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Natural history, treatment and prevention of hepatitis C recurrence after liver transplantation: Past, present and future

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Core tip: This paper reviews the evolution of our knowledge on the natural history of hepatitis C virus (HCV) recurrence after liver transplantation, including risk factors for disease progression, and antiviral therapy. It is necessary to define an innovative public health policy to improve HCV screening which is the only way of allowing non-tested HCV patients access to therapy before they develop advanced liver disease.

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Abstract

Hepatitis C virus (HCV)-related liver disease, including cirrhosis and hepatocellular carcinoma is the main indication for liver transplantation (LT) worldwide. Post-transplant HCV re-infection is almost universal and results in accelerated progression from acute hepatitis to chronic hepatitis, and liver cirrhosis. Comprehension and treatment of recurrent HCV infection after LT have been major issues for all transplant hepatologists and transplant surgeons for the last decades. The aim of this paper is to review the evolution of our knowledge on the natural history of HCV recurrence after LT, including risk factors for disease progression, and antiviral therapy. We will focus our attention on possible ways (present and future) to improve the final long-term results of LT for HCV-related liver disease.

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Key words: Hepatitis C; Liver transplantation; Recurrence; Fibrosis; Treatment

INTRODUCTION

Hepatitis C virus (HCV) has been estimated to infect 170 million people worldwide^[1]. Liver disease due to HCV, including cirrhosis and hepatocellular carcinoma (HCC) is the main indication for liver transplantation (LT)^[2,3]. Post-transplant HCV re-infection of the graft is reported to be universal and often results in accelerated progression from acute hepatitis to chronic hepatitis, and liver cirrhosis. Comprehension and treatment of recurrent HCV infection after LT have been major issues for all transplant hepatologists and transplant surgeons for the last 25 years. This is illustrated by the significant number of published papers in this field to date (1050 references in PubMed up to September 2013). The aim of this paper is to review the evolution of our knowledge on the natural history of HCV recurrence after LT including risk factors for disease progression, and antiviral therapy. We will focus our attention on possible ways (present and future)

to improve the final long-term results of LT for HCV-related liver disease.

NATURAL HISTORY OF HCV

RECURRENCE AFTER LT

Recurrence of HCV infection after LT is universal, however, the natural history of hepatitis C on the liver graft is variable. It must be pointed out that the evaluation of recurrent hepatitis C has been described from liver biopsy, which is the cornerstone of clinical management of patients in daily practice. Nevertheless, differentiation of recurrent hepatitis C from acute cellular rejection can be difficult. Regev *et al.*^[4] demonstrated, from 105 cases blindly reviewed by 5 pathologists, that histological distinction between recurrent hepatitis C and acute rejection had low interobserver and intraobserver agreement rates, and hence showed low reliability. It has been suggested that transient elastography may provide good accuracy in identifying patients with severe fibrosis, better than non-invasive indices based on clinico-serological parameters, in LT recipients^[5].

Histological recurrence is observed in 80% of HCV-infected patients within 5 years after LT^[6]. It is well known that liver disease caused by HCV infection progresses more rapidly in immunosuppressed than in immunocompetent individuals, and chronic HCV infection leads to cirrhosis in up to 20%-30% of individuals only five years after LT^[7-9]. In addition, the natural history of HCV recurrent cirrhosis is also accelerated after LT. The rate of decompensation is > 40% at 1 year and > 70% at 3 years in LT recipients *vs* < 5% and < 10%, respectively, in immunocompetent patients^[9,11]. The rate of progression from decompensation to death is also accelerated, with a 3-year survival of < 10% following the first decompensation *vs* > 60% in immunocompetent patients^[9,10]. Therefore, long-term graft and patient survival is significantly reduced in patients undergoing LT for HCV-related disease as compared to other indications^[12]. Disease progression (*i.e.*, fibrosis progression) depends on a large number of variables, including host, donor, viral, and external factors. Interestingly, early post-LT (1-year) liver biopsy has great prognostic value and must be performed in every LT recipient. The 5-year probability of graft cirrhosis is associated with the severity of necroinflammatory activity of recurrent hepatitis C on the liver graft at 12 mo^[13-15]. Similarly, the graft survival is significantly impaired in recipients with early HCV recurrence and fibrosis stage 3 and 4 at 1 year after LT^[16].

