

Full Reviews

An update on the management of hepatitis C virus-infected patients with stage 4–5 chronic kidney disease while awaiting the revised KDIGO Guidelines

Stanislas Pol^{1,2,3}, Michel Jadoul⁴ and Anaïs Vallet-Pichard^{1,2,3}

¹Université Paris Descartes, Paris, France, ²Hepatology Department, Cochin Hospital, APHP, Paris, France, ³INSERM UMS-20, Institut Pasteur, Paris, France and ⁴Department of Nephrology, Cliniques universitaires Saint-Luc, Université catholique de Louvain, Brussels, Belgium

Correspondence and offprint requests to: Stanislas Pol, E-mail: stanislas.pol@aphp.fr

ABSTRACT

The treatment of hepatitis C virus (HCV) infection has progressed markedly over the last 2 decades, with a dramatic acceleration the last 3 years. The combination of two or three direct-acting antiviral drugs (DAAs) targeting viral proteins [NS3/4A protease inhibitors, NS5B nucleos(t)idic and non-nucleos(t)idic polymerase inhibitors, NS5A replication complex inhibitors], with or without ribavirin but without interferon (interferon-free regimen), for 8–24 weeks, achieved high sustained virological response (>90%), whatever fibrosis stage, genotype and subtype, baseline viral load, prior therapeutic history of the patient (naïve or experienced) and pre-existing resistance-associated variants with a fair tolerance and reduced pill burden. International guidelines recommend to ideally treat all infected patients even if a prioritization of the most severe patients (extensive fibrosis or cirrhosis, symptomatic cryoglobulinaemic vasculitis...) appears to be the best cost-effective and urgent policy. Patients with stage 4–5 chronic kidney disease (CKD) have to be considered as priority patients. Updating of the Kidney Disease: Improving Global Outcomes recommendations is due to start soon, but awaiting their availability, we present here an overview of recent developments in the field.

INTRODUCTION

The treatment of hepatitis C virus (HCV) infection has progressed markedly over the last 2 decades, with a dramatic acceleration the last 3 years. The standard of care [the combination of pegylated interferon (IFN) alfa and ribavirin] [1, 2], which has led to a sustained virologic response (SVR; which

corresponds to a complete recovery) in ~45% of patients with HCV genotype 1, 65% with genotype 4, 70% with genotype 3 and ~85% with genotype 2 has been associated, in a first step, with a first-generation NS3/4A protease inhibitor (telaprevir or boceprevir) in genotype 1-infected patients, resulting in ~70% of patients with SVR and a reduction in the duration of therapy from 48 to 24 weeks [1]. The life expectancy of these first-generation regimens has been reduced to 3 years by the rapid development of several direct-acting antiviral drugs (DAAs) targeting viral proteins [NS3/4A protease inhibitors, NS5B nucleos(t)idic and non-nucleos(t)idic polymerase inhibitors, NS5A replication complex inhibitors]. The second step of this therapeutic revolution since 2014 combines two or three second-generation DAAs, with or without ribavirin but without IFN for 8–24 weeks according to baseline factors, including fibrosis stage, genotype and subtype, baseline viral load, prior therapeutic history of the patient (naïve or experienced) and pre-existing resistance-associated variants [3]. Most of these combinations have a high antiviral potency (SVR >90%) and a fair tolerance with a reduced pill burden. Despite limitations related to the screening for HCV infection and access to care, international guidelines recommend to ideally treat all infected patients even if a prioritization of the most severe patients (extensive fibrosis or cirrhosis, symptomatic cryoglobulinaemic vasculitis) appears to be the most cost-effective and urgent policy [3].

Treatment should be given priority in patients with stage 4–5 chronic kidney disease (CKD) because

- (1) HCV increases the incidence and prevalence of renal disease, end-stage renal disease (ESRD) and ESRD-related mortality in the general population [4–7] and the cumulative incidence of ESRD decreases with HCV treatment [8];

- (2) Despite the introduction of screening, improved hygiene and prevention measures, HCV prevalence is higher than in the general population in candidates for transplantation [9–11];
- (3) HCV increases the risk of mortality in dialysis patients [12–15], in whom survival is lower than in renal transplant recipients;
- (4) HCV is associated with reduced survival in HCV-infected versus HCV non-infected transplant recipients, mainly for liver disease or septic complications due to cirrhosis and/or immunosuppressive therapy [16, 17];
- (5) HCV impairs renal allograft survival due to *de novo* membrano-proliferative glomerulonephritis and may even perhaps favour chronic allograft rejection [16, 18];
- (6) HCV antibody positivity increases the incidence of hepatocellular carcinoma in kidney recipients [19].

