World Journal of Gastrointestinal Pharmacology and Therapeutics

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DOI: 10.4292/wjgpt.v6.i4.105

World J Gastrointest Pharmacol Ther 2015 November 6; 6(4): 105-110
ISSN 2150-5349 (online)

EDITORIAL

Pharmaceutical management of hepatitis B and C in liver and kidney transplant recipients

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Author contributions: Authors contributed equally in writing and editing of the article.

Conflict-of-interest statement: There are no conflicts of interest.

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Received: May 16, 2015
Peer-review started: May 18, 2015
First decision: June 24, 2015
Revised: July 5, 2015
Accepted: July 29, 2015
Article in press: August 3, 2015
Published online: November 6, 2015

Abstract

The combination of hepatitis B immune globulin with entecavir or tenofovir (at least for a certain period of time) seems to be the most reasonable prophylaxis against recurrent hepatitis B after liver transplantation. Entecavir represents an attractive option for treatment of naïve kidney transplant recipients, because of its high efficacy and the low rates of resistance. However antiviral treatment should be individualized in the view of kidney function and the previous resistance. To date, new captivating therapeutic strategies could make interferon-free regimens viable for treatment of hepatitis C virus positive liver transplant recipients. The recent combinations of sofosbuvir with simeprevir or daclatasvir or ledipasvir plus/minus ribavirin have boosted the on treatment and sustained virological response to rates approaching 100% within liver transplant recipients with recurrent chronic hepatitis C (CHC). Preliminary data showed that the second generation direct oral antivirals could result to high treatment rates of recurrent CHC in kidney transplant recipients as well. Ongoing studies will clarify the optimal treatment of recurrent CHC in kidney transplant recipients.

Key words: Viral hepatitis; Hepatitis C recurrence; Hepatitis B; Hepatitis C; Liver transplantation; Kidney transplantation hepatitis B recurrence

Core tip: Emphasis should be placed in the appropriate nucleo(s)tide analog selection for prevention of recurrent hepatitis B virus post liver and kidney transplantation; Second generation direct acting oral antivirals have demonstrated sustained virological response rates approaching 100%, minimal side effects and drug interactions on liver transplant recipients with chronic hepatitis C virus (HCV); Preliminary data showed outstanding response of kidney transplant recipients with chronic HCV to direct acting oral antivirals.

Pipili C, Cholongitas E. Pharmaceutical management of hepatitis

B and C in liver and kidney transplant recipients. *World J Gastrointest Pharmacol Ther* 2015; 6(4): 105-110 Available from: URL: http://www.wjgnet.com/2150-5349/full/v6/i4/105.htm DOI: http://dx.doi.org/10.4292/wjgpt.v6.i4.105

INTRODUCTION

Treatment of chronic hepatitis B (CHB) and chronic hepatitis C (CHC) infection in patients who have undergone liver or kidney transplantation represents a challenge for physicians. Efforts to develop effective antiviral medications have been robust over the last decade and the data review showed clinical outcomes comparable with that of the non-infected transplant recipients[1-4].

Recurrent hepatitis B post liver transplantation (Table 1)

Potent nucleos(t)ide analogues (NAs) with high-genetic barrier should be given in all patients with hepatitis B virus (HBV) decompensated cirrhosis in order to improve the liver function and achieve undetectable HBV DNA at the time of liver transplantation (LT)[5]. It is known that NAs prevent HBV recurrence at an acceptable level and lead to long-term survival after LT[6]. Furthermore, the combination of NAs with low-dose hepatitis B immune globulin (HBIG) can prevent HBV recurrence in more than 80% of LT recipients on long-term[6]. However, long-term HBIG administration requires additional measurement for hepatitis B surface antibody titers and it has been proven inconvenient and costly. Thus, various HBIG-elimination prophylactic regimes have been tried, resulting in encouraging efficiency results similar to continuing HBIG[7,8].

