

## Management of patients with hepatitis B and C before and after liver and kidney transplantation

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Received: December 3, 2013 Revised: March 10, 2014

Accepted: April 16, 2014

Published online: May 27, 2014

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**Key words:** Liver transplantation; Kidney transplantation; Hepatitis B; Hepatitis C; Recurrence

**Core tip:** While nucleos(t)ide analogs (NAs) offer a benign course in patients with hepatitis B virus before and after liver and renal transplantation, there is still scope for improvement. The administration of high genetic barrier NAs such as entecavir or tenofovir pre-transplant and the careful patient selection for hepatitis virus immunoglobulin-free regimens post-transplant contribute to improved medical care and facilitate its provision from a practical standpoint. Concordantly, attention has turned to new treatment strategies regarding hepatitis C virus recurrence after liver and renal transplantation. The addition of oral direct acting antivirals to the existing treatment marks a promising strategy for prognosis amelioration of these patients.

### Abstract

New nucleos(t)ide analogues (NAs) with high genetic barrier to hepatitis B virus (HBV) resistance (such as entecavir, tenofovir) have improved the prognosis of patients with HBV decompensated cirrhosis and have prevented HBV recurrence after liver transplantation (LT). NAs are considered the most proper approach for HBV infection in patients under renal replacement therapy but their doses should be adjusted according to the patient's creatinine clearance. In addition, physicians should be aware of the potential nephrotoxicity. However, patients with chronic hepatitis C and decompensated cirrhosis can receive only one therapeutic option before LT, as well as for Hepatitis C virus (HCV) recurrence after LT, which is the combination of subcutaneous Peg-IFN and ribavirin. Generally, therapy for HCV after renal transplantation should be avoided. Although the optimal antiviral therapy for HCV infection has not been established, attention has turned to a new, oral direct acting antiviral treatment which marks a promising strategy in prognosis and in amelioration of these diseases.

Pipili C, Cholongitas E. Management of patients with hepatitis B and C before and after liver and kidney transplantation. *World J Hepatol* 2014; 6(5): 315-325 Available from: URL: <http://www.wjgnet.com/1948-5182/full/v6/i5/315.htm> DOI: <http://dx.doi.org/10.4254/wjh.v6.i5.315>

### INTRODUCTION

The major breakthrough in the field of transplantation for patients with hepatitis B virus (HBV) and hepatitis C virus (HCV) is the application of nucleos(t)ide analogs (NAs) and direct acting antivirals (DAAs). NAs form the mainstay in the treatment of patients with HBV in the non-transplant setting as well as before and after liver and kidney transplantation. The preliminary data regarding the DAAs application favored its use in treatment of HCV recurrence after liver transplantation (LT) and in HCV renal transplant candidates.

**Table 1 Recommendations for the management of hepatitis B and C infection before and after liver or renal transplantation**

	Chronic hepatitis B		Chronic hepatitis C	
	Liver transplantation	Kidney transplantation	Liver transplantation	Kidney transplantation
Pre transplant		NAs <sup>1</sup>	Peg IFN ± RBV ± DAAs <sup>3</sup> (depending on genotype and type of DAA)	PegIFN plus very low dose RBV (plus DAAs) <sup>4</sup>
Post transplant	Prophylaxis and treatment Short term HBIG plus NA		No prophylaxis <sup>2</sup> Peg IFN ± RBV ± DAAs <sup>3</sup> (depending on genotype and type of DAA)	RBV+ sofosbuvir (?)

<sup>1</sup>Entecavir or tenofovir are the advisable NAs in adjusted doses regarding creatinine clearance; <sup>2</sup>Therapy is indicated in fulminant cholestatic hepatitis and de novo glomerulonephritis; <sup>3</sup>Records for boceprevir, telaprevir and sofosbuvir. Triple combination is preferable in cases of cirrhosis (METAVIR fibrosis stages 3 and 4), cholestatic hepatitis, previous virological failure and in the presence of predictors of poor response; <sup>4</sup>There are only cases for the use of DAAs in renal transplant candidates. HBV: Hepatitis B virus; HCV: Hepatitis C virus; NA: Nucleos(t)ide analog; HBIG: Hepatitis virus immunoglobulin; DAAs: Direct oral acting antivirals; Peg IFN: Peg interferon; RBV: Ribavirin.

