ISSN 1948-5182 (online)

World Journal of *Hepatology*

World J Hepatol 2017 July 8; 9(19): 833-866

Published by Baishideng Publishing Group Inc

World Journal of Hepatology

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Three issues per month Volume 9 Number 19 July 8, 2017

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World Journal of Hepatology
Volume 9 Number 19 July 8, 2017

NAME OF JOURNAL
World Journal of Hepatology

ISSN
ISSN 1948-5182 (online)

LAUNCH DATE
October 31, 2009

FREQUENCY
36 Issues/Year (8th, 18th, and 28th of each month)

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PUBLISHER
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7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
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E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
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PUBLICATION DATE
July 8, 2017

INSTRUCTIONS TO AUTHORS
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ONLINE SUBMISSION
http://www.f6publishing.com

World Journal of Hepatology

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World J Hepatol 2017 July 8; 9(19): 833-839

DOI: 10.4254/wjh.v9.i19.833

ISSN 1948-5182 (online)

MINIREVIEWS

Opportunities for treatment of the hepatitis C virus-infected patient with chronic kidney disease

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Author contributions: Ladino M, Pedraza F and Roth D contributed equally to this work.

Conflict-of-interest statement: There is no conflict of interest associated with any of the senior authors or other coauthors who contributed their efforts to this manuscript. Dr. Roth is on a Scientific Advisory Board for Merck Co. and AbbVie. Drs. Ladino and Pedraza have no disclosures to report.

Manuscript source: Invited manuscript

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Received: February 1, 2017
Peer-review started: February 7, 2017
First decision: March 28, 2017
Revised: April 13, 2017
Accepted: May 3, 2017
Article in press: May 5, 2017
Published online: July 8, 2017

Abstract

The prevalence of hepatitis C virus (HCV) infection amongst patients with chronic kidney disease (CKD) and end-stage renal disease exceeds that of the general population. In addition to predisposing to the development of cirrhosis and hepatocellular carcinoma, infection with HCV has been associated with extra-hepatic complications including CKD, proteinuria, glomerulonephritis, cryoglobulinemia, increased cardiovascular risk, insulin resistance, and lymphoma. With these associated morbidities, infection with HCV is not unexpectedly accompanied by an increase in mortality in the general population as well as in patients with kidney disease. Advances in the understanding of the HCV genome have resulted in the development of direct-acting antiviral agents that can achieve much higher sustained virologic response rates than previous interferon-based protocols. The direct acting antivirals have either primarily hepatic or renal metabolism and excretion pathways. This information is particularly relevant when considering treatment in patients with reduced kidney function. In this context, some of these agents are not recommended for use in patients with a glomerular filtration rate < 30 mL/min per 1.73 m^2. There are now Food and Drug Administration approved direct acting antiviral agents for the treatment of patients with kidney disease and reduced function. These agents have been demonstrated to be effective with sustained viral response rates comparable to the general population with good safety profiles. A disease that was only recently considered to be very challenging to treat in patients with kidney dysfunction is now curable with these medications.

Key words: Hepatitis C virus; Chronic kidney disease; Direct acting antiviral agents; Kidney transplantation

Core tip: Advances in the understanding of the molecular

biology of hepatitis C virus (HCV) have ushered in a new era in treatment. Recent studies have shifted the focus to the more difficult-to-treat cohorts of patients. The presence of chronic kidney disease and end stage renal disease were exclusion criteria for the pivotal clinical direct-acting antiviral agents trials, creating a group of patients with a large unmet medical need. This review will update the reader on the use of the direct acting antiviral agents in the HCV-infected patient with kidney disease. Recommendations for the timing of therapy, choice of agents and management of the kidney transplant candidate will be presented.

