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TOPIC HIGHLIGHT

2016 Liver Transplantation: Global view

Liver transplantation for viral hepatitis in 2015

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Abstract

Liver transplantation (LT) is a life-saving treatment for patients with end-stage liver disease and for patients with liver cell cancer related to liver disease. Acute and chronic liver diseases related to hepatitis viruses are between the main indications for liver transplantation. The risk of viral reinfection after transplantation is the main limiting factor in these indications. Before the availability of antiviral prophylaxis, hepatitis B virus (HBV) recurrence was universal in patients who were HBV DNA-positive before transplantation. The natural history of recurrent HBV was accelerated by immunosuppression, and it progressed rapidly to graft failure and death. Introduction of post-transplant prophylaxis with immunoglobulin alone first, and associated to antiviral drugs later, drastically reduced HBV recurrence, resulting in excellent long-term outcomes. On the contrary, recurrence of hepatitis C is the main cause of graft loss in most transplant programs. Overall, patient and graft survival after LT for hepatitis C virus (HCV)-associated cirrhosis is inferior compared with other indications. However, successful pretransplant or post transplant antiviral therapy has been associated with increased graft and overall survival. Until recently, the combination of pegylated interferon and ribavirin was the standard of care for the treatment of patients with chronic hepatitis C. Highly active antiviral compounds have been developed over the past decade, thanks to new *in vitro* systems to study HCV entry, replication, assembly, and release.

Key words: Liver transplantation; Hepatitis B virus; Hepatitis C virus; Recurrence post-transplantation; Antiviral therapy; Prophylactic therapy

Core tip: This review explores the available data in the literature concerning the treatment of hepatitis B virus and hepatitis C virus in the setting of liver transplantation in 2015. In particular, we will discuss regarding the possibilities to treat patients before and/or after the transplantation.

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INTRODUCTION

Liver transplantation (LT) is the only effective solution for patients with end-stage liver disease. Viral hepatitis B and C are among the most common causes of cirrhosis and hepatocellular carcinoma and the most frequent indications for liver transplantation.

Introduction of post-transplant prophylaxis with immunoglobulin alone first, and associated to antiviral drugs later, drastically reduced hepatitis B virus (HBV) recurrence, resulting in excellent long-term outcomes. On the contrary, recurrence of hepatitis C is the main cause of graft loss in most transplant programs. New antiviral therapies have been recently introduced in the market, while former therapeutic approaches were far from optimal, because sustained virologic responses were only achieved in one-third of treated patients, and adverse effects were common and severe.

The following manuscript will discuss, in turn, the approach to management of HBV and hepatitis C virus (HCV) patients in the setting of liver transplantation.

HBV IN LIVER TRANSPLANTATION

Despite massive vaccination campaigns, chronic hepatitis B (CHB) remains one of the most important causes of liver disease worldwide. About 25% of all chronic HBV carriers can develop serious liver diseases, such as chronic hepatitis, cirrhosis, and primary hepatocellular carcinoma[1], and HBV infection is responsible for a mortality rate of 2.7 and 3.5 persons per 100000 inhabitants per year[2,3]. Furthermore, cirrhosis or hepatocellular carcinoma (HCC) due to HBV infection represented one of the most important indications for liver transplantation in the last ten years (14.4%), without a decreasing rate in respect of the previous decade[4]. The introduction of new antiviral therapies has dramatically changed the clinical scenario, because of the improvement obtained either in the pre-transplant setting and after LT. The management of hepatitis B surface antigen (HBsAg) positive transplant patients can be divided into the pre-transplant, prophylactic post-transplant and therapeutic post-transplant approach. Moreover, HBV prophylaxis is needed for LT recipients who receive graft from anti-hepatitis B core (HBc) positive donors.