A systematic review and two studies carried out by our team[9-11] favored the use of HBIG with a high genetic barrier NAs instead of HBIG and lamivudine combined prophylaxis against HBV recurrence after LT[9], suggesting that the maintenance monotherapy with newer NAs [entecavir (ETV) or tenofovir (TDF)] was effective after discontinuation of HBIG prophylaxis[10]. Indeed, the most recent prospective study coming from our group[11] demonstrated that ETV or TDF monoprophylaxis following combination with low-dose HBIG six months post LT was highly effective and safe in twenty-eight cirrhotic patients with undetectable HBV DNA at the time of LT. Nevertheless, the long-term immunosuppressive therapy may cause considerable renal dysfunction, cardiovascular disease and cancer, in the context of HBV recurrence, that account for significant late mortality[12]. Interestingly, telbivudine administration for prophylaxis of HBV recurrence can improve renal function after LT[13,14].

Generally, some form of HBV prophylaxis should be continued indefinitely after LT[15]. Based on our recent review, that summarizes all the available relevant current data, the choice of therapy should be individualized in regards to patient's HBV-DNA levels before LT and the previous exposure to NA(s). LT recipients with a low risk of HBV recurrence (*i.e.*, undetectable HBV DNA levels before LT, which represents the majority of HBV positive candidates), might discontinue HBIG and maintain on long-term oral antiviral therapy[15]. Patients with high risk of HBV recurrence (high pretransplant HBV DNA levels, HIV coinfection and preexisting drug resistance or high risk of noncompliance to antiviral therapy) may need a more careful and close management[16]. Only few studies have considered HBIG-free prophylactic regimens from the first post-operative day; *i.e.*, the administration of newer NAs (ETV or TDF). In keeping with low cost, these studies[9,17] have given encouraging results, but this approach is still challenging and controversial.

Recurrent hepatitis B post kidney transplantation (Table 1)

Prior to the advent of NAs, HBV infection had such a severe negative impact on kidney transplantation (KT)[1], that many centres regarded HBsAg seropositivity as a contraindication for KT. In the era of NAs administration the 5-10 year survival rate of KT recipients with CHB is approaching that of HBsAg negative patients[1,18]. The introduction of NAs represents a major breakthrough in the field of KT accounting for minor liver complications, effective viral load suppression and better patient survival without compromising the kidney allograft outcome[19]. Nevertheless, the management of KT recipients with CHB should take into account the special therapeutic limitations and the features of an ideal regimen of this patient group. The limitations of NA use include nephrotoxicity, reported mostly after adefovir and tenofovir administration, high resistance rates after long term lamivudine use, and allograft function decline following interferon use[19,20].

The data on NA administration in KT recipients are scarce. Usually, KT candidates are started on antivirals before KT and carry on the same regimen post-KT unless liver disease deterioration or resistance accrues. Prophylactic antiviral therapy commenced prior to KT seems to better prevent the HBV related complications post KT[21]. In this case, ETV should be the first line therapy for KT recipients because of the high efficacy and safety profile and the low rates of resistance[20,22]. TDF is proposed as the best choice for cases with creatinine clearance > 60 mL/min, or history of resistance to lamivudine[23], while telbivudine should be considered for CHB patients with low viremia if the aim is the amelioration of glomerular filtration rate[13,24,25].

Recurrent hepatitis C post liver transplantation (Tables 1 and 2)

The rate of HCV recurrence has been extremely high in patients with HCV viremia at the time of liver transplantation, resulting to 70% decompensation (comparing with 10% in other immunocompetent groups), two thirds of graft failure and high death rates[26]. The introduction of direct oral acting antivirals (DAAs) has revolutionized the treatment of patients with

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

Chronic hepatitis B	Post-liver transplantation	Prophylaxis and treatment	HBIG (for short term) plus NA[1]
	Post-kidney transplantation		NAs[1]
Chronic hepatitis C	Post-liver transplantation	No prophylaxis	Sofosbuvir based regimens or "3D" regimen plus RBV (for genotypes 1 and 4)
	Post-kidney transplantation		Newer direct oral antivirals plus/minus RBV (studies are ongoing)[2]

