PEG-INF alpha (dose) | RBV dose (mg/day) | Time since LT | Treatment duration (months) | Growth factor | SVR, n (%) | Discontinuation n (%) | Dose reductions n (%) |
|-------------------------|------|-----------------------|--------------------|-----|---|-------------------|---------------|-----------------------------|---------------|------------|-----------------------|--------------------------|
| Schmidt et al. [221] | 2010 | 83 | 88 | NA | 2b: 1.0 µg/kg per week (n = 30), 2a: 180 µg/week (n = 53) | 400–1000 | 41 (0.6–144) | 12 | Yes | 31 (26) | 24 (29) | 49 (51) |
| Jain et al. [222] | 2010 | 60 | 93 | NA | 2b: 1–1.5 µg/kg per week (n = 200), 2a: 180 µg/week (n = 40) | 800 | 29 ± 28 | 12 | Yes | 21 (35) | 24 (40) | INF 21 (35), RBV 16 (27) |
| Al-Hamoudi et al. [223] | 2011 | 25 | 0 (All genotype 4) | NA | 2a: 180 µg/week (n = 25) | 400–1200 | 14 (1–72) | 12 | Yes | 14 (56) | 1 (4) | INF 0 (0), RBV 7 (28) |

Abbreviations: FCH: fibrosing cholestatic hepatitis; INF: interferon; LT: liver transplantation; NA: not available; PEG-INF: pegylated-interferon; RBV: ribavirin; SVR: sustained viral response.

time to start treatment, regimen used, and followup, but treatment duration is generally 48 to 52 weeks. Therefore, the results were also very different, with SVR rates ranging 0% to 56% (median: 33%). These results are lower than those obtained in nontransplant populations, possibly due to the immunosuppressive status, high prevalence of genotype 1, high viral load, the difficulty in maintaining adequate antiviral doses (especially RBV), and the difficulty in maintaining therapy for the ideal duration.

Factors affecting SVR rates after PEG-INF/RBV therapy have been aggressively investigated in these studies. Non-1 genotype [26, 27, 199, 202, 213, 218, 220, 234, 235], absence of prior antiviral therapy [194], early virologic response (evaluated after 3 months) [27, 28, 202, 205, 207–210, 214, 215, 217–221, 223, 235], rapid virologic response (evaluated after 1 month) [206, 208, 220], adherence to therapy [27, 202, 207, 211, 213, 216–218], low baseline viral load [27, 208, 211–213, 216, 221, 222], low pretreatment fibrosis stage [26, 28, 204], younger donor age [26, 28, 221, 234], polymorphisms close to the IL-28B gene [66–69], and cyclosporine-based immunosuppression [26, 234, 236] are associated with an improved SVR. Most studies demonstrated improved biochemical and histologic findings, even in virologic nonresponders [222, 237], but whether antiviral therapy slows disease progression in nonresponders has not yet been demonstrated. In addition, several recent retrospective studies with a considerable follow-up period revealed improved patient/graft survival in patients with an SVR [26, 73, 238, 239].

In the absence of controlled studies comparing different treatment regimens, it is not currently possible to determine whether to begin treatment with full or reduced doses and increase as tolerated, or whether individualized treatment is beneficial according to viral response kinetics. Therefore, the rules set out for the nontransplant population should be followed, but adherence to treatment is a major issue for posttransplant recipients. Dose reductions of RBV and/or PEG-INF are necessary in approximately 70% of patients and treatment discontinuation in approximately 30% (Table 2). Dose-dependent hemolytic anemia due to RBV is the major cause of dose reduction and treatment discontinuation in transplant recipients. Several authors have initiated RBV at low doses and then escalated according to tolerance in relation to hemoglobin levels and renal function. To avoid dose reduction, and thus achieve improved SVR, many authors used adjunctive therapy with erythropoietin or granulocyte colony stimulating factor (Table 2). While these drugs improve tolerability to antiviral treatment, there are no data confirming that they result in higher efficacy.

An increased risk of acute rejection in patients treated with PEG-INF/RBV (5%–6%) compared with those with INF/RBV (1%–3%) was suggested by recent systematic reviews [194–197], although controlled studies did not detect any differences in the rejection rate between treated patients and untreated controls [190, 215, 240]. Whether PEG-INF/RBV therapy increases the risk of rejection remains to be investigated, but acute or chronic rejection seems to be frequently associated with concomitant low or negative serum HCV RNA, leading to an improvement in

hepatic function after viral clearance, and resulting in lower serum immunosuppressant levels [241–244]. Thus, close monitoring of calcineurin inhibitor levels is necessary during antiviral treatment. Several authors reported cases with immune-mediated hepatitis observed during or shortly after antiviral treatment (mainly after viral clearance) that responded well to increased immunosuppression [245–247]. In patients under antiviral treatment, particularly in those with undetectable HCV RNA, any flare-up in liver enzymes would suggest rejection or “autoimmune hepatitis” and a liver biopsy should be performed.