Anti-HBV therapy in HBV decompensated cirrhosis

The aim of antiviral therapy is to reverse or delay complications of cirrhosis and the need for LT, and to decrease the risk of HBV re-infection in those who eventually undergo LT. Five oral nucleos(t)ide analogues (NAs) have been licensed for the treatment of CHB: three nucleoside [lamivudine (LAM), telbivudine (TBV), entecavir (ETV)] and two nucleotide [adefovir dipivoxil (ADF) and tenofovir disoproxil fumarate (TDF)] analogues[5]. Antiviral therapy should be started immediately in patients with HBV decompensated cirrhosis, regardless level of detectable serum HBV DNA and/or ALT activity. LAM (100 mg/die) was the first NA approved for treatment of CHB and its efficacy has been confirmed in randomized controlled trials and cohort studies showing stabilization or even improvement of liver function[6]. However, long-term LAM monotherapy is associated with progressively increasing rates of viral resistance due to YMDD mutations (15%-25% at year 1, 65%-80% at year 5)[7] and for these reason it is not currently recommended for patients with HBV decompensated cirrhosis. Furthermore, Lau *et al*[8] clearly demonstrated in 27 CHB patients that the HBeAg positive special population was at higher risk of LAM resistance (48 mo resistance 13/17 *vs* 1/10, $P < 0.0011$), due to a baseline higher HBV-DNA, ($P < 0.1$). ADF (10 mg/die) was the second NA approved for the treatment of CHB. However, due to the risk of resistance during long-term therapy in naive patients (29% at year 5), higher costs and worsening of renal function[9], it has been replaced by tenofovir, which is a more effective and cheaper NA. TBV is a potent nucleoside analogue, however, its use in CHB monotherapy is still associated with selection for YMDD mutations[10]. For these reasons, the role of telbivudine monotherapy in the treatment of HBV decompensated cirrhosis is unclear due to its unfavorable resistance profile compared to ETV and TDF; they are the newer potent NA with a minimal or even no risk of resistance[11], thus are currently considered the treatment of choice in patient with decompensated liver cirrhosis. Anyway, ETV monotherapy is not a good option for patients with lamivudine resistance, as HBV resistance develops in approximately 50% of lamivudine resistant patients after five years of ETV treatment[12]. Regarding NA side effects, lactic acidosis has been reported in small group of patients treated with ETV[13] and even thought similar rates of renal adverse events has been reported in patients treated with TDF or ETV, renal function should be carefully monitored[14].

Referral for liver transplantation

Patients with HBV infection are listed for LT for three main causes: presence of HCC within Milan criteria and well-compensated liver function; decompensated liver function, with or without development of HCC; acute liver failure or fulminant hepatitis.

HBV decompensated liver cirrhosis

Patients with HBV decompensated cirrhosis should be referred for LT[15]. While waiting for LT, the patients

should be monitored carefully at least every 3 mo for virologic response and possible virologic breakthrough in order to achieve serum HBV DNA undetectability[16]. In patients treated with lamivudine monotherapy levels of baseline HBV DNA have been independently associated with the outcome. In the same prospective multicenter study including 154 LAM-treated patients with HBV decompensated cirrhosis, most of the deaths (78%) occurred within the first 6 months suggesting that LAM may not be able to reduce the short-term mortality or the need for LT in patients with very advanced liver failure[17]. In contrast, initiation of antiviral therapy at earlier stages is associated with better chances of liver function recovery, since clinical benefit may take 3-6 mo. Whether these results are still valid with the current more potent anti-HBV agents is not clear. ETV and TDF are currently considered the treatments of choice in this group of patients, due to safety, tolerability, and efficacy; moreover, Buti in a systematic review demonstrated the cost-effectiveness of this new therapeutic alternatives[18]. In detail, ETV and TDF were considered safe, well tolerated and effective, as reported in a landmark study on 112 patients by Liaw *et al*[14]. Moreover, Chang *et al*[19] in 2010 demonstrated an histological improvement on 96% of 57 patients after 3-years therapy with ETV, showing that the reversal of cirrhosis could be an achievable goal with new NA. An immediate consequence of this histological improvement is the reduction of MELD score: Peng *et al*[20] in 2012 analyzed that the reduction of MELD score after oral therapy was about 2 points analyzing studies on oral therapies in HBV decompensated patients. Finally, a recent retrospective study on 5374 patients with CHB, demonstrated that ETV therapy was associated with a significantly lower risk of death or transplantation than LAM (HR = 0.42; 95%CI: 0.31-0.57; $P < 0.001$)[21]. Current guidelines state that in all decompensated patients lifelong treatment with ETV or TDF should be introduced, unless contraindicated[5]. The last point to highlight for patients awaiting LT is monitoring the effectiveness in the context of recurrence of HBV infection after LT. The main goal remains to reduce viral load under 100000 copies/mL before surgery, as demonstrated by Marzano *et al*[22] in a landmark study in 2005, in which the recurrence rate amongst recipients with pre-transplant viral load higher than the above mentioned values was extremely higher (50% and 0%, respectively). For these reasons, especially in those patients with long term therapy with LAM and listed for LT, the viral load should be carefully monitored.

