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Review Article

New Oral Direct-Acting Antiviral Agents for Treatment of Chronic Hepatitis-C Infection in Patients with Chronic Kidney Disease Including Dialysis Patients and Kidney Transplant Recipients

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Abstract

Chronic Hepatitis-C Virus (HCV) infection is associated with increased morbidity and mortality among patients with Chronic Kidney Disease (CKD), Hemodialysis (HD) patients and Kidney Transplant (KT) recipients. HCV infection is a frequent consequence of CKD. Blood transfusions (before effective screening of blood donors for HCV was instituted), nosocomial transmission in dialysis units, and transmission by kidney grafts all have contributed to the much higher prevalence of HCV infection in CKD Stage 5D and transplant patients than in the general population. Evaluation of HCV-positive/ End-Stage Renal Disease (ESRD) and HCV-positive/KT patients is warranted to determine the stage of disease and the appropriateness of antiviral therapy, despite such treatment is challenging especially due to tolerability issues. Treatment of such patients with conventional treatment which consists of pegylated- interferon and ribavirin is very rare and has more serious side effects. With the evolution of the new Direct-Acting Antiviral Drugs (DAAs), new DAAs treatments for HCV are more effective, easier to take and have fewer side-effects than older treatments. The treatment of such patients with the new DAAs can be done with Sustained Virologic Response (SVR) more than 90%. In this study, we review the FDA approved new DAAs such as sofosbufir (sofaldi), simeprevir (Olysio), sofosbuvir (sofaldi), ledipasvir and sofosbuvir (Harvoni), sofosbuvir and velpatasvir (Epclusa), dasabuvir, ombitasvir, paritaprevir,and ritonavir (Viekira Pak), grazoprevir and elbasvir (zepatier), and daclatasvir and ribavirin and their potential use among patients with CKD, HD patients and KT recipients.

Introduction

Hepatitis-C Virus (HCV) was recognized as an important cause and consequence of Chronic Kidney Disease (CKD). Indeed, HCV is a significant cause of some forms of Glomerulonephritis (GN), especially Membranoproliferative GN (MPGN) [1,2] and mixed essential cryoglobulinemia with renal damage [3].

In addition, HCV infection is a frequent consequence of CKD. Blood transfusions (before effective screening of blood donors for HCV was instituted), nosocomial transmission in dialysis units, and transmission by kidney grafts all have contributed to the much higher prevalence of HCV infection in CKD Stage 5D and transplant patients than in the general population [4].

As in the general population, the prevalence of HCV in CKD Stage 5D patients varies worldwide, ranging from as low as 1% to as high as over 70%. Overall, the current prevalence of HCV is below 5% in most of Northern Europe, around 10% in most of Southern Europe and the US, between 10 to 50% and up to 70% in many parts of the developing world, including many Asian, Latin American, and North African countries [5-9].

Not surprisingly, the prevalence of HCV infection in CKD transplant patients is also high. Consistent risk factors include the total time spent on dialysis, a history of and/or the number of blood transfusions and transmission by kidney grafts. The prevalence in a given population of CKD transplant patients parallels the prevalence in the general population of the same country or region. Recent population-based estimates of the prevalence of HCV infection in CKD transplant patients are not available [4].

Even less is known of the prevalence of HCV in the various stages of CKD before dialysis or transplantation. It is, however, apparent from several case series-admittedly relatively small-sized-that patients with CKD Stages 3-5 have a disproportionately high prevalence of HCV infection compared with the general population [4].

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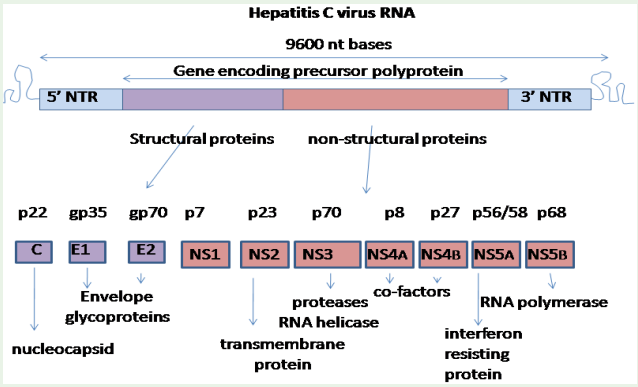

Figure 1: HCV RNA structure.