Recurrent HCV-related liver disease after LT begins with a first phase of acute hepatitis and thereafter can have two distinct clinical and histological patterns. The first one is the most frequent and is the same as that described in non-transplant, or non immunocompromised patients, and is characterized by the progression from chronic hepatitis to cirrhosis. Earlier onset of biochemical hepatitis and persistently elevated serum transaminases are associated with more rapid progression of fi-

bro sis^[17-20]. The second type of recurrent hepatitis C after LT is specific for immunosuppressed patients (including HIV-positive patients and organ-transplanted patients, or both), and has been described as fibrosing cholestatic hepatitis (FCH). FCH has been observed in the context of hepatitis B virus or HCV infection and is characterized by rapid and extensive dense portal fibrosis and cholestasis leading to an inexorable deterioration in liver function^[21,22]. Estimates of HCV-related FCH frequency after LT range from 2%-14%^[23-26]. It has been hypothesized that FCH could be related to direct viral cytotoxicity after immune escape^[27], associated with a deviation from a T helper 1 type intrahepatic cytokine response to a T helper 2 type response^[28]. As its prognosis is very poor (50% of patients die^[23]), predicting the onset of FCH and defining the patients at risk of developing this severe complication is a major goal. It has been suggested that FCH could be associated with older donor, corticosteroid treatment for acute rejection, stable quasispecies variants of HCV, earlier recurrence of HCV infection, higher HCV viral load, unfavorable recipient IL-28B polymorphism, and lower levels of immunosuppressive medications^[26,27,29,30]. Retransplantation for this specific complication remains controversial regarding its usual poor outcome^[31].

Besides FCH, many reports have identified a large number of pre-transplant and post-transplant factors associated with more rapid progression of fibrosis, without taking into account antiviral treatment. The vast majority of these studies were retrospective, and this can be explained by the necessity to have mid- and long-term (5- or 10-year) evaluation of the liver graft. Donor features are major non-viral factors which are strongly associated with fibrosis progression. Older age, liver steatosis and diabetes mellitus are all deleterious^[16,32-37]. Donor age is probably the most relevant factor, but significant cut-offs (defining "old" donor) range from 33 to 50 years old. In addition, hepatitis C recurrence after LT from a donor older than 60 years could be a major factor in female recipients compared to male recipients^[38]. During the past 20 years, donor age has considerably increased (mean age in France was 53.2 in 2012, with 42% of the donors over 60, from the annual report of French Agence de la Biomédecine) and the selection of young donors for HCV recipients is questionable. The role of recipient age is still debated. Selzner *et al.*^[39] evaluated the role of donor and recipient age in transplantation/ischemia-reperfusion injury and short- and long-term graft and patient survival in a large population of 822 LT recipients. The HCV patients who were \geq 50 years old and who were transplanted with an older graft (\geq 60 years) had significantly reduced 3- and 5-year graft survival. Interestingly, the use of HCV-positive donors has been reported not to alter the outcome after LT, and this is a way to enhance the number of available liver grafts^[40]. Recently, it has been suggested that the use of HCV-positive liver grafts from donors > 45 years could be associated with more advanced fibrosis^[41]. At the time of LT, it has been suggested that prolonged cold and/or warm ischemia times