Based on the present perspectives, it is compelling to conclude that there is currently no evidence to support the recommendation of antiviral treatment for recurrent graft hepatitis C due to the lack of clinical benefit and frequent adverse effects, as concluded by the recent Cochrane meta-analysis [198]. Recent retrospective cohort studies with a considerable follow-up duration found improved patient/graft survival in patients who obtained an SVR after antiviral treatment [26, 73, 238, 239]. Further randomized clinical trials with adequate trial methodology and adequate follow-up duration are necessary to confirm an actual survival benefit of antiviral treatment. At the same time, direct-acting antivirals such as protease, polymerase, or other nonstructural protein inhibitors should be investigated [248–250].

7. Living Donor Liver Transplantation in Patients with HCV Cirrhosis

In areas with low deceased donor organ availability like Japan, the indication of LDLT for HCV cirrhosis is similar to that of DDLT [3], whereas in Western countries, LDLT is conducted in an attempt to alleviate the shortage of donor organs and decrease the mortality among patients awaiting transplants. Early studies raised some concerns, however, regarding the outcomes of LDLT in HCV patients, such as a poorer graft outcome and earlier and more aggressive HCV recurrence after LDLT compared with DDLT [224, 225, 227]. Several theories have been proposed to explain the differences in HCV recurrence between LDLT and DDLT recipients. One possible explanation is that the intense hepatocyte proliferation that occurs in partial liver grafts may lead to increased viral translation and replication [225, 251–253]. Genetic donor-recipient similarity is another proposed mechanism for more severe HCV recurrence [254, 255]. Recent studies however, comparing outcomes of LDLT and DDLT in HCV-infected patients have not only failed to identify LDLT as a risk factor for more intense viral recurrence with impaired outcome, but also revealed improved results in LDLT recipients [21, 46–50, 226, 228–233], which do not support the aforementioned speculations. Alternatively, recent studies favored the theory that outcomes of LDLT for HCV cirrhosis could be better than those of DDLT due to the younger donor age and shorter ischemic time of LDLT grafts. The studies comparing outcomes between LDLT and DDLT in HCV-infected recipients are summarized in Table 3. While several studies demonstrated impaired patient/graft survival and severe histologic findings in LDLT [224, 225, 227],

TABLE 3: Studies comparing living donor liver transplantation and deceased-donor liver transplantation in patients with hepatitis C cirrhosis.