Multiple studies have shown an independent and significant association between HCV positivity and lower patient survival, despite adjustment for a number of comorbid conditions. The major complications of HCV related chronic liver disease (cirrhosis and hepatocellular carcinoma) have been implicated in the lower survival of anti-HCV-positive CKD Stage 5D patients [10-12]. Similarly, HCV infected CKD transplant patients have lower long-term graft and patient survival than uninfected CKD transplant patients [12]. In addition, the presence of HCV RNA in CKD transplant patients has been implicated in the development of post-transplant immune complex GN and a higher incidence of post-transplant diabetes mellitus. Very little is known of the natural history of chronic HCV infection and its prognostic impact in the earlier stages of CKD [4].

HCV infection has very rarely been treated among Hemodialysis (HD) patients internationally (1%) and they continue to go untreated even following the introduction of new, improved Direct-Acting Antiviral Agents (DAAs), despite a prevalence of 9.5% and the fact that infection is associated with hepatic complications and increased mortality [10-13]. Kidney Disease Improving Global Outcome (KDIGO) has recommended that HCV-infected HD patients awaiting renal transplantation should be treated and that other infected patients should be assessed on a case-by-case basis [4]. The undesirable side effects of traditional therapy with parenteral interferon and sometimes ribavirin, including fatigue, depression, and severe anemia, had to be weighed against the potential benefits. However, newer, oral DAAs have now been shown to have far higher viral response/cure rates and fewer side effects.

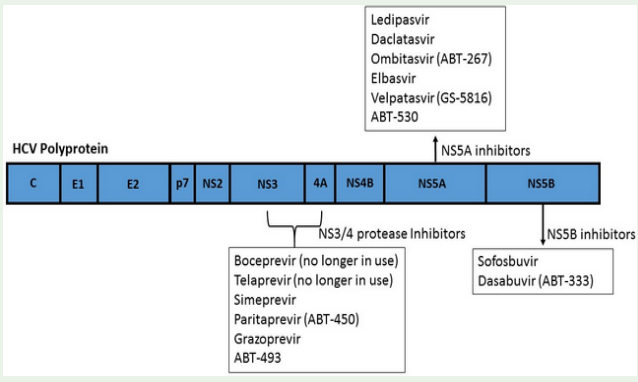

Figure 2: Molecular targets for new HCV direct-acting antiviral agents.

HCV is an enveloped, single-strand, positive-sense, RNA virus containing up to 9600 nucleotides that undergoes proteolytic cleavage [14]. The resultant components include two structural envelope glycoproteins and the core protein. The remainder components are non-structural proteins (NS2, NS3, NS4A, NS4B, NS5A, and NS5B) that are necessary for viral replication. NS2/3 and NS3/4A comprise proteases responsible for cleaving the HCV polyprotein [15]. NS5B is an RNA dependent RNA polymerase required for viral replication. NS5A is involved in assembly of the cytoplasmic membrane-bound replication complex (Figure 1). A greater understanding of the HCV genome and proteins has enabled efforts to improve efficacy and tolerability of HCV treatment. Notably, this has led to the development of multiple DAAs, which are medications are that target specific nonstructural proteins of the virus (Figure 2) and results in disruption of viral replication and infection. There are four classes of DAAs, which are defined by their mechanism of action and therapeutic target. The four classes are Nonstructural Proteins 3/4A (NS3/4A) Protease Inhibitors (PIs), NS5B nucleoside polymerase inhibitors (NPIs), NS5B Non-Nucleoside Polymerase Inhibitors (NNPIs), and NS5A inhibitors [16,17]. In this study, we review the FDA approved new DAAs such as sofosbufir (sofaldi), simeprevir (Olysio), sofosbuvir (sofaldi), ledipasvir and sofosbuvir (Harvoni), sofosbuvir and velpatasvir (Epclusa), dasabuvir, ombitasvir, paritaprevir,and ritonavir (Viekira Pak), grazoprevir and elbasvir (zepatier), and daclatasvir and ribavirin and their potential use among patients with CKD, HD patients and KT recipients.

FDA approved new oral DAAs and ribavirin

Direct-Acting Antivirals (DAAs), also known as "Specifically Targeted Antiviral Therapy for Hepatitis C" (STAT-C), are the most important new therapeutical options for HCV. There are different kinds of DAAs that interfere at different stages of the replication cycle.

Boceprevir (Victrelis) and Telaprevir (Incivek)

Boceprevir (Victrelis) is a PI used to treat HCV Genotype (GT) 1 [18,19]. It binds to the HCV nonstructural protein 3 active site [20]. It was approved by the FDA in May 2011 [21].