Ladino M, Pedraza F, Roth D. Opportunities for treatment of the hepatitis C virus-infected patient with chronic kidney disease. *World J Hepatol* 2017; 9(19): 833-839 Available from: URL: http://www.wjgnet.com/1948-5182/full/v9/i19/833.htm DOI: http://dx.doi.org/10.4254/wjh.v9.i19.833

INTRODUCTION

Hepatitis C virus (HCV) infection is a recognized public health concern with global implications that affects approximately 170 million individuals worldwide[1-4]. Infection with HCV is associated with an increased morbidity and mortality secondary to hepatic injury and associated complications[4]. The infection, however, can also affect other organs with significant extrahepatic manifestations (Figure 1). Most noteworthy of these include insulin resistance, cryoglobulinemic vasculitis, sicca syndrome, neurocognitive dysfunction, B-cell non-Hodgkin lymphoma and an increase in cardiovascular adverse events[5-11]. On note, patients with HCV infection also have an increased incidence of proteinuria and chronic kidney disease (CKD)[5], often in the setting of essential mixed cryoglobulinemia or "idiopathic" membranoproliferative glomerulonephritis[5,9,12]. Furthermore, it has also been well established that patients with end stage renal disease (ESRD) have an even higher prevalence of HCV infection that is likely a consequence of greater blood product exposure and patient-to-patient transmission of disease within the dialysis clinics due to breakdowns in universal precautions[12,13].

This review will summarize the most recent data and treatment options recommended for HCV-infected patients with kidney disease. A population of patients that for years had extremely limited options for therapy can now be successfully and safely treated for eradication of HCV.

HCV AND THE KIDNEY

HCV-related glomerulonephritis with or without cryoglobulinemia

The HCV has an unusual tropism for B lymphocytes through linkage of envelope protein 2 and the CD81 molecule on the B cell. B cell activation can result in expansion of malignant cell lines or the production of unique antibodies that are of the IgM isotype and possess rheumatoid factor like activity[14-16]. As a consequence of these events, clinical syndromes including mixed cryoglobulinemia, lymphoproliferative disorders and glomerulonephritis with distinct histological patterns including membranous or membranoproliferative glomerulonephritis can be seen[5,6,17,18]. Of note, co-infected HIV/HCV patients have an increased mortality and an overall worse prognosis[19,20].

The glomerular diseases commonly associated with HCV infection are a consequence of the formation of circulating immune complexes that become trapped in the glomerular basement membrane. The clinical expression of this process can occur through type 2 mixed cryoglobulinemia with resulting type 1 membranoproliferative glomerulonephritis (GN), mesangial proliferative and focal proliferative GN, IgA nephropathy, membranous GN and polyarteritis nodosa[6,14,18]. Typically, the patient that develops cryoglobulinemia has been infected with HCV for many years. These patients may present with a skin rash (palpable purpura), polyneuropathy, multi-organ vasculitis, hypertension and the nephritic syndrome[14].

Suppression of viral replication is necessary to interrupt immune-complex production and subsequent injury to the kidney. The VASCUVALDIC study described the use of sofosbuvir and ribavirin in 24 patients with HCV-vasculitis syndrome and cryoglobulinemia. Patients were treated with direct-acting antiviral agents (DAAs) for 24 wk and achieved a sustained viral response at week 12 (SVR_{12}) of 74% with minimal side effects[21]. The less common presentation of an active vasculitic syndrome as part of the cryoglobulinemic syndrome requires a more aggressive treatment strategy targeted at the ongoing endothelial inflammatory process. Options include high dose corticosteroids, rituximab and therapeutic plasma exchange in addition to appropriate DAA therapy to eradicate viral replication[21-24].