Hepatocellular carcinoma

The incidence of HCC in CHB is estimated to be different between treated and untreated patients, ranging from 2.8% to 6.4%, respectively[23]. Two main factors contribute to development of HCC in CHB, which is 100-fold higher than in non infected: first, the viral replication, whose load was strictly connected with the risk of HCC - independently of HBeAg antigen, presence of liver cirrhosis and serum ALT level - in a large coohort of Taiwanese patients[24]; second, the cytokine release mediated by the immune response, which ensures acceleration of hepatocyte cell cycles and genetic alterations[25]. Available treatments for HBV infection were demonstrated to be effective in reducing oncogenic damage due to HBV replication and integration. In a recent paper, Vlachogiannikos reviewed the most important metanalysis which evaluated the role of antiviral therapy among HCC development[26]. Interestingly, six metanalysis[23,27-31] agreed that the use of NAs or IFN-based regimes were effective in reducing the risk of HCC, but relevant issues about the benefit on different ethnic backgrounds and presence of absence of cirrhosis were not completely cleared; the authors stated that the higher risk coohort - cirrhosis - could reach the higher benefit from treatment. Nervertheless, the reduced risk of decompensation of liver disease could not be counterbalanced by a similar reduction of the risk of HCC development; thus all the patients, treated and untreated, have to perform six-months active surveillance.

Acute-fulminant hepatitis B

In patients with acute liver failure due to acute or acute-on-chronic hepatitis B the treatment strategy remains not well defined. In case of fulminant hepatitis, specific supportive care is still considered the treatment of choice, even though efficacy of NA, and in particular LAM, has been already proved for prevention of post-transplant recurrence[32]. In the latter setting, acute flare in chronic HBV infection is mainly noted amongst immunosuppressed patients or in patients taking immunomodulant drugs, as anti-TNF alfa or monoclonal antibodies; in those who require LT, introduction of lamivudine in naive patients, or treatment modification with another NA if mutations have been identified, could be a rational approach[33]. On the other side, trials assessing the efficacy played by newer antivirals seem to be very difficult to perform and only few cases are currently reported in literature[34,35]. In a prospective study, Chen *et al*[36] demonstrated that treated patients with acute-on-chronic liver failure experienced better long-term survival than untreated ones (64.7% *vs* 36.2%, $P = 0.006$), even though in the first three months there were no difference between the cohorts.

Prevention of recurrence after LT

The introduction of newer therapies has reduced the recurrence of HBV infection after LT, which was considered a major problem in the past, because of severe reduction of graft and patient survival. These encouraging data were also confirmed by a recent study published on the ELTR registry, which stated that disease recurrence is going to be no

longer a significant cause of death/graft loss. HBV decompensated patients had a significantly better patient and graft survival at 1, 3, 5, and 10 years (83%, 78%, 75%, and 68% and 80%, 74%, 71%, and 64% respectively), compared to HBV/HCC patients (84%, 73%, 68%, 61%, and 81%, 70%, 65%, and 58%; P = 0.001 and P = 0.026 respectively)[37]. If untreated, recurrence after LT is universal and its association with rapidly progressive hepatitis that jeopardizes long-term patient and allograft survival. In fact, recurrence is initially characterized by serum HBsAg and HBV-DNA reappearance, and followed by biochemical, histological and clinical evidence of recurrent liver disease.

A multicentric study published in 1993 by Samuel investigated risk factors for recurrence among 201 LT recipients with HBV-related cirrhosis from 17 Centers in Europe. Long-term Immunoglobulin administration (P < 0.01), HBV-DNA negativization before LT (P < 0.05), and the abscence of HBeAg before LT (P < 0.001) were evaluated as major factors against recurrence at multivariate analysis[38]. More rencently, Xu *et al*[39] identified pre-transplant HBV DNA level, presence of HCC, antiviral treatment and post transplant viral mutation as the major risk factors associated with recurrence after LT. However, the first point is matter of debate. Analyzing data from ELTR registry, the proportion of recipients with HBV-DNA negative at LT progressively decreased (from 81.2% to 51% and from 82% to 57.4% in HCC patients, respectively; each P < 0.001), without statistical difference in terms of patient and graft survival. Initially, prophylaxis against HBV re-infection was successfully performed with anti-HBV immunoglobulins (HBIg), as showed by Samuel *et al*[38] in 1993, and then with the use of LAM in a pilot study provided in 1996 by Grellier[40]. Then, other NAs have been tested after LT, with good results. At present, LAM and/or ADV in combination with HBIg are still considered the treatment of choice for prevention of HBV re-activation, since they reduced the risk of graft infections to less than 10%[5].