could negatively impact graft and patient survival^[42]. Some recipient characteristics also have a significant impact on HCV recurrence after LT. The reported impact of IL-28B genotypes (donor and recipient) on progression to cirrhosis after hepatitis C recurrence has been inconsistent^[43]. Reactivation of herpes group viruses [cytomegalovirus (CMV) and human herpes virus-6 (HHV-6)] may play a role in HCV recurrence after LT. Some reports have suggested that herpes virus infection could accelerate fibrosis progression^[44,45]. Recently, a retrospective study of 347 first LT recipients showed that CMV infection was associated with an increased risk of fibrosis stage ≥ 2 and inflammation grade ≥ 2 ^[46]. However, the widespread use of highly effective CMV prophylaxis regimens has probably reduced any potential effect of herpes virus reactivation on recurrent hepatitis C during the last decade. The risk of *de novo* diabetes mellitus after LT is increased in patients with HCV infection, especially in patients treated with tacrolimus (Tac)^[47], and the presence of diabetes is associated with more rapid fibrosis progression^[48]. Similarly, alcohol consumption after LT also acts as co-factor and accelerates fibrosis progression in HCV patients^[49]. Some studies have suggested that HLA class I and II matching could increase fibrosis progression, without interfering with rejection^[50,51]. The prevalence of cryoglobulinemia is about 15%-20% in patients with end-stage HCV-related liver disease and almost 30% in LT recipients with recurrent hepatitis C. This has been found to be associated with reduced graft survival from more severe HCV recurrence and increased incidence of hepatic artery thrombosis^[52-54]. In summary, regarding the potential deleterious effect of all of these donor/recipient characteristics, from which a vast majority is not modifiable, the use of a non steatotic liver graft from a young donor (< 50 years) could be recommended to reduce cold ischemia time, and to actively prevent CMV reactivation or primo-infection in each case of HCV LT recipient.

In addition to donor/recipient characteristics, the second major factor which can modify the natural history of recurrent hepatitis C after LT is HCV itself. First of all, higher HCV RNA levels (in serum and/or liver) at the time of LT are associated with increased risk of progression to cirrhosis, graft loss, and death^[55,56]; higher viral load in the early post-transplant period has also been associated with more rapid progression^[57]. The data on the relationship between HCV genotype and recurrent hepatitis C infection are more conflicting, and the impact of response to antiviral treatment induces major interferences. Nevertheless, genotypes 1b and 4 could be associated with more severe recurrent hepatitis C^[13,58-61]. During the last decade, human immunodeficiency virus (HIV)-HCV co-infection has emerged as a new indication for LT because of the major progress in the treatment of HIV infection. Duclos-Vallée *et al.*^[62] first compared the survival and severity of recurrent HCV infection after LT in 35 HIV-HCV-co-infected and 44 HCV-monoinfected patients. The 2-year and 5-year survival rates were signifi-

cantly reduced in co-infected patients: 73% and 51% vs 91% and 81% in monoinfected patients, respectively. The progression of fibrosis was significantly higher in the co-infected group. Therefore, improvement of prognosis in this specific indication is a major challenging issue for LT hepatologists.

Finally, the third goal in the field of transplantation is the impact of the immunosuppressive regimen on the severity of HCV recurrence. The effects of steroids on recurrent hepatitis C are complex. High-dose intravenous steroid boluses for acute rejection lead to a significant increase in HCV viral load and are associated with more rapid progression of recurrent hepatitis C^[55]. In addition, adjuvant antibody therapy (anti-thymocyte globulins, OKT3) for steroid-resistant rejection may be associated with more rapid progression to severe fibrosis^[63,64]. More recent data suggest that maintaining low-dose steroids over a long period could have beneficial effects on the progression of recurrent hepatitis C^[65-67] and the steroid-free regimen did not show an advantage in HCV recurrence^[68]. Similarly, the long-term use of azathioprine as part of maintenance immunosuppression therapy may be beneficial^[20,66,69]. The role of calcineurin inhibitors (CNIs), Tac and cyclosporine (CsA), on the severity of recurrent hepatitis C after LT is highly controversial. CsA might offer potential advantages over Tac. First, CsA directly suppresses HCV replication *in vitro* by binding to cyclophilin B and inhibiting HCV RNA polymerase^[70]. Moreover, Tac, but not CsA, indirectly enhances HCV replication *in vitro* through inhibition of phosphorylation and nuclear translocation of STAT-1, thereby blocking interferon signaling pathways^[71]. These experimental data could explain the findings of some retrospective studies which showed lower progression of fibrosis in patients receiving CsA instead of Tac^[32,69,72]. Nevertheless, several prospective randomized controlled studies comparing CsA and Tac as primary immunosuppressive drugs in HCV LT recipients have observed no differences in liver fibrosis and graft or patient survival^[73-76]. These results must be interpreted with caution since all endpoints measurement were probably too premature (< 5 years) to reach clinical relevance, especially in patients who received antiviral treatment. The influence of mTOR inhibitors requires further attention, since their inhibitory effects on transforming growth factor β and procollagen will delay liver graft fibrosis in LT patients with recurrent hepatitis C^[77]. In summary, regarding the lack of evidence regarding the potential role of immunosuppressive regimens on HCV recurrence after LT, it is recommended that the use of high doses of steroids and/or anti-thymocyte globulins or OKT3 for the treatment of acute rejection should be avoided.