Telaprevir (Incivek) inhibits the HCV NS3.4A serine protease [22]. Telaprevir is only indicated for use against HCV GT1. It was approved by the FDA in August 2011. Telaprevir (3 tablet (tablet 375 mg) twice daily) and boceprevir (800 mg (capsule 200 mg) three times daily) are new medications that can be added to a Pegylated-Interferon/Ribavirin (PEG-IFN/RBV) regimen for people with GT 1 HCV mono-infection. Telaprevir and boceprevir are not prescribed on their own (without Peg-IFN/RBV) and they are not prescribed together.

However, these new drugs have very rarely been studied in patients with renal impairment. Boceprevir and telaprevir are metabolized in the liver, and renal clearance contributes minimally to the elimination of these drugs. Therefore, it is not expected that renal impairment will have an important influence on the pharmacokinetics of HCV PIs. No clinically significant difference in the pharmacokinetic parameters of boceprevir was observed between patients with End-Stage Renal Disease (ESRD) and healthy subjects, so there appears to be no dose adjustment required [23].

Recently, Durmortier et al., reported four ESRD patients with HCV GT1b who did not respond to a prior course of PEG-IFN and

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RBV; while awaiting Kidney Transplantation (KTx), they received a second-line antiviral regimen of PEG-IFN, RBV, and telaprevir. After 12 weeks of therapy, tolerance was acceptable and HCV-RNA became undetectable in three of the four patients [24].

In a small study, 16 GT 1 HCV patients with ESRD, awaiting KTx at two centers. All patients received PEG-IFN, RBV, and either boceprevir or telaprevir. The study demonstrated that 44% of patients on triple therapy achieved viral eradication with minimal side effects, irrespective of the form of PI therapy. In comparison to prior studies, the Sustained Virologic Response (SVR) is considerably lower than conventional therapy with PEG-IFN/RBV therapy and small population size may have played a major factor in the lack of efficacy [25].

Although boceprevir and telaprevir were promising DAAs that had impact in HCV treatment field during 2011 to 2013, they were subsequently replaced by newer DAAs that were more effective, better tolerated, and more convenient. Vertex pharmaceuticals discontinued the sales and distribution of telaprevir in the United States in October 2014 [26] and in January 2015, Merck announced that they would be voluntarily withdrawing boceprevir from the market due to the overwhelming superiority of newer direct-acting antiviral agents, such as ledipasvir/sofosbuvir [27].

Simeprevir (Olysio)

Simeprevir has provided an excellent alternative to the older first-generation NS3/4A PIs (boceprevir and telaprevir) for the treatment of patients with GT 1 HCV. Simeprevir is convenient (150 mg once-daily dosing), well-tolerated, and has less extensive drug-drug interactions than the first-generation PIs [28]. It was approved by the FDA in November 22nd, 2013.

No dose adjustment of simeprevir is required in patients with mild, moderate or severe renal impairment. The safety and efficacy of simeprevir have not been studied in patients with a creatinine clearance below 30 ml/min or ESRD, including patients on dialysis. However, because simeprevir is highly protein bound, dialysis is unlikely to result in significant removal of simeprevir [29].

No dose changes are required when used in combination with the immunosuppressants tacrolimus and sirolimus, although routine monitoring of blood concentrations of the immunosuppressant is recommended. In contrast, the use of simeprevir with cyclosporine resulted in significantly increased plasma concentrations of simeprevir (due to hepatic uptake transporter inhibition), such that it is not recommended to co-administer the drugs.

However, the combination of simeprevir plus PEG-IFN/RBV for GT 1 is no longer a recommended, primarily because of the toxicity and long duration of treatment associated with the use of PEG-IFN/RBV. In contrast, the combination of simprevir and sofosbuvir, with or without RBV in patients with GT 1 has been very well tolerated and has generated overall SVR12 rates greater than 90% [30].

Sofosbuvir (sofaldi)

Sofosbuvi Inhibits the NS5B RNA polymerase that HCV uses to replicate its RNA. It was FDA approved in December, 2013). Sofosbuvir is used for the treatment of chronic HCV, genotypes 1, 2, 3, 4, 5, and 6, usually in combination with other medications depending on the specific GT. For the treatment of genotypes 1, 4, 5, and 6, sofosbuvir is used in combination with the viral NS5A inhibitor ledipasvir. For the treatment of other genotypes, sofosbuvir is used in combination with weight-based RBV alone in GT 2 HCV and together with PEG-IFN in GT 3 HCV infections [31].