In general, the induction of immunosuppressive therapy carries the risk of HBV reactivation, leading to liver graft loss and fatal complications<sup>[1,2]</sup>. NAs have dramatically improved the clinical course of patients with HBV decompensated cirrhosis, reducing the need for LT, and have further improved the prognosis of HBV transplant patients<sup>[3,4]</sup>. At present, due to high rates of resistance<sup>[3,4]</sup>, lamivudine is preferable only when short term immunosuppression is scheduled. Entecavir and tenofovir are the first choice NAs because they have very high efficacy and low resistant rates<sup>[5,6]</sup>. NAs administration implies detailed renal function monitoring. Telbivudine may improve renal function but it has an unfavorable resistance profile<sup>[7]</sup>.

In regards to transplantation in patients with chronic hepatitis C (CHC), improvements in the understanding of the viral cycle have led to development of the first generation DAAs (telaprevir and boceprevir) which belong to HCV NS3/4 protease inhibitors<sup>[8,9]</sup>. Their addition to the standard of treatment [pegylated interferon (Peg-IFN) and ribavirin (RBV)] has improved the response rates in a small number of liver transplant recipients and in a few cases of renal transplant candidates. When DAAs are used, calcineurin inhibitors doses should be adjusted<sup>[10]</sup> and the hemoglobin levels should be regularly monitored. The present review focuses on the current treatment of patients with HBV and HCV before and after liver and kidney transplantation.

## MANAGEMENT OF PATIENTS WITH HEPATITIS B AND C BEFORE AND AFTER LT

The management of patients with hepatitis B and C listed for LT contains a three step approach. Targeted therapy should start before transplantation and continue after transplantation, becoming more intensive immediately post-transplant when the immunosuppression is higher. Therapy escalation in an early post-transplant stage is imperative mainly for avoidance of HBV recurrence, while routine prophylactic therapy for HCV recurrence is not recommended<sup>[11,12]</sup> (Table 1).

### HBV positive and HCV positive liver transplant candidates

Before transplantation, treatment aims to eliminate viral load, to keep it undetectable at the time of transplantation in order to lower the risk of HBV recurrence and improve the outcome<sup>[13,14]</sup>. HBV DNA clearance pre-transplant has reduced the rate of HBV recurrence in patients with HBV infection<sup>[15]</sup>. Similarly, HCV RNA eradication pre-transplant resulted in amelioration of fibrosis and long term survival in patients with HCV infection<sup>[13,15-18]</sup>. The suppression of HCV viremia in LT candidates and the undetectable HBV DNA at the time of LT are the most important goals for each particular infection.

The current management of patients with cirrhosis and CHB before LT is based on NAs<sup>[3,15]</sup> and modification of lifestyle, comorbidities and drug interactions<sup>[19]</sup>. Generally, the institution of NAs has ameliorated the transplant prognostic scores to such a high level that many LT candidates with CHB have delisted<sup>[20-22]</sup>, presenting with great clinical improvement and better survival<sup>[23-25]</sup>. NA administration as monotherapy or in combination are the current guidelines for LT candidates with HBV decompensated cirrhosis<sup>[26-28]</sup>. The high genetic barrier antivirals entecavir and tenofovir are recommended as monotherapy. Entecavir has reduced the HBV DNA in patients with decompensated cirrhosis, has improved their underlying liver function up to 70% and has presented with very low resistant rates<sup>[22,29-31]</sup>. Tenofovir has also been an effective initiation therapy, accounting for high fibrosis resolution over five years administration<sup>[32-34]</sup> with almost negligible resistance. When administered in patients with decompensated cirrhosis, it led to virological, biochemical and clinical improvement with very good tolerance<sup>[35]</sup>.

Nevertheless, entecavir should not be applied in patients with proven lamivudine-resistance because there are high chances of resistance and treatment failure<sup>[30]</sup>, while tenofovir should be used with caution because of potential tubular injury and osteomalacia<sup>[34]</sup>. However, recent trials have doubted tenofovir nephrotoxicity after ten years of therapy in large groups of HIV infected patients<sup>[36,37]</sup> or even the nucleotide nephrotoxicity in LT recipients<sup>[38]</sup>.