The Kidney Disease: Improving Global Outcomes (KDIGO) recommendations devoted to hepatitis C in CKD and published in 2008 [12, 20] have taken these harmful consequences into account. There is an urgent need to update, but awaiting their availability, we present here an overview of recent developments in the field.

DO WE STILL NEED LIVER BIOPSY IN EVALUATING HCV-INFECTED PATIENTS WITH RENAL IMPAIRMENT?

The liver biopsy remains the gold standard in candidates for transplantation or in transplant recipients to assess liver fibrosis according to the KDIGO guidelines [12]. The biochemical non-invasive markers, including Fibrotest, Apri, Forns and the FIB-4 index, and elastography have a lower accuracy to evaluate liver fibrosis in patients with stage 4–5 CKD than in the general population [21]. The primary objective of liver biopsy was to diagnose cirrhosis, which contraindicated kidney transplantation because of the risk of liver-related mortality after kidney transplantation and indicated a combined liver–kidney transplant. Non-invasive methods, including elastography, are sufficiently reliable to evaluate extensive fibrosis/cirrhosis [21, 22]. Thus, the place of the liver biopsy to evaluate liver fibrosis in HCV-infected patients with stage 4–5 CKD is now challenged by the high SVR rates due to high antiviral potency of the DAAs. SVR is associated with sustained and long-lasting suppression of necro-inflammation and may result in regression of cirrhosis, which helps in decreasing disease-related morbidity and improving survival. Renal transplantation alone is feasible in inactive compensated cirrhosis.

WHO WILL BE TREATED IN THE NEPHROLOGY SETTING?

DAAs should be considered in all patients with symptomatic cryoglobulinemic vasculitis, which corresponds to a third of patients with renal involvement.

DAAs should be given to all dialysis patients, since HCV infection increases morbidity and mortality in this population

regardless of the fibrosis stage. To date, in some countries, dialysis patients are not considered to be ‘priority patients’ (in contrast to transplanted patients. While awaiting the expanded therapeutic indications, patients with severe renal impairment and significant liver fibrosis, including candidates for kidney transplantation, should be considered for antiviral treatment. However, it should be noted that the absence of antiviral therapy might be considered as an opportunity to be transplanted earlier with an HCV-infected allograft for dialysis patients without significant liver fibrosis.

DAAs should be given to all HCV-infected kidney recipients, with expected benefits similar to those reported for hepatitis B virus (HBV) [23].

Thus, there is now a need for more aggressive treatment of HCV in contrast to the current very low treatment rate of HCV in the nephrology setting [24].

WHAT DAA THERAPY TO RECOMMEND IN PATIENTS WITH STAGE 4–5 CKD

The standard of care for HCV infection in the general population is currently a DAAs combination that allows to reach a SVR in more than 90% of cases. The KDIGO guidelines suggest a monotherapy with standard interferon for HCV-infected patients on maintenance haemodialysis are clearly out-dated and should be up-dated in the next future [12].

Treatment with DAAs should be proposed to any patient with renal impairment in order to (i) reduce the progression of the liver disease, especially after transplantation; (ii) reduce the risk of renal-related morbidity and mortality; (iii) reduce the risks of diabetes, cardio- or cerebrovascular disease and extrahepatic cancers and (iv) improve well-being.

To date, the best regimen for patients with renal impairment is unknown. The combination of grazoprevir (protease inhibitor) and elbasvir (NS5A inhibitor) which does not require dose adjustment to eGFR, led to 99% SVR in per protocol analysis in a randomized controlled study in genotype 1–infected patients with CKD stage 4–5 [25]. Waiting for availability of this antiviral treatment, we have to rely on the available DAAs. The best antiviral potency of simeprevir, a second-generation protease inhibitor and daclatasvir, an NS5A inhibitor, is achieved in combination with sofosbuvir, a first-in-class nucleotidic inhibitor that is the backbone of most antiviral combinations. The use of the standard four-times-a-day dosing of sofosbuvir (400 mg/day), which is metabolized by the kidney, is not recommended in patients with a GFR <30 mL/min, as well as Harvoni (which is a co-formulation, in a single tablet regimen, of sofosbuvir and the NS5A inhibitor ledipasvir). Disappointing results (~40% SVR) have been reported with lower daily doses of sofosbuvir (200 mg/day) and ribavirin (200 mg/day), which remains difficult to manage in dialysis patients [26]. Better SVR results have been anecdotally reported with the standard dose of sofosbuvir (400 mg/day) in association with other DAAs in patients with GFR <30 mL/min [27] but ~20% of them had deterioration of GFR. Antiviral treatment with sofosbuvir 400 mg daily ($n = 8$) or only on the day of haemodialysis ($n = 5$) combined with daclatasvir in 9, ledipasvir in 1, simeprevir in 2 and ribavirin in