Costs, patient's compliance and viral mutation represent the most intriguing factors which lead clinicians to find the optimal type of treatment. A meta-analysis published by Katz *et al*[41] in 2010 analyzed ten studies which compared the combination therapy (NA + HBIg) and mono-therapy with LAM or ADV: treatment with HBIg and LAM was demonstrated to be better than HBIg alone in reducing HBV recurrence (RR = 0.28; 95%CI: 0.12-0.66, 10 studies, I^2 = 60.7%) and HBV DNA levels (RR = 0.21; 95%CI: 0.04-0.98, I^2 = 0%), all-cause mortality (RR = 0.44; 95%CI: 0.25-0.77, I^2 = 6.4). More recently, Wang *et al*[42] performed a systematic review which demonstrated that, evaluating a total of 1484 patients of seventeen studies, treatment with HBIg reduced HBV recurrence (P < 0.001; RR = 0.16; 95%CI: 0.12-0.20) and viral mutations (P < 0.001; RR = 3.13; 95%CI: 1.86-5.26), and improved patient's early survival (1-year survival P = 0.03; RR = 0.08; 95%CI: 0.01-0.15; 3-year survival P = 0.005; RR = 0.17; 95%CI: 0.05-0.28). Interestingly, the Authors showed that the efficacy of HBIg administration was demonstrated only in the subgroup of patients who were HBV-DNA positive before LT (P < 0.001; RD = 0.42; 95%CI: 0.32-0.52). If the results were confirmed, the use of HBIg should be limited only in high selected or limited fields, even though the difference in survival has not been confirmed when evaluating long term follow-up. Other Authors recently proposed an "on-demand therapy", personalized on the individual risk: for instance, Cholongitas demonstrated in a prospective study that 28 patients with HBV DNA levels undetectable before LT were safely treated against HBV infection with 6 mo therapy with HBIg and then with monotherapy with TDF or ETV[43]. Also Hu in a recent study demonstrated that on demand dose HBIg (adjusted for anti-HBs titer) plus ETV were efficient in preventing HBV recurrence, which developed only in 2/145 (1.37%) patients[44]. The choice between TDF or ETV should depend only on the presence of LAM resistance before transplant: in this case, TDF should be preferred.

Two more factors should be considered when choosing the best therapy for HBV transplanted patients: costs and adherence; in fact, in a retrospective study, Chang *et al*[45] demonstrated that non-compliance to HBIg was equal to 14% in a small cohorts of LT patients, and that also amongst these patients anti-HBs titers were satisfactorily achieved. For these reasons, many studies assessing the efficacy of monotherapy have been published[46], but more efforts to investigate stronger risk factors of recurrence and to individualize treatment should be performed.

Lastly, vaccination after LT has been investigated and used as a prophylactic tool against HBV recurrence. It was currently used either in pre and in the post transplant setting before introduction of HBIg[47]. In a pilot study performed in 2000, Sanchez Fueyo *et al*[48] demonstrated that HBV vaccination after 1-year therapy with HBIg was useful and cost-effective in a small cohort of 16 selected patients, who were transplanted for cirrhosis or fulminant HBV hepatitis. However, at present long term follow-up data evaluating this strategy amongst large cohorts of patients are still missing.

Treatment of recurrence after LT

In those patients who experience post-LT HBV reactivation (for non compliance, viral mutations), viral recurrence determines the rapid development of severe liver dysfunction, comprising graft loss and death. Fortunately, huge cases of fibrosing cholestatic hepatitis due to HBV after LT are rare[49]. The role of TDF or ETV for the treatment of recurrence seems to be optimal, but two main aspects have to be considered: first, HBV mutation: patients who experience post-LT HBV reactivation during LAM therapy should be treated with TDF instead of ETV; second: renal function, which is a major problem in all LT patients

due to immunosuppression, aging, pre-transplant hepatorenal syndrome. TBV was demonstrated to be effective in improving renal function: in a recent prospective study by Cholangitas *et al*[50], 17 patients who received TBV after 12 mo of standard therapy presented a significant improvement of renal function if compared to controls. Another retrospective study highlighted a significant decrease of eGFR in CHB patients after 17 mo treatment of TDF ($P < 0.001$), with a recurrence rate of 0%; TDF was considered a risk factor at multivariate analysis together with diuretic treatment and chronic renal failure[51]. This study showed data similar to what reported in TDF-treated HIV population, who have experienced a time-dependent impairment of renal function ($P < 0.007$)[52], even though contrasting data and confounding factors, as multiple drugs co-administration, have to be taken into account. In this setting, some new trials focused on LT population and comparing effectiveness about HBV recurrence and renal function between ETV and TDF, should be encouraged.

Prophylaxis of patients who receive livers from anti-HBc positive donors

Anti-HBc grafts represent a major source of organs worldwide, having a prevalence ranging from 10% to 50% in endemic HBV areas[53]. Use of anti-HBc graft is considered safe, since it does not affect graft or patient survival[54,55]. However, patients who receive these organs have an increased risk of *de novo* HBV infection; however, this is not the only way to develop a *de novo* HBV infection after LT: for instance, a recent study published by Xie *et al*[56] highlighted that occult HBV infection had a prevalence of > 40% in alcohol related liver transplanted recipients.