[1]Frontline analogues are considered entecavir or tenofovir in renal proper doses (consider telbivudine in the presence of renal dysfunction); [2]Interferon is contraindicated due to the high risk of allograft rejection. HBIG: Hepatitis B immune globulin; NAs: Nucleos(t)ide analogues; 3D: Paritaprevir (plus ritonavir)/ombitasvir/dasabuvir for genotype 1 and paritaprevir (plus ritonavir)/ombitasvir for genotype 4; RBV: Ribavirin.

CHC and represents a major breakthrough especially for difficult to treat populations, involving the patients with cirrhosis Child-Pugh stage B and C, HCV genotype 1 and previous intolerance or non-response to interferon (IFN)-based therapy[3]. First generation DAAs (*i.e.*, telaprevir and boceprevir) improved significantly the sustained virological response (SVR) but their common interactions with the calcineurin inhibitors and the poor tolerance prevented their wide implementation in LT recipients. Various IFN-free combinations, including potent second generation DAAs with non-overlapping resistance profiles, have provided rapid and potent suppression of viral replication. The current available reports[27,28] indicated that the undetectable HCV RNA peritransplant has led to successful prevention of recurrent CHC post LT. In this line, the new DAA combinations have ensured excellent safety with minimal CNI interactions on LT recipients with recurrent CHC after LT (with the good results to be extended to LT recipients with fibrosing cholestatic hepatitis as well). The recent combinations of sofosbuvir with simeprevir or daclatasvir or ledipasvir plus/minus ribavirin (RBV) have boosted the SVR response to rates approaching 100% within LT recipients with CHC recurrence[29-31]. Similarly, SVR and HCV recurrence prevention was reported in a second LT recipient with decompensated cirrhosis without pre-LT SVR commenced on an novel antiviral combination immediately post-LT[32].

The latest data derived from the Coral study[33] showed 97% SVR at four and 12 wk after four-drug administration: Paritaprevir (potent NS3/4A protease inhibitor), ombitasvir (potent NS5A inhibitor), dasabuvir (non-nucleoside NS5B polymerase inhibitor) and RBV. The Cosmos study group reported complete treatment in 27 LT recipients with CHC genotype 1 by using sofosbuvir plus simeprevir for 12 wk underlining minor side effects such as mild transient rash, indirect hyperbilirubinemia and cyclosporine withdrawal (due to simeprevir interaction)[34]. Based on all these striking results, the European Association for the Study of the Liver[35] recommends that: (1) all patients with CHC listed for LT should receive antiviral therapy in order to prevent graft infection after LT; and (2) HCV recurrence post LT should be treated with one of the above antiviral combinations, irrespectively of the severity of liver disease: Sofosbuvir and RBV for 12 wk in genotype 2; fixed dose sofosbuvir, ledipasvir and RBV for 12 wk in genotypes 1, 4, 5, 6; sofosbuvir, daclatasvir plus RBV for 12 wk in all genotypes. In addition, patients without cirrhosis or with Child-Pugh class A post-LT could be also treated with: (1) sofosbuvir and simeprevir plus RBV if there are genotype 1, 4; and (2) paritaprevir/ombitasvir/dasabuvir and RBV for 12 wk if they are genotype 1b and for 24 wk if they are genotype 1a with cirrhosis; if they are genotype 4: Paritaprevir/ombitasvir plus RBV for 12 wk in non-cirrhotics or 24 wk in cirrhotics.