Furthermore, it has been hypothesized that an antiviral combination might achieve higher virological response rates and lower resistance rates compared to monotherapy. However, emtricitabine plus tenofovir (200 mg and 300 mg daily respectively) have not been found to have superior antiviral potency compared to entecavir and tenofovir monotherapy<sup>[35]</sup>. In addition, the higher cost of antiviral combination compared to monotherapies limits its use in clinical practice. In conclusion, all patients on NA therapy should be monitored every three months for virological response and possible virological breakthrough with serum HBV-DNA testing<sup>[39,40]</sup>.

Contrary to LT candidates with CHB, patients with CHC and decompensated cirrhosis have only one therapeutic option before LT. This is the combination of subcutaneous Peg-IFN and RBV, leading to reduced cirrhosis-related complications and improving histological changes<sup>[41]</sup>, but in an unsatisfactory percentage of patients (5%-33% in genotype 1 and 14%-100% in genotypes 2/3)<sup>[12,42-45]</sup>. IFN-based regimens have also been related to poor tolerability and many side effects<sup>[42,44]</sup>, such as anemia, infections and neuropsychiatric disorders<sup>[46]</sup>, which require either erythropoietin and granulocyte colony-stimulating factors or antibiotics to sustain drug regimen optimal doses<sup>[47]</sup>. The aim is undetectable HCV RNA or SVR at LT to reduce the frequency of HCV recurrence<sup>[13]</sup>.

### **HBV positive and HCV positive liver transplant recipients**

The primary goal in this step is the prevention of HBsAg appearance in a patient with erased HBV infection (HBV recurrence) and a new HBV DNA finding in a patient with negative HBsAg (virological breakthrough)<sup>[48]</sup>. The combination of HBV immunoglobulin (HBIG) with high genetic barrier NA (entecavir or tenofovir) for the long term is the most effective prophylactic approach for HBV recurrence prevention<sup>[49,50]</sup>. However, the high cost of HBIG and the fact that the majority of patients receive a transplant with undetectable or minimal HBV DNA since they have been on NAs before LT led to the use of short term HBIG or HBIG-free regimens in the post-transplant period. In the first case, LT recipients take a combination of HBIG and NA for a short period post-transplant, continuing with NA monotherapy long term<sup>[49]</sup>. In a group of LT recipients with low risk for HBV recurrence (only 4.5% had detectable HBV DNA at the time of LT), entecavir or tenofovir monoprophyllaxis after HBIG discontinuation was similarly effective, with no difference in renal adverse events<sup>[38,49]</sup>.

Regarding the HBIG-free prophylactic regimens, dual NAs such as tenofovir and emtricitabine or tenofovir plus entecavir<sup>[51-54]</sup> accounted for undetectable HBV DNA after 26 mo treatment post LT, but they did not eliminate cases of recurrence<sup>[49,52]</sup>. Entecavir and tenofovir should be the first-line options for HBIG-free prophylaxis. It is advisable that entecavir not be used in patients with previous lamivudine resistance who should be preferably treated with tenofovir. Until the optimal HBIG-free prophylactic regimen is determined, the combination of

HBIG (at least for a short period) and one high genetic barrier NA appears to be the most reasonable post-transplant approach<sup>[49,55]</sup>.

Physicians should individualize the therapeutic regimen according to the pre-transplant type of liver disease, the patient's viremic status and the risk of reactivation<sup>[56,57]</sup>. HBV DNA clearance and HBeAg negativity at the time of LT, fulminant HBV and hepatitis D virus coinfection may allow HBIG reduction or withdrawal strategies<sup>[48]</sup>. At present, more and more patients maintain HBV DNA undetectable peritransplant so their prognosis has improved<sup>[3]</sup>. In our clinical setting, we use maintenance therapy with entecavir or tenofovir monoprophyllaxis after a short course with low dose HBIG plus entecavir or tenofovir as antiviral prophylaxis against HBV recurrence after LT. Striking techniques such as covalently closed circular DNA (cccDNA) could detect occult HBV (HBV infection with negative HBsAg test) in hepatic and extrahepatic sites early. Nevertheless, Lenci *et al*<sup>[58]</sup> showed that many patients had a recurrence after cessation of any anti-viral prophylaxis despite negative cccDNA.