There is some debate on the optimal strategy after liver transplantation when anti-HBc organs are allocated. The current guidelines recommend indefinite prophylaxis with LAM for HBsAg negative recipients[5]. This recommendation was retrieved by a landmark study made by Cholongitas *et al*[57], who reviewed the entire literature of the field. The Authors confirmed the need to allocate the anti-HBc organs preferentially to HBSAg positive or anti-HBc positive donors, but also stated that the risk of HBV infection after LT can be higher than 40% without prophylaxis. The study provided also interesting data regarding treatment: if vaccination alone seemed to be ineffective (100% infection rate), combination therapy with LAM + HBIg seemed inadequate, due to costs, compliance and good results provided by LAM monotherapy (2/75, 2.6% of infection rate). Interestingly, the Authors proposed an algorithm for therapy which takes into account the serological status of the recipient, assessing the need to combined therapy with HBIg and LAM only in antiHBc donor/HBSAg Recipient matching. Similarly, Brock *et al*[58], analyzing 958 patient from UNOS database, demonstrated that use of HBIg alone could confer less risk of mortality if compared to LAM therapy; notwithstanding, costs and absence of significance about HBV-associated graft failure seemed to discourage this therapeutic alternative.

HDV IN LIVER TRANSPLANTATION

HDV coinfection has a variable prevalence among CHB patients. In a recent Chinese study, 426 out of 6604 patients were positive for HDV IgM[59]. The coinfection is a known risk factor for end-stage liver disease, thus the main goal in such patients is represented by suppression of HDV replication. However, treatment options are very limited, because NAs used for the treatment of HBV are ineffective and decompensated cirrhosis could not benefit from IFN based regimens. Thus, LT often remains the main choice in this setting[60]. Coinfection has remained a stable indication for LT in the last two decades, having a prevalence of 2%[4]. Furthermore, analyzing data from ELTR Registry, HDV co-infection was associated with better short and long term patients survival (1-5-10 years survival: 92%, 89%, 86%, and 83%,75%, 60%, each $P < 0.001$); These data were confirmed also for grafts (1-5-10 years graft survival: 81%, 85%, 80%; 80%, 71%,64%; each $P < 0.001$). The better survival amongst coinfected patients is presumably due to inhibition of HBV replicative cycle performed by HDV[37]. Conversely, no difference in terms of patients and graft survival was seen among patients with HCC.

HCV IN LIVER TRANSPLANTATION

Nowadays, cirrhosis secondary to chronic hepatitis C, with or without hepatocellular carcinoma, is the leading indication for LT worldwide. Recurrent hepatitis C infection of the allograft is universal if HCV is detectable at the moment of transplant surgery. Approximately one third of the patients will progress to liver cirrhosis in the graft within only 5 years after transplantation and, subsequently, graft and patient survival are significantly worse in patients undergoing LT for HCV-related cirrhosis than in those transplanted for other causes[61,62]. Two strategies, including pre-transplant treatment of HCV infection in cirrhotic patients and post transplant treatment of liver graft infection, can be adopted for achieving sustained virological response (SVR), virus eradication and finally improving clinical outcomes of HCV-infected recipients.

Antiviral treatment in waiting list for liver transplantation

The aim of antiviral treatment while on the waiting list is to achieve either an SVR or an on-treatment undetectable HCV-RNA at time of transplantation to avoid HCV infection of the graft. Few studies have shown that peg-IFN + ribavirin (RBV) treatment can prevent graft infection in patients who achieve viral clearance (undetectable HCV-RNA) during therapy before LT[63,64]. As expected, response rates are mainly

influenced by genotype (better results in non-G1 patients) and, in those patients who achieve viral clearance, it appears that duration of treatment may be relevant (> 16 wk of therapy is associated with prevention of graft infection after LT)[63]. Overall, efficacy of this therapy was suboptimal (30% of SVR rates).

The first direct acting antivirals (DAAs) approved in 2011, the protease inhibitors telaprevir and boceprevir, increased the efficacy of Peg-IFN-RBV, both in cirrhotic patients treated in waiting list (WL) (pTVR up to 67%), as well as in transplant recipients (SVR12 up to 62%). In HCV-infected patients awaiting LT limited data were reported. Verna *et al*[65] showed results of triple therapy in a small series of HCV-infected G1 cirrhotics (*n* = 20) in the waiting list for LT; patients underwent therapy for a median time of 14 wk. Most of them were previous non responders, 20% had ascites and 45% had a hepatocellular carcinoma at the time of treatment initiation. Post-transplant SVR12 was 67% (8 out of 12 transplanted patients). From safety point of view, serious adverse events occurred in nine patients (31%), including one death (3%) and 8 hospitalizations (28%). Despite these results, the proportion of patients on the waiting list that may benefit from triple therapy with telaprevir (TPV) or boceprevir (BOC) is small, for several reasons: in decompensated patients IFN-based therapies are contraindicated, efficacy rates are very low in cirrhotic patients who are previous null-responders to PR (a common situation in patients awaiting LT) and PI-based regimens in real-life compensated cirrhotic patients are associated with serious adverse events and even death[66]. More importantly, with the recent approval of IFN-free regimens, the use of boceprevir and telaprevir are no longer recommended[67].