| Author | Year | n (LDLT/DDLT) | MELD score (LDLT/DDLT) | Donor age (LDLT/DDLT) | Cold ischemia time (h) (LDLT/DDLT) | Follow up (mo) | Histologic progression | Patient survival (%) (LDLT/DDLT) | Graft survival (%) (LDLT/DDLT) | Comments |
|--------------------------------|------|------------------|--|-------------------------------------|--|----------------------|------------------------------|--|--|---|
| | | | | | | | | | | |
| Gaglio et al. [224] | 2003 | 68 (23/45) | 12.6/28* | NA | NA | 24 | NA | 87/89 | 87/85 | No difference in outcomes, increased risk of cholestatic hepatitis in LDLT |
| Shiffman et al. [46] | 2004 | 76 (23/53) | 13.5 ± 1.1/16.2 ± 1.0 | 47.6 ± 2/47.8 ± 0.8 | NA | 36 | No difference | 79/82 | 76/82 | No difference in outcomes |
| Humar et al. [48] | 2005 | 51 (12/39) | 17 (14–27)/24 (17–40)* | 37.7 ± 9.2/42.8 ± 16.2 [¶] | 10.2 ± 4.2/<1 [†] | 28.3 | Significantly severe in DDLT | 92/90 | NA | LDLT may be at a low risk for HCV recurrence |
| Garcia-Retortillo et al. [225] | 2004 | 117 (22/95) | 11 (5–24)/11 (2–28) | 31 (19–58)/47 (13–86) [¶] | NA | 22 | Significantly severe in LDLT | NA | NA | Severe hepatitis C recurrence in LDLT |
| Maluf et al. [226] | 2005 | 126 (29/97) | 13.2 ± 1.1/21 ± 0.8* | NA | 0.6 ± 0.2/7.5 ± 2.8 [†] | 72 | NA | 67/70 | 64/69 | No difference in survival, more rejection in DDLT and biliary complications in LDLT |
| Thuluvath and Yoo [227] | 2004 | 619 (207/412) | NA | 35.8 ± 0.4/38.9 ± 18.1 [¶] | 3.9 ± 7.3/8.4 ± 4.5 [†] | 24 | NA | 79/81 | 74/73 | Lower graft survival in LDLT |
| Russo et al. [228] | 2004 | 4234 (279/3955) | NA (TB, PT and Cre were significantly worse in DDLT) | 37/40 [¶] | 8.1/2.6 [†] | 24 | NA | 83/81 | 72/75 | No difference in outcomes |
| Bozorgzadeh et al. [229] | 2004 | 100 (35/65) | 14.9 ± 4/15.9 ± 5.3 | 34.6 ± 9.7/49.2 ± 20.4 | NA | 39 | No difference | 89/75 | 83/64 | No difference in outcomes |
| Van Vlierberghe et al. [230] | 2004 | 43 (17/26) | 15 ± 9/15 ± 8 | 31 ± 8/48 ± 17 | 3.1 ± 1.3/11.1 ± 2.6 [†] | 12 | No difference | No difference (Presented with only figure) | No difference (Presented with only figure) | No difference in outcomes in short-term |
| Schiano et al. [231] | 2005 | 26 (11/15) | 14 (9–19)/18 (10–31) P = 0.05 | 33 (20–54)/47 (13–73) | 0.6 (0.3–1.0)/10 (4.4–20) [†] | 24 | NA | 73/80 | 73/80 | No difference in survival, accelerated viral load increase in LDLT |
| Guo et al. [49] | 2006 | 67 (15/52) | 16.9 ± 6.9/19.0 ± 8.3 | NA | NA | 24 | No difference | 93/96 | 87/94 | No difference in outcomes |
| Terraault et al. [50] | 2007 | 275 (181/94) | 14 (6–40)/18 (7–40)* | 38 (19–57)/41 (9–72) | 0.8 (0.1–8)/6.7 (0.2–10) [†] | 36 | No difference | 74/82 | 68/80 f | No significant difference in patient/graft survival in experienced LDLT centers |
| Schmeding et al. [47] | 2007 | 289 (20/269) | NA | 38.6 ± 15.2/44.2 ± 12 | NA | 60 | No difference | Better in DDLT (P = 0.011) | Better in DDLT (P = 0.006) | LDLT does not increase the risk and severity of HCV recurrence, No difference in patient/graft survival when HCC beyond Milan excluded. |

TABLE 3: Continued.

| Author | Year | n (LDLT/DDLT) | MELD score (LDLT/DDLT) | Donor age (LDLT/DDLT) | Cold ischemia time (h) (LDLT/DDLT) | Follow up (mo) | Histologic progression | Patient survival LDLT/DDLT (%) | Graft survival LDLT/DDLT (%) | Comments |
|--------------------------------|------|------------------|---------------------------|--|---|----------------------|--|---|---------------------------------------|---|
| Selzner et al. [232] | 2008 | 201 (46/155) | 14 (7-39)/17 (6-40) | 38 (19-59)/46 (11-79) [†] | 1.5 (0.5-4.9)/7.5 (1.1-16) [†] | 60 | Significantly severe in DDLT | 84/78 | 76/74 | Donor age, rather than transplant approach affects the progression of HCV |
| Gallegos-Orozco et al. [21] | 2009 | 200 (32/168) | 14.6 ± 4.7/25.5 ± 5.9* | 35 ± 12/40 ± 16 P = 0.05 | NA | 60 | No difference | 81/81 | NA | LDLT is a good option for HCV cirrhosis |
| Jain et al. [233] | 2011 | 100 (35/65) | 14.5 ± 3.9/16.8 ± 7.3* | 34.3 ± 9.3/47.2 ± 19.8 [†] | 11 ± 3.1 in DDLT | 84 | Significantly severe in DDLT at all time points | 77/65 | 71/46 | Both patient/graft survival and histologic findings were better in LDLT |

* MELD score is significantly higher in DDLT.

[†] Donor age is significantly higher in DDLT.

[†] Cold ischemia time is significantly longer in DDLT.