Regarding HCV positive liver transplant recipients, recurrence of HCV infection occurs in virtually all patients transplanted for HCV-related liver disease after LT. Additionally, three years post-transplant, decompensation developed in 70% of recipients compared with other immunocompetent groups in which the same proportion was less than 10%<sup>[59]</sup>. Post-transplant prophylaxis (preemptive) against HCV recurrence is not recommended because randomized trials have not confirmed its superiority regarding treatment when there was recurrence and it was associated with high cost and poor tolerability<sup>[11,12,60]</sup>. Interferon (IFN) use on the basis of high immunosuppression has not been effective and has been related to sepsis and rejection episodes<sup>[13,61]</sup>. Indications for antiviral therapy are fibrosing cholestatic hepatitis and significant fibrosis<sup>[61]</sup> [METAVIR score > F1<sup>[62]</sup>, hepatic venous gradient > 6<sup>[63]</sup> and liver stiffness > 8.7 kPa<sup>[64]</sup>], but not fibrosis level > 3 because those patients cannot tolerate therapy<sup>[18]</sup>. Emphasis should be given to prompt diagnosis of histological evidence of HCV recurrence. Patients with female gender, steatosis of the graft, older donor age<sup>[65-67]</sup>, cytomegalovirus and human herpes virus 6 infection<sup>[68]</sup> require sustained attention with protocol graft biopsies, regardless of normal liver function tests and good clinical condition. Non-invasive diagnostic methods such as elastography, serum and molecular fibrosis markers should also be used simultaneously<sup>[47]</sup>.

The combination of Peg-IFN with RBV is again the standard of care for HCV recurrence after LT. Likewise, the regimen's efficacy is frustrating because after 72 wk of administration, SVR stabilization was achieved in only 30% of recipients<sup>[69-71]</sup>. The currently used DAAs, boceprevir and telaprevir, on the top of the old regimen have shown very promising results for the treatment of HCV reinfection in LT recipients with CHC<sup>[61]</sup>. Five studies<sup>[72-76]</sup> have demonstrated that the institution of the triple regimen obtained SVR in 50%-89% of LT

**Table 2** Safety and efficacy of the combined regimen, interferon, ribavirin and protease inhibitors to treat hepatitis C after liver transplantation

	Boceprevir (n)	Telaprevir (n)	Complete virological response	Side effects
Coilly <i>et al</i> <sup>[72]</sup>	18	19	58% TVR 89% BOC	Anemia 92% Infections 27% Fatal events 8%
Pungpapong <i>et al</i> <sup>[73]</sup>	31	35	86% TVR 48% BOC	Anemia 95% Infections 10% Renal dysfunction 76% Fatal events 3%
Werner <i>et al</i> <sup>[74]</sup>	-	9	88.80%	Anemia 75% Rash 33% Renal dysfunction 33%
Stravitz <i>et al</i> <sup>[75]</sup>		50	62%	Anemia 82% Renal failure Fatal events 7%
Ann Brown <i>et al</i> <sup>[76]</sup>	-	46	60%	Anemia 48% Rash 35% Pruritus 22% Renal failure 22% Infections 22%
Forns <i>et al</i> <sup>[77]</sup>	Sofosbuvir 115		78%	Anorectal symptoms 41% Fatal events 16%

BOC: Boceprevir; TVR: Telaprevir.

recipients with CHC, mostly with genotype 1, when administered for 12 to 66 wk (Table 2). Serious side effects, fatal events, were recorded in two studies<sup>[73]</sup>. Although the place of DAAs in the management of LT recipients has not been totally clarified, two reported algorithms<sup>[19,61]</sup> may guide therapy. According to them, the triple regimen should be applied in cases of cirrhosis (METAVIR fibrosis stages 3 and 4), cholestatic hepatitis, previous virological failure and in the presence of predictors of poor response. Interestingly, sofosbuvir (NS5B inhibitor) combined only with RBV with or without PEG IFN demonstrated strong antiviral potency and disease improvement of CHC recurrence in LT recipients<sup>[77]</sup>. These are all very promising data but need to be tested in large multicenter prospective trials to become the standard of care.

In line with reducing severity of HCV recurrence after LT, immunosuppression is one of the major factors that accounts for accelerated HCV recurrence. For example, both steroid boluses as well as their very rapid tapering have been associated with aggressive HCV recurrence and graft loss. Interestingly, the long term maintenance immunosuppression with azathioprine, tacrolimus and prednisolone delayed the appearance of histologically proven severe fibrosis, while the sirolimus therapy led to HCV RNA elimination without antiviral treatment<sup>[78,79]</sup>.