The use of DAAs has been a step forward in the treatment of chronic hepatitis C. The combination of several of these drugs in the absence of interferon (IFN-free regimens), has shown high SVR rates and a significantly better tolerance when compared with IFN-containing regimens. The results from the first clinical trial including patients in waiting list for LT treated with an IFN-free regimen, was the proof of concept that eradicating HCV before LT is possible in a large proportion of patients[68]. In this phase 2, open-label study, 61 patients with HCV of any genotype and cirrhosis (Child-Turcotte-Pugh score, ≤ 7) who were on waiting list for LT for HCC, received up to 48 wk of Sofosbuvir (SOF) and RBV before LT. Thus, 70% of transplanted patients treated with SOF and RBV during the WL, who had HCV-RNA levels < 25 IU/L prior to transplant, get SVR 12 wk after LT. All patients included in this study had compensated cirrhosis and hepatocellular carcinoma, as indication for transplantation. Importantly, the time of RNA target not detectability before LT (> 30 d) has emerged as the only crucial factor for preventing HCV recurrence.

Data from clinical trials and real-life cohorts including compensated or decompensated cirrhotic patients not in waiting list are very encouraging, as high safety and efficacy can be obtained with several regimens. The safety and efficacy of the combination Sofosbuvir and Simeprevir (SIM) with or without RBV was assessed in COSMOS trial[69] and in large real-life cohorts. In the primer, the combination was assessed for 12 or 24 wk in 167 G1 patients including 80 previous null responders without significant fibrosis (F0-2) and 87 treatment naïve or prior null responders with significant fibrosis (F3-4). The global SVR rate was 92% and remained high (93%) when decompensated cirrhotic patients (*n* = 41) were considered separately. In the TRIO network real-life cohort[70], the subgroup of patients with cirrhosis (*n* = 125) achieved SVR rates of 75%, significantly lower than non cirrhotic patients.

Another high efficacious IFN-free regimen is the fixed-dose combination of sofosbuvir and ledipasvir, that was explored in three large clinical trials of G1 patients (ION-1, ION-2 and ION-3). The ION-1 and ION-2[71,72] evaluated this combination with or without RBV in G1 treatment-naïve and experienced patients, respectively. In both studies SVR rate was excellent, irrespectively of the presence of cirrhosis. Moreover, a pooled integrated analysis including of all the G1 cirrhotic patients (*n* = 513) treated with Sofosbuvir plus ledipasvir (LDV) along the phase Ⅱ and Ⅲ trials was conducted[73]. In naïve cirrhotic patients (*n* = 161), neither treatment duration nor RBV use showed to have a significant impact on SVR12 (96%-100%). Regarding treatment-experienced cirrhotic patients (*n* = 352), 90% of patients achieved SVR12 after 12 wk without RBV, 96% after 12 wk with RBV, 98% after 24 wk without RBV, and 100% after 24 wk with RBV, suggesting a beneficial role for RBV or extension of treatment duration in this group.

A phase Ⅱ, randomized, prospective, multicenter trial, using fixed-dose combination of SOF + LDV plus RBV for 12 or 24 wk in treatment-naive and treatment-experienced patients with GT1 or four and decompensated liver disease who were awaiting LT, was recently reported[74]. The exclusion criteria were as follows: Child-Pugh scores from 13 to 15; history of major organ transplant, including liver; presence of HCC; total bilirubin ≥ 10 mg/dL; hemoglobin ≤ 10 g/dL; creatine clearance ≤ 40 mL/min; and platelets ≤ 30000. Fifty-three patients were treated for 12 wk, including 30 CTP B and 23 CTP C patients, while 55 patients were treated for 24 wk, including 29 CTP B and 26 CTP C patients. Patients were predominantly male (67%), Caucasian (93%), and had been previously treated for HCV (65%). Mean baseline HCV-RNA was 5.8 log10 IU/mL range 3.2-7.1 log10 IU/mL. Twenty-eight patients (26%) had a MELD score > 15. At baseline, 96% of CPT class C patients had ascites and 88%-91% encephalopathy, in the 12- and 24-wk arms, respectively. Overall, the SVR12 was 87% and 89% for the patients treated for 12 and 24 wk, respectively. No significant difference was observed

for the CTP B patients (87% *vs* 89%) or for the CTP C patients (86% *vs* 90%). Biochemical and clinical improvement of the patients with successful HCV therapy (documented by an improvement in MELD score as well as an increase in serum albumin) was reported. However, clinical condition of some patients stabilized, while it worsened in other patients, meaning that cirrhosis was already too advanced to improve despite obatining SVR.