Recurrent hepatitis C post kidney transplantation (Tables 1 and 2)

CHC has been related with poor patient and graft survival after KT that corresponded to the pre-existing HCV infection before KT (the level of HCV RNA and the liver complications)[36,37]. Consequently, substantial attention should be applied to treat HCV infection before KT. Very few studies reported the use of first generation DAAs (boceprevir and telaprevir) on the top of reduced dose IFN and RBV in kidney transplant candidates. The results are promising in regards to efficacy, but side effects such as anemia have been still of concern[38-40]. The new DAAs administered as IFN- and RBV-free combinations might be proved the treatment of choice against HCV infection in KT patients. However DAA-efficacy, -tolerability and effect on graft function still warrant thorough evaluation. So far, the use of new antivirals in KT recipients has been reported solely in few cases and is being tested in two ongoing trials[41-43]. Fibrosing cholestatic hepatitis was successfully treated either with sofosbuvir combined with pegylated-IFN and RBV[41] or with sofosbuvir and simeprevir without IFN or RBV in combined kidney-liver transplant recipients[42]. Moreover, sofosbuvir combined with low dose RBV was efficient, presented minimum adverse events such as pruritus and mylalgia and did not require tacrolimus dose adjustments in eight KT recipients with HCV genotype 1, creatinine clearance higher than 30 mL/min and hemoglobin higher than 10 g/dL[44]. The antivirals tested in the ongoing trial among KT recipients with HCV are sofosbuvir and ledipasvir and no initial data have been published yet[43]. Concerns emerge in regards to performance of sofosbuvir in recipients with kidney function deterioration, since sofobusvir is renally excreted and is not appropriate for creatinine clearance below 30 mL/min. Initiation of sofusbuvir - based regimens post KT once glomerular filtration rate > 30 mL/min as a prophylaxis could be

Table 2 Main characteristics of the approved direct acting antivirals that are currently used in interferon-free regimens for the treatment of chronic hepatitis C

Name	Category, antiviral activity	Doses	Adjustments
Simeprevir	Second-wave NS3/4A protease inhibitor, genotypes 1 and 4	150 mg daily, orally	No renal adjustment is needed Contraindicated in patients with Child-Pugh B/C Contraindicated cyclosporine co-administration
Sofosbuvir	NS5B RNA Polymerase nucleotide inhibitor, pangenotypic	400 mg daily, orally	Only in glomerular filtration rate > 30 mL/min No CNI adjustment is needed
Daclatasvir	NS5A inhibitor, genotypes 1, 3 and 4	60 mg daily, orally	No renal adjustment is needed No CNI adjustment is needed
Ledipasvir	NS5A inhibitor genotypes 1, 3 and 4	90 mg daily, orally (fixed dose with sofosbuvir)	No renal adjustment is needed[1] No CNI adjustment is needed
Dasabuvir	Non-NUC NS5B polymerase inhibitor genotype 1	250 mg every 12 h	No renal adjustment is needed
Paritaprevir/Ritonavir/Ombitasvir	Ritonavir boosted NS3/4A protease inhibitor/NS5A inhibitor, genotypes 1 and 4	75/50/12.5 mg x 2 once daily	No safety data in Child-Pugh B, contraindicated in Child-Pugh C Cyclosporine: 20% of pretreatment total daily dose; tacrolimus: 0.2 mg/72 h or 0.5 mg once weekly

[1]Ledipasvir in combination with sofosbuvir should not be given in patients with glomerular filtration rate < 30 mL/min. CNI: Calcineurin inhibitor.

one option. Nevertheless, recent studies have reported acceptable safety and tolerance profile of sofosbuvir in CHC patients with end stage renal disease (glomerular filtration rate < 30 mL/min) or under hemodialysis[45].

CONCLUSION

Substantial progress is acknowledged in the field of antiviral treatment of HBV and HCV positive LT recipients, even if the existing data are preliminary. The applications of novel antiviral combinations are viable in concept, but provisionally under way for HBV and HCV positive KT recipients. However, the high antiviral cost, the drug resistance and the nephrotoxicity will be barriers to optimal therapy access.

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P- Reviewer: Gwak GY, Ikura Y, Montasser IF, Sharma D
S- Editor: Ji FF **L- Editor**: A **E- Editor**: Li D

Published by **Baishideng Publishing Group Inc**
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