I was well and equally tolerated in a recent pilot study in 13 dialysis patients, including 8 patients with cirrhosis, without sofosbuvir or its metabolite SOF-007 accumulation [28]. Additional clinical trials of DAAs in late CKD are definitely needed.

Finally, the KDIGO guidelines recommend only standard IFN for HCV-infected kidney transplant recipients: this has to be updated since the SVR-associated benefits clearly outweigh the risks [20]. Published data on DAAs in kidney transplant recipients are scarce. Our anecdotal results with compassionate use are excellent, and two recent pilot studies reported 100% SVR in kidney transplant recipients treated with sofosbuvir-based antiviral therapy with or without ribavirin [29, 30]. We are waiting for the results of an international trial combining sofosbuvir and ledipasvir for 12 or 24 weeks in renal transplant recipients with GFR >40 mL/min. The HCV-infected kidney recipients have to be rapidly treated given the high risk of both liver- and extra-hepatic-related mortality. In HBV-infected kidney recipients treated with antivirals, sustained viral suppression has been associated with a dramatic reduction of liver-related mortality: same results are expected in HCV infected patients using DAAs [23].

In conclusion, awaiting the update of the KDIGO recommendations on HCV in CKD, we summarize here the major recent changes in the field. Liver fibrosis in HCV-infected patients with stage 4–5 CKD should be evaluated mostly non-invasively. Patients have to be treated either if they have symptomatic vasculitis, or if they are kidney recipients. Hemodialysis patients should be considered for antiviral therapy, whether or not they are candidates to renal transplantation and whether or not they have significant fibrosis. In those with no significant fibrosis treatment may be postponed to the post-transplantation period which may allow to be transplanted earlier with an HCV-infected graft [31].

CONFLICT OF INTEREST STATEMENT

S. P. has received consulting and lecturing fees from Bristol-Myers Squibb, Boehringer Ingelheim, Janssen, Vertex, Gilead, Roche, MSD, Novartis, Abbvie, Sanofi and Glaxo Smith Kline, and grants from Bristol-Myers Squibb, Gilead, Roche and MSD. M. J. is co-chair of the KDIGO workgroup updating the HCV in CKD guidelines. He has been a speaker and Administrative Board member for Merck Sharp & Dohme. A. V.-P. has received lecturing fees from Bristol-Myers Squibb, Janssen, Gilead, Roche, MSD, Abbvie and consulting fees from Janssen.