Abbreviations: Cre: creatinine; DDLT: deceased donor liver transplantation; LDLT: living donor liver transplantation; MELD: model for end-stage liver disease; NA: not available; PT: prothrombin-time; TB: total bilirubin.

the majority of studies reported equal or even improved outcomes both in patient/graft survival and in fibrosis progression in LDLT [21, 46–50, 226, 228–233]. These data should be interpreted with caution, however, because of the important clinical distinction between LDLT and DDLT. At the time of transplantation, DDLT recipients are far sicker than LDLT recipients as represented by a significantly higher MELD score, donor age is higher, and graft ischemic time is longer, as shown in Table 3. All these factors, as discussed earlier, are considered independent prognostic factors for severe HCV recurrence and impaired patient/graft outcome. Additionally, as Terrault et al. [50] reported, the learning curve for the LDLT procedure may have a considerable impact on the outcome of LDLT for HCV cirrhosis. Jain et al. [233], who recently reported that both patient/graft survival and histologic findings are better in LDLT, found in a sub-analysis of the study that adjusting for MELD score (<25) and donor age (<50) resulted in similar outcomes.

Based on accumulating reports comparing LDLT and DDLT for HCV cirrhosis, hepatitis C recurrence by itself does not seem to explain the differences in patient/graft survival between LDLT and DDLT, and even improved outcomes could be achieved in LDLT due to the better quality of the graft and less sick recipient condition at the time of transplantation. Thus, LDLT could be strongly recommended for HCV-positive patients whenever it is available.

8. Retransplantation for Graft Failure Due to Recurrent Hepatitis C

Graft reinfection by HCV is universal with a faster progression to fibrosis and cirrhosis compared with nontransplanted patients, and in those with decompensated graft cirrhosis, retransplantation is the only potentially curative option, although HCV infection has been identified as a risk factor in previous studies [12, 256–263]. Recipient and donor age, bilirubin and creatinine levels, UNOS status, MELD score, time to retransplantation (<1 year), and HCV infection have been identified as independent risk factors in these studies. The International Liver Transplantation Society Expert Panel established that bilirubin ≥ 10 mg/dl, creatinine ≥ 2.0 mg/dl, recipient age < 55, donor age > 40, and early HCV recurrence (cirrhosis within 1 year after transplant) are variables associated with a worse outcome after retransplantation [2].

Due to the lack of a clear consensus with a variety of reported factors, several models based on logistic regression analysis of donor and recipient factors have been developed in the decision-making process for elective retransplantation in HCV-infected patients. These models include the Rosen score [264], the MELD score [12, 262, 265], the Child-Turcotte-Pugh score [258, 262, 266], and the Donor Risk Index [267]. Among these, the Rosen score [264], calculated based on recipient age, bilirubin and creatinine levels, and retransplantation interval, is most widely used and validated. Patients with a Rosen score ≤ 16 had the best 1- and 3-year survival rates (75% and 70%, resp.), while patients with a Rosen score ≥ 20.5 had survival rates of only 42% and 38%, respectively. Two recent studies [263, 266] using the

Rosen score as a screening tool revealed similar survival rates in HCV-infected patients and non-HCV-infected patient. Overall, liver retransplantation is not contraindicated in HCV-infected patients, yet in patients with a high risk of death after retransplantation (e.g., ≥ 20.5 in Rosen score) the use of a new organ seems unreasonable.

9. Conclusion

Hepatitis C is here to stay and will remain the most common indication for liver transplantation. Physicians treating HCV-infected candidates and recipients of liver transplantation must be aware of important issues that affect the natural history of recurrent HCV. At present, factors modifiable by clinicians include proper graft allocation, preservation injury, immunosuppression, and antiviral treatment, but many factors among these aspects remain to be determined in future well-designed prospective studies. LDLT can be performed as safely and effectively as DDLT for HCV-infected patients in experienced centers.

Abbreviations

| | |
|------------|---|
| ALT: | Alanine aminotransferase; |
| AST: | Aspartate aminotransferase; |
| ATG: | Antithymocyte globulin; |
| CMV: | Cytomegarovirus; |
| DDLT: | Deceased donor liver transplantation; |
| FCH: | Fibrosing cholestatic hepatitis; |
| HCV: | Hepatitis C virus; |
| HIV: | Human immunodeficiency virus; |
| IL: | Interleukin; |
| INF: | Interferon; |
| LDLT: | Living donor liver transplantation; |
| MELD: | Model for end-stage liver disease; |
| MMF: | Mycophenolate mofetil; |
| mTOR: | Mammalian target of rapamycin; |
| PEG-INF: | Pegylated interferon; |
| RBV: | Ribavirin; |
| RNA: | Ribonucleic acid; |
| ROC: | Receiver operating characteristics; |
| SVR: | Sustained viral response; |
| UNOS/OPTN: | The United Network for Organ Sharing/Organ Procurement and Transplantation Network. |

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