TREATMENT OF HCV RECURRENCE AFTER LT: PAST AND PRESENT

The available evidence suggests that the best way to improve long-term outcome after LT for HCV-related

liver disease is to cure HCV infection. For this purpose, three different strategies have been evaluated: (1) antiviral treatment before LT; (2) early antiviral (pre-emptive) treatment after LT; and (3) antiviral treatment at the time of biopsy-proven recurrent hepatitis C on liver graft. The majority of relevant available data concerns antiviral combination therapy using pegylated alpha-interferon (PegIFN) and ribavirin (RBV).

The limits of antiviral treatment in patients awaiting LT include reduced efficacy in cirrhotic patients, the necessity to maintain the treatment for a relatively long period of time (in case of virological response), from 6 to 12 mo, problems in achieving full doses of PegIFN and RBV due to side effects (mainly hematological), and the risk of severe, sometimes lethal, complications (mainly infectious), especially in patients with decompensated cirrhosis^[78]. The best candidates for therapy are Child-Pugh class A patients, with a relatively long expected time before LT (patients with HCC), especially in patients with a non-1 genotype, and the treatment should be maintained only in the case of early (or rapid) virological response^[79]. The first generation direct acting antivirals (DAA), telaprevir and boceprevir, have not dramatically modified this algorithm, as better efficacy is counterbalanced by the high risk of severe infectious events in compensated cirrhotic patients^[80]. Similarly, early (first month post-LT) pre-emptive antiviral treatment is usually not feasible and associated with poor hematological tolerance^[81-85]. As a result, the vast majority of patients receive antiviral therapy when recurrent HCV hepatitis on liver graft is established, usually at least one year after LT. With PegIFN and RBV, the reported rate of viral clearance ranged from 20%-48%^[86-92]. Factors associated with lower response when compared to non-LT patients include high viral load and high prevalence of genotype 1. Older donor age may also hinder the success of post-transplantation antiviral therapy^[93-95]. Moreover, dose reduction and discontinuation of treatment were common in all studies (approximately 75% and 25%, respectively), due to adverse events and possibly represented the most important obstacles to attainment of viral clearance^[96]. Interestingly, RBV dose reduction due to renal impairment probably has lower clinical impact as efficient plasma RBV concentrations can be obtained^[97]. In addition, acute rejection often occurred during treatment (especially when protocol biopsies were performed^[98]), which can induce graft dysfunction, and in some rare cases, graft failure and patient death^[91]. Finally, it has been suggested that CsA may increase the antiviral effect of interferon-based therapy, when compared to Tac, by reducing the rate of relapse after an end-of treatment viral clearance^[92,99-101]. The use of telaprevir and boceprevir after LT is a challenge, due to potential toxicity and drug-drug interactions with CNIs^[102]. The first experience from 9 patients suggested that telaprevir-based triple therapy could be highly effective in LT patients, and that drug-drug interactions between telaprevir and immunosuppressants could be handled appropriately by the close monitoring of trough levels and adequate dos-

age adjustments^[103]. Further experience has recently been reported in a US cohort of 60 patients and in a French cohort of 37 patients^[104,105]. In the French study, the end of treatment virological response rate was 72% in the boceprevir group and 40% in the telaprevir group^[105]. When used with boceprevir, CsA dose was reduced by 36% and Tac dose by 78%; when used with telaprevir, CsA dose was reduced by 48% and Tac dose was reduced by 95%. Infections occurred in 27% of patients, with a fatal outcome in one third. The most common adverse effect was anemia (92%), treated with erythropoietin and/or RBV dose reduction; 35% of the patients received red blood cell transfusions. These preliminary results suggest that first generation triple therapy is effective in LT recipients, particularly after failure of previous treatment, but is associated with poor tolerance. In the US cohort, according to an intention-to-treat analysis, 14 of 21 telaprevir-treated patients (67%) and 10 of 22 patients who received boceprevir (45%) achieved undetectable HCV RNA at week 24 without viral breakthrough at the last follow-up^[104]. These contradictory results are probably related to patient-related differences as these two cohorts report preliminary experiences in an open-label design.