Hepatitis C and CKD

HCV infection is highly prevalent in CKD patients[5] and HCV-infected patients have an increased risk for the development of CKD and proteinuria[5,25,26]. Furthermore, emerging data suggests that the rate of CKD progression to ESRD is greater when compared to non-infected patients[26-31]. In this context, HCV-infected patients with CKD stages Ⅰ (GFR > 90 mL/min per 1.73 m^2), Ⅱ (GFR 60-89 mL/min per 1.73 m^2) and Ⅲa (GFR 45-59 mL/min per 1.73 m^2) should be considered for DAA therapy with the goal to slow the progression of CKD. HCV-infected patients with CKD stages Ⅲb (GFR 30-44 mL/min per 1.73 m^2), Ⅳ (GFR 15-29 mL/min per 1.73 m^2) and Ⅴ (GFR < 15 mL/min per 1.73 m^2) will require a more individualized approach depending on the renal replacement therapy options being considered. The major decision point in this context is whether treatment should

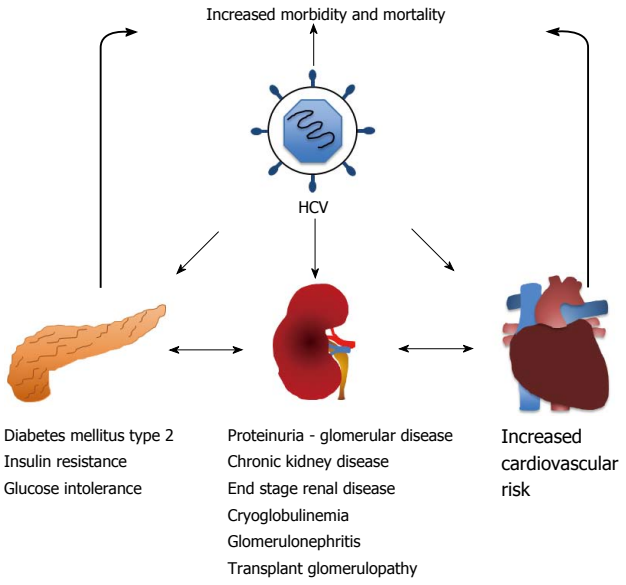

Figure 1 Extrahepatic manifestations of hepatitis C virus. HCV: Hepatitis C virus.

be recommended before or after kidney transplantation. Patients with a living kidney donor should be treated to achieve a SVR prior to transplantation. For the patient that is going to receive a deceased donor kidney the options may include delaying antiviral treatment in order to receive a kidney from an anti-HCV positive donor with the initiation of DAA treatment post transplantation. Alternatively, the patient could be treated pre-transplant and then transplanted with a kidney from an anti-HCV negative donor. Since not all centers currently accept kidneys from anti-HCV positive donors, this option is not available for all patients. Initial reports have demonstrated that accepting a kidney from a positive donor is associated with substantially shortened waiting time on the deceased donor waiting list in the United States[32-34]. Recent studies have demonstrated the safety and efficacy of DAAs in the kidney transplant recipient, with sustained viral response rates equal to that obtained in the general population with minimal side effects[35-37].

HCV in the ESRD patient

It is estimated that 5%-10% of the United States dialysis population is infected with HCV[38]. Many studies have demonstrated that HCV infection is associated with an increased risk of mortality and worse clinical outcomes in ESRD patients[39-43]. In a meta-analysis of ESRD patients, Fabrizi *et al*[41] found that HCV infection was associated with a relative risk of mortality of 1.35 (95%CI: 1.25-1.47). The increased morbidity and mortality associated with HCV infection emphasizes the systemic impact of this disease which can manifest with multiple extrahepatic manifestations and complications[5,40]. In this context, an increased cardiovascular risk attributable to HCV infection has been demonstrated in the ESRD patient[40]. In a recent update from the Dialysis Options and Practice Patterns Study data, it was concluded that HCV infection in ESRD patients was associated with an increased risk of death and hospitalization, anemia and worse quality of life scores for physical function, pain, vitality and mental health[44]. Relevant to any discussion on the associated risks accompanying HCV infection is whether successful treatment delivers a positive impact on outcomes. In this context, Hsu *et al*[45] reported that IFN-based therapy increased survival in HCV-infected ESRD patients. In another report, ESRD patients receiving IFN plus ribavirin obtained improved renal and cardiovascular outcomes compared to those who were untreated[46]. Prospective studies in ESRD patients will be necessary to determine if viral eradication alters the long-term outcome of this challenging population of patients with multiple co-morbidities.