Administration of LDV/SOF + RBV in patients with decompensated cirrhosis has been evaluated in US (SOLAR 1) and Europe, Canada, Australia and New Zealand (SOLAR 2), the largest study of such patients to be evaluated to date[75]. Amongst patient with Child B liver cirrhosis SVR4 was observed in 24/28 patients (86%) and 11/11 patients (100%) in 12 and 24 wk arms, respectively. 14/16 patients (88%) and 3/6 patients (50%) Child C patients achieved SVR4 in 12 and 24 arms, respectively. In the same cohort the drug safety was evaluated. Among 215 patients with liver cirrhosis (117 Child B and 98 Child C) only 22 (Child B) and 35 (Child C) experienced serious adverse events, mainly anemia due to RBV.

Safety and efficacy of 12-wk combination regimen with daclatasvir and sofosbuvir in patients with advanced liver disease were recently presented[76]. If the patients were transplanted during treatment they could receive 12 wk of extended treatment immediately posttransplant, regardless of treatment duration before transplant. Sixty patients with liver cirrhosis were included of whom 40% were treatment-naive and 75% G1. The prevalence amongst Child-Pugh classes was 20% A, 53% B, and 27% C. MELD score ranged from 8 to 27. Overall, 83% of patients in the cirrhosis cohort achieved SVR12, with higher SVR12 rates in patients with Child-Pugh class A or B disease than in those with class C. SVR12 rates were comparable regardless of prior treatment experience or baseline demographic characteristics. Four cirrhotic patients received a liver transplant during treatment; 3 of 4 extended treatment posttransplant and all 4 achieved SVR12. The most common AEs (any grade) were headache, fatigue, anemia, diarrhea, and nausea, without serious ones.

The clinical and biochemical improvements experienced by decompensated cirrhotics who achieved SVR take on great relevance in LT setting, as some patients may be delisted and improve their quality of life. So far this event has been reported only as anecdotal case[77], concerning a 67-year old woman who was listed for LT for decompensated cirrhosis (CTP 12, MELD 16), refractory ascites, and chronic encephalopathy. After successful treatment with Sofosbuvir and Ribavirin and SVR12, liver function and clinical status improvement allowed for her to be removed from the liver transplant waiting list. At the present time, criteria for de-listing patients have not been identified yet, and a successful treatment before LT is not always correlated to a clinical and biological improvement. Patients with advanced liver disease and high MELD scores will probably not benefit from a viral clearance. However, it is true that in the next years the availability of interferon-free highly effective therapies of HCV infection promise to bring about a 'revolution' in the field of end-stage liver disease, as did NAs in patients with HBV infection, representing a life-saving therapy that could also reduce the burden of patients needing liver transplantation. Efficacy results from clinical trials cannot be totally translated to waiting list scenario, being the waiting time unpredictable and the treatment duration as well. More results from clinical trials will be needed for allowing a better selection of patients who have higher chance to eradicate HCV before receiving a new liver. Anywise, for those patients in whom treatment in waiting list will not be efficacious a good option is the post-transplant antiviral treatment.

Antiviral treatment after liver transplantation

One of the main characteristics of hepatitis C recurrence after LT is the accelerated course of the disease when compared to immunocompetent patients[78-80]. This accelerated fibrosis rate impacts both the allograft and recipient survival, which is significantly reduced when compared with non-HCV liver recipients[81]. It is well established that the presence of significant fibrosis in the graft (F $\geqslant$ 2, METAVIR)[82,83] or significant portal hypertension (HVPG $\geqslant$ 6)[84] one year after LT identifies patients with aggressive hepatitis C recurrence. The most common approach to treat hepatitis C after LT has been to start Peg-IFN + RBV once histological damage is confirmed in the graft. Overall SVR rates with combined therapy were low, ranging between 30% to 40% across different series, which have been combined thereafter in three systematic reviews[85-87]. These poor virological results were mainly explained by high rates of treatment discontinuation, dose reductions and poor tolerance or adverse events. Despite these results, the positive impact of SVR on survival was well demonstrated. Patients achieving SVR after LT have better survival curves compared to non-responders, as shown by Berenguer *et al*[85]. Carrion *et al*[88] also demonstrated the positive impact of SVR on HVPG when performed before and after antiviral treatment: portal pressure decreased or stabilized in responders compared to non responders, in whom HVPG increased rapidly overtime.