## MANAGEMENT OF PATIENTS WITH HEPATITIS B AND C BEFORE AND AFTER KIDNEY TRANSPLANTATION

### HBV positive and HCV positive renal transplant candidates

Antiviral therapy advances for HBV and HCV infec-

tion on renal transplantation (RT) have indicated great benefits in pre-transplantation and post-transplantation management and results<sup>[80-83]</sup>. However, antiviral therapy for HCV is hardly tolerated by RT candidates, especially if they have comorbidities and dialysis-related complications. It may not be wise for HCV positive patients with congestive heart failure, uncontrolled diabetes and with short life expectancy to receive antiviral therapy<sup>[84,85]</sup>.

HBV and HCV positive candidates for RT should preferably undergo liver biopsy. The transjugular route is preferable since coagulation abnormalities are very common<sup>[86]</sup>. Fibroscan and other noninvasive techniques are supplementary. The presence of cirrhosis precludes patients from sole RT, while in patients with decompensated cirrhosis combined liver and kidney transplantation is the recommended option<sup>[87-90]</sup>.

HBV positive RT candidates should initiate antiviral therapy when HBV DNA > 2000 IU/mL or HBV DNA ≤ 2000 IU/mL two weeks before RT<sup>[39,91,92]</sup>. Therapy should be instituted as long as immunosuppressive therapy lasts whatever the HBV DNA level is<sup>[2]</sup> or for at least the first 2 years when immunosuppressive therapy is most intense<sup>[91]</sup>. HCV positive RT candidates should receive therapy when there is active viral replication (HCV RNA positive) and a biopsy proven chronic hepatitis<sup>[93]</sup>. Before transplantation, the goal is the accomplishment of HBV DNA clearance to prevent post-transplant virological relapse and liver-related complications<sup>[26,80,94]</sup>. The disappearance of viral load is a prerequisite for a HBV or HCV positive patient on hemodialysis to be enrolled in the RT list. Therapy with entecavir, tenofovir or lamivudine on adjusted doses for renal function is included in the current guidelines for prophylaxis of HBV positive RT candidates<sup>[26,80,91,94]</sup>. The NA optimal regimen has not been pro-



posed yet, so prophylaxis may start before or at the time of RT and continue thereafter<sup>[91,92]</sup>. Entecavir should be the first line option for avoidance of short term resistance and adefovir nephrotoxicity<sup>[91]</sup>, while tenofovir had better be applied in case of lamivudine resistance.

Guidelines for HCV positive RT candidates recommend treatment with interferon  $\alpha$  ( $\alpha$ -IFN) in adjusted doses for renal function<sup>[93,95]</sup>, although studies in this population<sup>[96,97]</sup> have shown the advantage of IFN and RBV to provide persistent SVR. The very severe anemia and heart failure caused by the combinative regimen avert clinicians from using it in clinical practice<sup>[97]</sup>. However, the addition of very low doses RBV (200-400 mg three times weekly) under thorough monitoring (weekly measure of hemoglobin, application of high erythropoietin doses and iron supplementation) could result in HCV RNA clearance and allow more patients to get on to the list<sup>[93]</sup>. The preliminary results for five RT candidates with CHC treated with the triple regimen of IFN, RBV and DAAs (four received telaprevir and one boceprevir)<sup>[98,99]</sup> are very promising. Telaprevir and boceprevir has not required dose adjustment to renal function so far. After 12 to 48 wk of triple therapy, viral load disappeared in 4/5 of patients, while moderate, almost expected side-effects were noted. These were dysgeusia, diarrhea and anemia, leading to the increase of the doses of erythropoietin and the modification of RBV doses.

### **HBV positive and HCV positive renal transplant recipients**

The high doses of immunosuppressants (steroids and anti-CD3 antibody) required to avoid graft rejection post-transplant may be responsible for rapidly progressive liver disease and fibrosing cholestatic hepatitis<sup>[100,101]</sup>. Initially, HBV positive RT recipients should be under close surveillance and continue the same treatment started before RT. Entecavir is again the therapy of choice. It has been tried in naïve, lamivudine or adefovir resistant RT recipients for 33 mo<sup>[102-106]</sup>, providing excellent results regarding HBV DNA reduction, without aggravation of creatinine clearance, microalbuminuria or allograft rejection. Discontinuation of applied NA is desirable in cases of fibrosing cholestatic hepatitis and resistance, which may occur as hepatic flare and rarely as hepatocellular carcinoma (HCC) and fatal liver decompensation<sup>[105,107]</sup>. Tenofovir (245 mg daily) adapted to creatinine clearance could be a safe alternative subsequent to resistance<sup>[108]</sup> on the condition that tubular injury is of great concern. If renal allograft dysfunction is in progress and the HBV positive RT recipient presents with a low viral load, the inception of telbivudine could potentially lead to renal function recovery<sup>[120,109-111]</sup>.