HCV and kidney transplantation

Kidney transplantation is associated with an increase in long-term survival for ESRD patients with HCV infection[47,48]. This was clearly demonstrated in a longitudinal cohort study in which there was a decreased risk of death post-transplantation for the HCV-infected kidney transplant recipients when compared to those remaining on the waiting list[49]. This survival benefit was largely the result of a decrease in cardiovascular events within the first-year post-transplant[50].

HCV infection has been linked to several extra-hepatic manifestations that combine to increase morbidity and mortality after kidney transplantation[51]. It has been well established that HCV is the primary cause of liver disease in kidney allograft recipients[52] and these patients express an increased risk of insulin resistance and diabetes mellitus[53-58]. Furthermore, HCV-infected kidney recipients have a higher probability of developing transplant glomerulopathy[59] and recurrent membranoproliferative glomerulonephritis secondary to immune-complex injury to the renal allograft[60,61].

DIRECT ACTING ANTIVIRAL TREATMENT OPTIONS IN PATIENTS WITH CKD AND POST KIDNEY TRANSPLANT

The availability of DAAs with high SVR rates and favorable adverse event profiles allowed for the study of these drugs in patients with kidney disease, a group that had been excluded from of all the large pivotal trials. Emerging data are now demonstrating an excellent safety and efficacy profile in this patient population (Tables 1 and 2). The HCV-TARGET is a real-world study that collects data on the use of sofosbuvir-based regimens in HCV-infected patients. A total of 73 patients with a GFR $\leqslant$ 45 mL/min per 1.73 m^2 (n = 18 with GFR $\leqslant$ 30 mL/min per 1.73 m^2 and n = 5 on hemodialysis) were included in the analysis[62]. The SVR rate was 83% in patients with GFR $\leqslant$ 45 mL/min per 1.73 m^2 which was similar to patients with GFR > mL/min per 1.73 m^2, however patients with a GFR $\leqslant$ 45 mL/min per 1.73 m^2 had higher rates

Table 1 Direct acting antiviral agents: Dose and use in chronic kidney disease Ⅳ, Ⅴ, end stage renal disease and kidney transplant patients

Medication dose	Use in CKD stage Ⅳ, Ⅴ and ESRD	Use in kidney transplant patients - interactions with Immunosuppressant
Sofosbuvir/Simeprivir 400 mg daily/150 mg daily	CKD IV - GFR 15-29 mL/min: Not recommended CKD V - GFR < 15 mL/min: Not recommended ESRD (dialysis): Not recommended	Decrease in TAC levels with Simeprivir Increase levels of both CyA and Simeprivir Increase or decrease levels of SRL with Simeprivir No changes in TAC, CyA and SRL with Sofosbuvir
Sofosbuvir/Velpatasvir 400 mg/100 mg daily	CKD IV - GFR 15-29 mL/min: Not recommended CKD V - GFR < 15 mL/min: Not recommended ESRD (dialysis): Not recommended	Increase in TAC levels with Velpatasvir No changes in CyA levels with Velpatasvir Increase in SRL levels with Velpatasvir No changes in TAC, CyA and SRL with Sofosbuvir
Sofosbuvir/Daclastavir 400 mg daily/60 mg daily	CKD IV - GFR 15-29 mL/min: Not recommended CKD V - GFR < 15 mL/min: Not recommended ESRD (dialysis): Not recommended	No changes in TAC levels with Daclastavir No changes in CyA levels with Daclastavir Increase in SRL levels with Daclastavir No changes in TAC, CyA and SRL with Sofosbuvir
Sofosbuvir/Ledipasvir 400 mg/90 mg daily	CKD IV - GFR 15-29 mL/min: Not recommended CKD V - GFR < 15 mL/min: Not recommended ESRD (dialysis): Not recommended	No changes in TAC levels with Ledipasvir No changes in CyA levels with Ledipasvir No changes in SRL levels with Ledipasvir No changes in TAC, CyA and SRL with Sofosbuvir
Ombitasvir/Paritaprevir/ritonavir/Dasabuvir 12.5 mg/75 mg/50 mg × 2 tabs/250 mg × 2 tabs	CKD IV - GFR 15-29 mL/min: Dose adjustment not required CKD V - GFR < 15 mL/min: Dose adjustment not required ESRD (dialysis): Dose adjustment not required. Dialysis population studied. Minimal adverse events in patients with advanced CKD and ESRD on hemodialysis	Increase in TAC levels (ritonavir) Increase in CyA levels (ritonavir) Increase in SRL levels (ritonavir) No changes in TAC, CyA and SRL with Ombitasvir/Paritaprevir/Dasabuvir
Grazoprevir/Elbasvir 100 mg/50 mg daily	CKD IV - GFR 15-29 mL/min: Dose adjustment not required CKD V - GFR < 15 mL/min: Dose adjustment not required ESRD (dialysis): Dose adjustment not required. Dialysis population studied. Minimal adverse events in patients with advanced CKD and ESRD on hemodialysis	Increase in TAC levels with Grazoprevir Use of both CyA and Grazoprevir increase levels of Grazoprevir, contraindicated to use together Increase in SRL levels with Grazoprevir