REFERENCES

- European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of hepatitis C infection. *J Hepatol* 2011; 55: 245–264
- Gordon CE, Francis J. Hepatitis C treatment in dialysis patients: is a new dawn approaching? *Am J Kidney Dis* 2014; 64: 178–180
- European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C 2015. *J Hepatol* 2015; 63: 199–236
- Su F-H, Su CT, Chang SN *et al.* Association of hepatitis C virus infection with risk of ESRD: a population-based study. *Am J Kidney Dis* 2012; 60: 553–560
- Lee MH, Yang HI, Lu SN *et al.* Chronic hepatitis C virus infection increases mortality from hepatic and extrahepatic diseases: a community-based long-term prospective study. *J Infect Dis* 2012; 206: 469–477
- Molnar MZ, Alhourani HM, Wall BM *et al.* Association of hepatitis C viral infection with incidence and progression of chronic kidney disease in a large cohort of US veterans. *Hepatology* 2015; 61: 1495–1502
- Park H, Adeyemi A, Henry L *et al.* A meta-analytic assessment of the risk of chronic kidney disease in patients with chronic hepatitis C virus infection. *J Viral Hepat* 2015; 22: 897–905
- Hsu YC, Ho HJ, Huang YT *et al.* Association between antiviral treatment and extrahepatic outcomes in patients with hepatitis C virus infection. *Gut* 2015; 64: 495–503
- Fissell R, Bragg-Gresham J, Woods J *et al.* Patterns of hepatitis C prevalence and seroconversion in hemodialysis units from three continents: the DOPPS. *Kidney Int* 2004; 65: 2335–2342
- Thompson ND, Perz JF, Moorman AC *et al.* Nonhospital health care-associated hepatitis B and C virus transmission: United States, 1998–2008. *Ann Intern Med* 2009; 150: 33–39
- Sauné K, Kamar N, Miédouké M *et al.* Decreased prevalence and incidence of HCV markers in haemodialysis units: a multicentric French survey. *Nephrol Dial Transplant* 2011; 26: 2309–2316
- Kidney Disease: Improving Global Outcomes. KDIGO clinical practice guidelines for the prevention, diagnosis, evaluation, and treatment of hepatitis C in chronic kidney disease. *Kidney Int Suppl* 2008; 109: S1–S99
- Goodkin DA, Bragg-Gresham J, Koenig KG *et al.* Association of comorbid conditions and mortality in haemodialysis patients in Europe, Japan, and the United States: the Dialysis Outcomes and Practice Patterns Study (DOPPS). *J Am Soc Nephrol* 2003; 14: 3270–3277
- Fabrizi F, Dixit V, Messa P. Impact of hepatitis C on survival in dialysis patients: a link with cardiovascular mortality? *J Viral Hepat* 2012; 19: 601–607
- Fabrizi F, Takkouche B, Lunghi G *et al.* The impact of hepatitis C virus infection on survival in dialysis patients: meta-analysis of observational studies. *J Viral Hepat* 2007; 14: 697–703
- Fabrizi F, Martin P, Dixit V *et al.* Hepatitis C virus antibody status and survival after renal transplantation: meta-analysis of observational studies. *Am J Transplant* 2005; 5: 1452–1461
- Scott DR, Wong JK, Spicer TS *et al.* Adverse impact of hepatitis C virus infection on renal replacement therapy and renal transplant patients in Australia and New Zealand. *Transplantation* 2010; 90: 1165–1171
- Morales JM, Pascual-Capdevila J, Campistol JM *et al.* Membranous glomerulonephritis associated with hepatitis C virus infection in renal transplant patients. *Transplantation* 1997; 63: 1634–1639
- Cruzado J, Carrera M, Torras J *et al.* Hepatitis C virus infection and de novo glomerular lesions in renal allografts. *Am J Transplant* 2001; 1: 171–178
- Hoffmann CJ, Subramanian AK, Cameron AM *et al.* Incidence and risk factors for hepatocellular carcinoma after solid organ transplantation. *Transplantation* 2008; 86: 784–790
- Kidney Disease: Improving Global Outcomes. Clinical practice guideline for the care of kidney transplant recipients. *Am J Transplant* 2009; 9(Suppl 3): S52–S57
- Jadoul M, Horsmans Y. Impact of liver fibrosis staging in hepatitis C virus (HCV) patients with kidney failure. *Nephrol Dial Transplant* 2014; 29: 1108–1110
- Coscone S, Fontaine H, Meritet JF *et al.* Benefits associated with antiviral treatment in kidney allograft recipients with chronic hepatitis B virus infection. *J Hepatol* 2015; 57: 55–60
- Goodkin DA, Bieber B, Gillespie B *et al.* Hepatitis C infection is very rarely treated among hemodialysis patients. *Am J Nephrol* 2013; 38: 405–412
- Roth D, Nelson D, Burchfield A *et al.* Grazoprevir plus elbasvir in treatment-naïve and treatment-experienced patients with hepatitis C virus genotype 1 infection and stage 4–5 chronic kidney disease (the C-SURFER Study): a combination phase 3 study. *Lancet* 2015; 386: 1537–1545
- Gane EJ, Robson RA, Bonacini M *et al.* Safety, and anti-viral efficacy and pharmacokinetics (PK) of sofosbuvir (SOF) in patients with severe renal impairment [abstract]. *Hepatology* 2014; 60: 133A
- Saxena V, Korashy FM, Sise M *et al.* Safety and efficacy of sofosbuvir-containing regimens in hepatitis C infected patients with reduced renal function: real-world experience from HCV-target [abstract]. *J Hepatol* 2015; 62: LP08 S267