In 2016, the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) jointly published a recommendation for the management of HCV. In this recommendation, sofosbuvir and ledipasvir, or sofosbuvir and RBV, with or without PEG-IFN, are parts of all first-line treatments for HCV genotypes 1 to 6, and are also parts of some second-line treatments [31].

Sofosbuvir should be administered at the dose of 400 mg (one tablet) once per day, with or without food. Approximately 80% of sofosbuvir is renally excreted, whereas 15% is excreted in faeces. The majority of the sofosbuvir dose recovered in urine is the dephosphorylation-derived nucleoside metabolite GS-331007 (78%), while 3.5% is recovered as sofosbuvir. Renal clearance is the major elimination pathway for GS-331007 with a large part actively secreted. Thus, currently, no sofosbuvir dose recommendation can be given for patients with severe renal impairment with estimated glomerular filtration rate (eGFR <30 ml/min/1.73 m2) or with ESRD due to higher exposures (up to 20-fold) of GS-331007. Sofosbuvir exposure is not significantly changed in patients with mild liver impairment, but it is increased 2.3-fold in those with moderate liver impairment [30].

Sofosbuvir is well tolerated over 12 to 24 weeks of administration. The most common adverse events observed in combination with RBV were fatigue and headache. The most common adverse events observed in combination with PEG-IFN-a and RBV were fatigue, headache, nausea, insomnia and anaemia. Slight elevations of creatine kinase, amylase and lipase without clinical impact were also observed [30].

Ledipasvir and sofosbuvir (Harvoni)

Two-drug combination for the treatment of HCV. It is administered as a single daily pill containing 90 mg of NS5A inhibitor ledipasvir and 400 mg of sofosbuvir, a nucleotide inhibitor of the viral RNA polymerase NS5B.

Ledipasvir/sofosbuvir was FDA approved and developed by the pharmaceutical company Gilead Sciences and first marketed in October 2014. Taken daily for 8–12 weeks, it provides cure rates of 94% to 99% in people infected with GT 1, the most common form of HCV in the U.S. and some European countries, irrespective of the presence or absence of liver cirrhosis or prior unsuccessful treatment. It has also been evaluated for the treatment of infection with other HCV genotypes, and has shown promising results in genotypes 3 and 4 [32,33].

Biliary excretion of unchanged ledipasvir is the major route of elimination with renal excretion being a minor pathway (approximately 1%), whereas sofosbuvir is principally renally excreted, as noted above. The median terminal half-lives of sofosbuvir and its predominant metabolite GS-331007 following administration of sofosbuvir/ledipasvir were 0.5 and 27 h, respectively. Neither sofosbuvir nor ledipasvir are substrates for hepatic uptake transporters; GS-331007 is not a substrate for renal transporters [30].

Ledipasvir plasma exposure (AUC) was similar in patients with severe hepatic impairment and control patients with normal hepatic function. Population pharmacokinetics analysis in HCV infected patients indicated that cirrhosis (including decompensated cirrhosis) had no clinically relevant effect on the exposure to ledipasvir [30].

While no dose adjustment of sofosbuvir and ledipasvir is required for patients with mild or moderate renal impairment, the safety of the sofosbuvir-ledipasvir combination has not been assessed in patients with severe renal impairment (eGFR <30 ml/ min/1.73 m2) or ESRD requiring HD. Relative to patients with normal renal function (eGFR >80 ml/min/1.73 m2), the sofosbuvir area under cuve (AUC) was 61%, 107% and 171% higher in patients with mild, moderate and severe renal impairment, while the GS-331007 AUC was 55%, 88% and 451% higher, respectively. Thus, no dose adjustment is required for patients with mild or moderate renal impairment, but no dose recommendation can currently be given for patients with severe renal impairment (eGFR <30 ml/min/1.73 m2) or with ESRD [30].

The most common adverse reactions reported with this combination were fatigue and headache.

Sofosbuvir and velpatasvir (Epclusa)

Gilead's Epclusa® FDA approved June 28,2016 is a once-daily, fixed-dose combination of Sovaldi with velpatasvir (GS-5816) a pangenotypic NS5A inhibitor, for the treatment of genotypes 1-6 chronic HCV infection.