GFR: Glomerular filtration rate; CKD: Chronic kidney disease; ESRD: End stage renal disease; TAC: Tacrolimus; CyA: Cyclosporine; SRL: Sirolimus.

of anemia, worsening kidney function and increased adverse events irrespective of the use of ribavirin[62]. Two open label treatment studies with simeprevir and dose-adjusted sofosbuvir exhibited high rates of SVR with a low incidence of adverse events in patients with advanced CKD and ESRD[63,64]. The RUBY-I trial evaluated the 3D regimen [ombitasvir (OBV)/paritaprevir (PTV)/ritonavir (r) plus dasabuvir (DSV)] in patients with advanced CKD (stages 4/5) and on dialysis. SVR rates were 90% for patients with HCV genotype (GT) 1 with minimal side effects except for the patients with genotype 1a who received ribavirin as part of the protocol[65]. This group had more anemia events and required erythropoietin dose adjustments. Grazoprevir and elbasvir were studied in HCV-infected GT 1 patients with advanced CKD and ESRD in the C-SURFER trial. Sustained viral response rates of 99% were reported with a minimal adverse events profile[66]. The RUBY-I Cohort 2 study included patients with stage F4 fibrosis and GT 1a who were treated for 24 wk with the 3D regimen plus ribavirin. SVR_{24} rates of 89% were reported for this cohort with minimal side effects[67]. The RUBY-Ⅱ study evaluated the use of the 3D regimen in CKD 4 and 5 patients with HCV GT 1a (n = 13) infection without the addition of ribavirin. Genotype 4 patients received OBV/PTV/r without DSV (n = 5). Modified intention to treat (mITT) SVR_{12} rates of 100% were obtained in both groups[68]. Finally, a recent report described the use of glecaprevir (NS3/4A inhibitor) and pibrentasvir (NS5A inhibitor) in patients with advance kidney disease and HCV genotype 1-6 infection (n = 104). In this trial, patients with a GFR < 30 mL/min per 1.73 m^2 (n = 13 with GFR 15-29 mL/min per 1.73 m^2, n = 6 with stage 5 CKD and n = 85 on hemodialysis) obtained a 98% ITT SVR_{12} with no serious adverse events[69] and no viral relapses.

IFN-based protocols have not been recommended after kidney transplantation due to an unacceptably high incidence of rejection events. In contrast, DAA use in kidney transplant recipients has been shown to be safe and effective with minimal side effects[34-37]. Caution to avoid drug-drug interactions related to different drug metabolism/interactions (Table 1) is necessary in addition to high vigilance to maintain therapeutic calcineurin inhibitor levels as HCV viremia is suppressed[34,37].