Therapy of HCV after RT should only be considered in RT recipients with fibrosing cholestatic hepatitis or de novo glomerulonephritis<sup>[93,112]</sup>.  $\alpha$ -IFN alone or  $\alpha$ -IFN plus RBV post-transplantation are contraindicated because a high percent of irreversible and steroid resistant acute allograft rejection and low efficacy levels have

been recorded<sup>[113,114]</sup>. In our clinical setting, HBV positive and HCV positive RT recipients are screened for liver enzymes, bilirubin and prothrombin time at each visit. Ultrasonography with triplex of splenoportal axis and/or transient elastography is monitored annually. HBV DNA and HCV RNA as well as  $\alpha$ -fetoprotein are tested every year. In patients with cirrhosis, endoscopy for detection or monitoring of varices is performed every 1-2 years. All HBV positive and HCV positive RT recipients should avoid alcohol and hepatotoxic drugs. In the case of fever, effective antibiotics are started immediately. Liver biopsy and modulation of antivirals is considered in patients with abnormal liver function and/or increased viral load.

## **SELECTION OF PATIENTS WHO NEED CLOSE MONITORING**

High HBV viral load pre and peritransplant predispose to closer patient surveillance and stronger prophylactic antiviral regimens. This group of patients is more likely to progress to decompensation and to HCC<sup>[115]</sup>. It is preferable that they be treated with entecavir or tenofovir and often be monitored for signs of decompensation. In a case of severe decompensation, patients receiving antivirals are at higher risk of lactic acidosis so physicians should be vigilant. LT candidates with HCV compensated cirrhosis are more vulnerable to IFN-related hematological toxicities since the splenomegaly caused by portal hypertension magnifies the risk for cytopenias<sup>[116]</sup>. Therefore, IFN dose modification and close regular monitoring is recommended. Furthermore, therapy in patients with Child-Turcotte-Pugh (CTP) score C (or MELD score > 18) is challenging and should be carried out in dedicated and experienced centers because IFN may cause sepsis and is associated with a low sustained virological response (SVR) rate<sup>[61]</sup>. Careful monitoring should also be applied to patients with CTP score B. They need individualization of treatment decisions regarding non-genotype 1, high viral load, treatment naïve or relapse from previous antiviral therapies<sup>[13]</sup>.

RT recipients with severe liver disease should receive non aggressive immunosuppressive protocols (cannot always be applied in immunologically high risk patients) and a selected immunosuppressive regimen with minimal or preferably no steroid use. All antivirals should be modified continuously regarding current renal function. Additionally, HBsAg-positive RT recipients with cirrhosis are at risk for hepatic decompensation after isolated RT and therefore they require simultaneous liver and kidney transplantation<sup>[86]</sup>. In conclusion, we should be on the alert for all HCV positive RT recipients which means screening them regularly for HCC<sup>[117]</sup>, emergence of diabetes, renal thrombotic microangiopathy<sup>[118]</sup>, glomerulonephritis<sup>[119,120]</sup>, renal graft nephropathy<sup>[118]</sup> and sepsis<sup>[121]</sup>.

## **SPECIAL TREATMENT CONSIDERATIONS**

Generally, entecavir and tenofovir are the preferable an-

**Table 3** Prophylactic schemes against hepatitis B virus recurrence after liver and renal transplantation when grafts are from hepatitis B virus positive donors

	Donor	Recipient	Prophylaxis
Liver transplantation	Anti-HBc positive	HBsAg positive	HBIG plus NA
		HBsAg negative	No prophylaxis
		Anti-HBc positive	
		Anti-HBs positive	
		Anti-HBc negative	Long term lamivudine
		Anti-HBs negative	
Kidney transplantation	HBsAg positive	Anti-HBc positive	HBIG plus NA
		HBsAg negative	No prophylaxis
	Anti-HBc positive		Treatment when HBV DNA increases
		HBsAg positive	HBIG plus lamivudine
		HBsAg negative	Long term lamivudine
		(HBV DNA negative)	