The beneficial effect of antiviral treatment and viral clearance on liver fibrosis and survival is intuitive and has been suggested by a randomized controlled study^[90] and some uncontrolled studies^[106-111]. Nevertheless, a lack of impact of HCV eradication on liver fibrosis in some other studies has also been reported^[86,112-116]. This might be related to (1) an insufficient statistical power due to a small number of cases; (2) a too short period of follow-up (12-18 mo), because fibrosis improvement was probably delayed; (3) the inability of the fibrosis score to show mild improvement; and (4) interferences from other determinants of fibrosis than chronic viral hepatitis in some cases (rejection, biliary complications, ...). On the other hand, it has recently been suggested that maintenance antiviral treatment might slow fibrosis progression, even in cases of persistent HCV infection^[111,117].

The ultimate treatment of recurrent HCV-related cirrhosis after LT is retransplantation. A number of studies have reported poor overall survival after retransplantation for this specific indication^[118-123]. Although the decision to relist these patients can be difficult, a score could help to select candidates with the best potential outcome. Recently, a score which includes donor age, serum creatinine, international normalized ratio (INR) and serum albumin at the second transplantation, recipient age at the first transplantation, and the interval between first and second transplantations, has been proposed, and requires further evaluation^[124].

TREATMENT AND PREVENTION OF HCV RECURRENCE AFTER LT: FUTURE PERSPECTIVES

As LT is the ultimate step in the natural history of HCV

infection, major advances in antiviral treatment would probably dramatically change the management of LT recipients in daily practice in the next decade.

The next and promising step in antiviral therapy will be the use of second generation DAA, before and after LT, with the aim of obtaining viral eradication in more than 90% of cases, in both naïve patients and non-responders to previous therapy infected with all genotypes. Nevertheless, the second generation DAA, which have recently been submitted for registration (sofosbuvir and simeprevir) still need to be combined with PegIFN and RBV in patients infected with HCV genotype 1^[125]. IFN-free regimens will be the ultimate step for future therapies consisting of combinations of novel DAA which are under investigation, such as daclatasvir or asunaprevir^[126,127]. The good tolerance and lack of clinically apparent drug-drug interactions with CNIs make these new DAA very attractive for future use in LT recipients^[127,128]. The first case of successful IFN-free therapy (sofosbuvir and daclatasvir) in the setting of FCH has already been reported^[127].

As the use of PegIFN, RBV and new DAA may be limited by resistance, adverse effects, and high costs, the development of new alternative preventive and/or therapeutic antiviral strategies is highly relevant. For example, HCV entry into hepatocytes is required for initiation, spread, and maintenance of infection, and could be the target of novel drugs, such as neutralizing antibodies for HCV envelope glycoproteins, blocking antibodies specific for host factors, or small molecular compounds against host factors or viral proteins^[129-137]. Such strategies would be highly effective in the field of LT in order to prevent graft infection, and could be associated with other antiviral therapies.

Finally, emerging HCV treatments will impact on morbidity and mortality, and therefore, candidates for LT (presenting with HCC and/or decompensated cirrhosis) might significantly decrease during the next decades. Deuffic-Burban *et al.*^[138] recently simulated the progression of yearly-HCV-infected cohorts from the beginning of the epidemic and calculated 2013-2022 candidates for LT up to 2022 without and with therapies, in France. Overall, current treatment would enable an 88% and 42% reduction in the gap between LT and HCC and decompensated cirrhosis candidates, respectively. Interestingly, although HCV infection is treated with the same therapies in different countries, the effects of these therapies on morbidity and mortality vary significantly, suggesting that there is a need for public health policies based on population-guided therapy, in addition to common guidelines based on virological response-guided therapy^[139].

In conclusion, regarding current major progress in HCV treatment, we hope that HCV-related liver disease will become a marginal indication for LT in one or two decades. Thus, as an important proportion of HCV patients are unaware of their condition, it is necessary to define an innovative public health policy to improve HCV screening, which is the only way of allowing non-

tested HCV patients access to therapy before they develop advanced liver disease.

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