The availability of DAA agents has dramatically changed the way HCV-infected patients with CKD and ESRD can be managed. While providing outstanding results, these excellent outcomes raise new questions as to which patients should be treated and when is the best time to initiate therapy. Further studies will be

Table 2 Direct acting antiviral agent options for patients with kidney disease

HCV/kidney disease consideration	Complications and observations from HCV infection	DAA options	Other DAA options/notes
HCV related acute glomerulonephritis with or without cryoglobulinemia	HCV has tropism for B-cells with subsequent: Mixed cryoglobulinemia Glomerulonephritis with distinct histological patterns: Membranous nephropathy Membranoproliferative GN	Sofosbuvir 400 mg/d combined with Simeprivir 150 mg/d Daclastavir 60 mg/d Velpatasvir 100 mg/d Ledipasvir 90 mg/d	Can use: Grazoprevir 100 mg/elbasvir 50 mg/d Ombitasvir 12.5 mg/paritaprevir 75 mg/ritonavir 50 mg × 2 tabs/dasabuvir 250 mg × 2 tabs
The HCV-infected patient with stage 1-3a chronic kidney disease (GFR > 45 mL/min)	Increased risk for CKD development Increased rate of CKD progression to ESRD Higher mortality rate	Sofosbuvir 400 mg/d combined with Simeprivir 150 mg/d Daclastavir 60 mg/d Velpatasvir 100 mg/d Ledipasvir 90 mg/d	Can use Grazoprevir 100 mg/elbasvir 50 mg/d Ombitasvir 12.5 mg/paritaprevir 75 mg/ritonavir 50 mg × 2 tabs/dasabuvir 250 mg × 2 tabs
The patient with advanced stage 3 and stage 4/5 chronic kidney disease (GFR < 45 mL/min)	Receiving an anti-HCV positive allograft decreases waiting times for a deceased donor kidney	Sofosbuvir 400 mg/d combined with Simeprivir 150 mg/d Daclastavir 60 mg/d Velpatasvir 100 mg/d Ledipasvir 90 mg/d	Sofosbuvir not recommended with GFR < 30 mL/min Can use Grazoprevir 100 mg/Elbasvir 50 mg/d Ombitasvir 12.5 mg/Paritaprevir 75 mg/ritonavir 50 mg × 2 tabs/dasabuvir 250 mg × 2 tabs
The ESRD patient on dialysis	Increased risk of mortality and poor clinical outcomes in ESRD patients Increased cardiovascular risk	Grazoprevir 100 mg/Elbasvir 50 mg/d Ombitasvir 12.5 mg/Paritaprevir 75 mg/ritonavir 50 mg × 2 tabs/dasabuvir 250 mg × 2 tabs	Grazoprevir/elbasvir, ombitasvir/paritaprevir/ritonavir/dasabuvir, Dialysis population studied Minimal adverse events in patients with advanced CKD and ESRD on hemodialysis
The kidney transplant recipient with eGFR > 30 mL/min	DAA use after kidney transplant is safe and well tolerated with SVR > 97%	Sofosbuvir 400 mg/d combined with Simeprivir 150 mg/d Daclastavir 60 mg/d Velpatasvir 100 mg/d Ledipasvir 90 mg/d	Can use Grazoprevir 100 mg/elbasvir 50 mg/d (caution with cyclosporin) Ombitasvir 12.5 mg/paritaprevir 75 mg/ritonavir 50 mg × 2 tabs/dasabuvir 250 mg × 2 tabs

DAA: Direct-acting antiviral agent; GFR: Glomerular filtration rate; CKD: Chronic kidney disease; ESRD: End stage renal disease; HCV: Hepatitis C virus; DAA: Direct-acting antiviral; SVR: Sustained viral response.

necessary to answer these important questions.

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P- Reviewer: Grassi A, Irshad M, Komatsu H, Tsuchiya A, Zhu X
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