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Full Review

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

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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 DDAs 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 1 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.

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