HBV: Hepatitis B virus; NA: Nucleos(t)ide analog; HBIG: Hepatitis virus immunoglobulin.

tiviral treatment for post LT or RT recipients due to its high resistance barrier, the favorable safety profile and the regression of fibrosis with long term application<sup>[34,122]</sup>. However, entecavir is not advisable for patients with lamivudine resistance and it should be applied carefully in patients with decompensated cirrhosis with MELD score  $\geq 22$  because cases of lactic acidosis have been recorded with its administration<sup>[115]</sup>. Tenofovir is the only effective choice practically for patients with resistance to lamivudine or any nucleoside analogue<sup>[39]</sup> but there are concerns about creatinine clearance decline and acute tubular nephropathy during long term therapy, especially in group of patients with high risk for renal dysfunction over time such as RT and LT recipients<sup>[122]</sup>. Telbivudine is the only NA with a renal protective effect but its use in the RT and LT setting has still not been tested. Other NA limitations are the indefinite course and the relatively high cost of therapy which complicate patient compliance. Similar concerns exist about the cost and efficacy of HBIG continuation in HBV positive LT recipients. The duration of HBIG prophylaxis in HBV positive LT recipients is controversial and challenging and should be discussed on a case-by-case basis. The access to optimal therapy for HCV positive RT and LT recipients is limited by the low tolerance or contraindication of IFN-based regimens and the lack of experience of the efficacy and safety of first generation DAAs. Newer DAAs (such as sofosbuvir) need further evaluation in this setting.

## HBV AND HCV POSITIVE DONORS

Many studies have shown that liver grafts from anti-HBc positive donors can be used safely in: (1) HBsAg negative but anti-HBc/antiHBs positive recipients without antiviral prophylaxis<sup>[123]</sup>; (2) in HBsAg positive recipients on the condition that dual therapy HBIG and NAs is applied<sup>[123]</sup>; and (3) anti-HBc and/or antiHBs negative recipients when receiving long term prophylaxis with lamivudine, dual therapy or no prophylaxis<sup>[123,124]</sup>. Heterogeneity of data exists regarding the use of liver grafts from HBsAg positive donors<sup>[125-128]</sup>.

Similarly, renal grafts from anti-HBc positive donors can be used in HBsAg negative recipients without prophylaxis<sup>[129]</sup>. It is acceptable practice for renal grafts from HBsAg positive donors to be used in HBsAg positive or HBsAg negative recipients with subsequent long term NA administration with or without HBIG<sup>[130,131]</sup>. In all cases, serial HBV DNA measurements regardless of normal liver biochemistry are required. In particular, in LT or RT recipients who are not on any antiviral prophylaxis, an increase in viral load indicates NA initiation. On the other hand, when immunosuppression is reduced and complete viral clearance has been achieved, NA interruption could be considered<sup>[103]</sup> (Table 3).

LT candidates with HCV-related cirrhosis can undergo LT from HCV positive donors if they are not HCV RNA positive because early hepatitis C recurrence may occur<sup>[132,133]</sup>. Renal grafts from HCV positive donors are acceptable only for HCV positive RT candidates<sup>[93]</sup>. In this setting, the survival of HCV positive RT recipients increases compared to their survival rates if they remain on hemodialysis<sup>[134,135]</sup>. Renal grafts from HCV positive donors should not be distributed to HCV negative recipients because many fatal liver complications have been recorded<sup>[136,137]</sup>.

## CONCLUSION

Current knowledge on the management of patients with HBV offers effective and safe options for liver or renal transplantation. Individualization and determination of less nephrotoxic and finite duration antiviral treatment will enhance the quality of their treatment and prognosis. Various types of vaccinations (S and pre-S antigen vaccines, DNA vaccination, T cell vaccines) and some monoclonal antibodies (exbivirumab and libivirumab) are promising for preventing HBV recurrence and are being evaluated in clinical trials. Subcutaneous HBIG and hyperimmune anti-HBs plasma may prove to be alternative options with a lower cost and the same efficacy levels. The optimal antiviral therapy has not been established yet for LT or RT candidates with CHC. The DAAs in-

stitution marks a bright new era for treatment approach of these patients. Control randomized studies involving DAAs use in patients with decompensated cirrhosis and in RT candidates and recipients are in high need. Moreover, the optimal use and benefits of granulocyte growth factors and erythropoietin in improving SVR rates should be further researched and become established practice.

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