28. Desnoyer A, Pospai D, Le MP *et al.* Sofosbuvir in hemodialysis: 400 mg daily or only the day of hemodialysis. 16th International Workshop on Clinical Pharmacology of HIV and Hepatitis Therapy, 28 May 2015, Washington, DC, USA.
29. Kamar N, Marion O, Rostaing L *et al.* Efficacy and safety of sofosbuvir-based antiviral therapy to treat hepatitis C infection after kidney transplantation. *Am J Transplant* 20 Nov 2015; doi:10.1111/ajt.13518
30. Sawinski D, Kaur N, Ajeta A *et al.* Successful treatment on hepatitis C in renal transplant recipients with direct-acting antiviral agents. *Am J Transplant* 5 Feb 2016; doi:10.1111/ajt.13620
31. Jadoul M, Horsmans Y. Towards eradication of the hepatitis C virus from dialysis units? *Lancet* 2015; 386:1514–1515

Received for publication: 2.12.2015; Accepted in revised form: 25.12.2015

Nephrol Dial Transplant (2017) 32: 35–41
doi: 10.1093/ndt/gfv361
Advance Access publication 19 October 2015

A review of direct-acting antivirals for the treatment of hepatitis C in patients with advanced chronic kidney disease

Anna Maruyama¹, Nilufar Partovi², Eric M. Yoshida³, Siegfried R. Erb³, Vladimir Marquez Azalgara³ and Trana Hussaini⁴

¹Pharmaceutical Sciences, University of British Columbia, Vancouver, BC, Canada, ²Pharmaceutical Sciences, Vancouver General Hospital, Vancouver, BC, Canada, ³The Division of Gastroenterology, Vancouver General Hospital, Vancouver, BC, Canada and ⁴Pharmaceutical Sciences Clinical Service Unit, Vancouver General Hospital, Vancouver, BC, Canada

Correspondence and offprint requests to: Trana Hussaini; E-mail: trana.hussaini@vch.ca

ABSTRACT

Historically, standard treatment of hepatitis C virus (HCV) infection in patients with renal impairment has been limited by low cure rates and poor tolerability. The introduction of direct-acting antivirals (DAAs) has revolutionized the treatment of HCV with impressive cure rates >90% and low rates of adverse events. Despite these major advancements, treatment of patients with HCV and advanced chronic kidney disease (CKD) is a major challenge due to the lack of efficacy and safety data in this patient population. The purpose of this review is to summarize the available data for efficacy and safety of the following DAAs in treating HCV patients with advanced Stage 4 and 5 CKD: simeprevir, sofosbuvir, ledipasvir, ombitasvir, paritaprevir, dasabuvir, grazoprevir, elbasvir and daclatasvir.

Keywords: chronic renal failure, CKD, direct-acting antivirals, ESRD, hepatitis C

INTRODUCTION

Hepatitis C virus (HCV) infection is a leading cause of chronic liver disease, affecting >170 million people worldwide [1–3], and HCV infection in the setting of renal impairment is not uncommon. For more than a decade, standard

treatment for HCV infection in patients with advanced chronic kidney disease [CKD Stage 4 or 5 with a glomerular filtration rate (GFR) <30 mL/min] consisted of peginterferon (PEG) alone or in combination with ribavirin (RBV) [4]. Unfortunately, both regimens have been associated with poor virologic response rates and intolerable adverse effects, requiring dosage adjustments and careful monitoring, especially in those with end-stage renal disease (ESRD) [1]. The use of RBV, which remains a component of some interferon-free antiviral regimens, is particularly challenging in advanced renal disease. RBV, which is renally eliminated, will accumulate in the setting of renal dysfunction, compounding its severe adverse events, including hemolytic anemia. RBV dosing, therefore, must be dramatically curtailed in advanced CKD from the standard dosages of 800–1200 mg/day to as little as 200 mg thrice weekly to daily [5, 6]. Moreover, RBV is poorly removed by hemodialysis (HD) [7].

Recently, there have been major advancements in the treatment of HCV with the development of new direct-acting antivirals (DAAs), which have shown impressive sustained virologic responses (SVRs) >90% and few adverse effects with as short as 8–12 weeks of therapy. Despite these major advancements, treatment of patients with HCV and advanced CKD remains a major challenge due to the lack of reported efficacy and safety data of DAAs in this patient population. Adding to this