Regarding triple therapy with PIs in the post-LT setting, several studies have evaluated the safety and efficacy of such regimens in liver transplant recipients[89,90]. Most of the patients had an advanced fibrosis stage (METAVIR F $\geqslant$ 2) or cholestatic HCV. SVR12 rates ranged between 48% and 62%[91,92]. Even though the addition of PI to PEG/RBV increased SVR rates, the major drawbacks of triple therapy in LT recipients were the high rate of severe adverse events leading to treatment discontinuation and drug-drug interactions especially with immunosuppressive drugs.

In the last year, multicentric clinical trials, com-

passionate use programs and real-life cohorts combining oral DAAs for treating HCV-infected liver transplant recipients have reported very good SVR12 rates, ranging from 70% to 96%. The first multicenter, open-label pilot study including transplant recipients assessed the safety and efficacy of the combination of sofosbuvir and ribavirin for 24 wk[93]. The cohort included 40 patients, 40% of them with cirrhosis. SVR12 rate was 70%. The excellent efficacy and safety profile of this regimen was confirmed from sofosbuvir compassionate use program results. Fifty-nine percent of patients, who received up to 48 wk of sofosbuvir and ribavirin, with or without pegylated Peg-IFN, achieved SVR12. Importantly, those with a cholestatic hepatitis C (including fibrosing cholestatic hepatitis) showed higher viral responses (SVR 73%) compared to patients with cirrhosis (SVR 43%)[89].

The combination of LDV-SOF-RBV has demonstrated high rates of SVR in a part of the SOLAR-I study. Recipients infected with HCV genotype 1 or 4 received this combination for 12 or 24 wk[94]. In patients with Child-Pugh class B or C, there was a reduction in SVR rates as compared to patients with mild disease. Specifically, among individuals with Child-Pugh C class, the SVR rates were 60% and 67%, respectively. Of note, the number of patients included was very small (8 total across the 2 arms).

The combination of SOF and SIM was assessed in 68 liver transplant recipients included in the real-life HCV TARGET study[90]. The overall SVR4 rate was 90%, that remained higher in cirrhotic patients (86%). The efficacy and safety of this combination was investigated in another real-life study[95] that showed excellent results: 91% of liver transplant recipients achieved an SVR12 after receiving 12 wk with or without RBV. In both studies slower SVR12 were showed in subtype 1a than subtype 1b patients (83% *vs* 95%, respectively; and 88% *vs* 96% respectively. Most importantly in the later study all failures in F3-F4 patients were in subtype 1a patients.

The open-label phase Ⅱ CORAL-I study[96] assessed treatment with 24 wk of ombitasvir/paritaprevir/ritonavir with dasabuvir and ribavirin in a cohort of 34 orthotopic liver transplantation recipients with a METAVIR score of 2 or less and recurrent genotype 1 HCV infection. The SVR12 rate was excellent (97%).

Even though small data are available for daclatasvir (DAC) combined with SOF or SIM, mostly from real-life cohort and compassionate use programs, high rates of SVR were observed in patients with post transplant HCV recurrence treated with these combinations[97-99].

From a safety point of view, very few severe adverse events were reported so far throughout studies. Most deaths occurred in cirrhotic patients were drug-unrelated. Regarding drug interactions, neither SOF nor LDV showed any important drug-drug interactions with the calcineurin inhibitors. Conversely, because of significantly increased plasma concentrations of SIM, the concomitant use of SIM and cyclosporine is not recommended in liver transplant recipients. Using the combination of ritonavir-boosted paritaprevir, ombitasvir, plus dasabuvir with ribavirin adjusted doses of tacrolimus and cyclosporine are needed.

CONCLUSION

Viral hepatitis, such as HBV and HCV, is still the largest indication for liver transplantation.

The antiviral therapy with NA - especially with TDF or ETV - represent the most efficacious therapy for HBV related cirrhotics awaiting liver transplantation, in whom the viral load should be carefully evaluated. Continuation therapy after LT, adding HBIg, minimize the risk of HBV recurrence. Liver grafts from anti-HBc positive donors can be safely used, also in HBsAg negative recipients, preferentially anti-HBc/anti-hepatitis B surface antibody positive ones.

To prevent HCV recurrence after LT, the ideal strategy might be to achieve HCV eradication before transplant, having more than 30 d of HCV-RNA TDN. However, data on patients who are in the waiting list are still scarce, and in special population (*i.e.,* seriously ill recipients, HCC), the choice to start treatment of HCV before the transplant have to be carefully evaluated; furthermore, several DAAs regimens are now available for successfully treat patients who experience HCV recurrence after LT. As we become more experienced in treating these patients, we will gain more information about which patients would benefit from treatment before transplantation and for which patients it would be best to treat after transplantation.

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