Sofosbuvir and velpatasvir are available in a two-drug fixed-dose combination containing 400 mg of sofosbuvir and 100 mg of velpatasvir in a single tablet. The recommended dose of the combination is one tablet taken orally once daily with or without food [30].

Velpatasvir is metabolised in vitro by CYP2B6, CYP2C8 and CYP3A4. However, due to the slow turnover, the vast majority of drug in plasma is the parent drug. Biliary excretion of the parent drug is the major route of elimination. The median terminal half-life of velpatasvir following administration of sofosbuvir and velpatasvir is approximately 15 h.

Velpatasvir plasma exposure (AUC) is similar in subjects with moderate and severe hepatic impairment compared to subjects with normal hepatic function. Cirrhosis (including decompensated cirrhosis) has no clinically relevant effect on velpatasvir exposure in a population pharmacokinetic analysis in HCV infected subjects.

The pharmacokinetics of velpatasvir were studied in HCV negative patients with severe renal impairment (eGFR <30 ml/ min/1.73 m2). Relative to subjects with normal renal function, velpatasvir AUC was 50% higher and this was not considered to be clinically relevant [30].

The safety assessment of sofosbuvir and velpatasvir was based on pooled Phase III data. Headache, fatigue and nausea were the most commonly reported adverse events, at a similar frequency to placebo-treated patients [30].

Dasabuvir, ombitasvir, paritaprevir,and ritonavir (Viekira Pak)

On December 19, 2014, FDA approved VIEKIRA Pak (ombitasvir, paritaprevir, ritonavir fixed dose combination tablets copackaged with dasabuvir tablets) for use with or without RBV for the treatment of patients with GT 1 HCV infection including those with compensated cirrhosis.

July 25, 2016, FDA approved a New Drug Application (NDA) for VIEKIRA XR™ (dasabuvir, ombitasvir, paritaprevir and ritonavir; PrOD) VIEKIRA XR is a once-daily, extended-release co-formulation of the active ingredients in VIEKIRA PAK® (ombitasvir, paritaprevir, and ritonavir tablets; dasabuvir tablets) and is for the treatment of patients with chronic GT1 HCV infection, including those with compensated cirrhosis (Child-Pugh A). VIEKIRA XR is not for people with decompensated cirrhosis.

Currently, VIEKIRA PAK is taken twice daily as three tablets in the morning and one tablet in the evening, taken with a meal. **VIEKIRA XR** *fixed-dose formulation is given once-daily as three oral tablets and must be taken with a meal.*

Paritaprevir is an NS3-4A PI which is metabolized primarily by CYP3A4 and is given with a low dose of the CYP3A inhibitor ritonavir as a pharmacokinetic enhancer. This enables once daily administration and a lower dose than would be required without ritonavir. Ombitasvir is an NS5A inhibitor given in a fixed-dose combination with paritaprevir/ritonavir.

The recommended dose of this combination is two tablets of ritonavir/ paritaprevir/ombitasvir (50 mg/75 mg/12.5 mg per tablet) taken orally once daily with food. Dasabuvir is a non-nucleoside inhibitor of HCV RNA-dependent RNA polymerase (NS5B) in 250 mg tablets administered twice daily in combination with ritonavir/ paritaprevir/ombitasvir in GT 1 patients.

Paritaprevir is excreted predominantly into the faeces. Ombitasvir shows linear kinetics, and is predominantly eliminated in the faeces. Dasabuvir is metabolised in the liver, and its predominant metabolite is mainly cleared via biliary excretion and faecal elimination with minimal renal clearance [30].

The AUC of paritaprevir was increased 45% in patients with severe renal impairment (creatinine clearance 15–29 ml/min), that of ritonavir 114%, and dasabuvir 50%. Currently, no dose adjustment is required for patients with mild, moderate or severe renal impairment. Whether paritaprevir, ombitasvir and/or dasabuvir are partly removed by dialysis is unknown [30]. The most common side effects reported with the combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir were fatigue and nausea.

Grazoprevir and elbasvir (zepatier)

January 28, 2016-FDA approved Zepatier (Grazoprevir and elbasvir) with or without RBV for treatment of chronic HCV GT 1 and 4 in adult patients.

Grazoprevir and elbasvir are available in a two-drug fixed-dose combination containing 100 mg of grazoprevir and 50 mg of elbasvir in a single tablet. The recommended dose of the combination is one tablet taken orally once daily with or without food. Grazoprevir and elbasvir are partially metabolized by CYP3A4, but no circulating metabolites are detected in plasma. The principal route of elimination is biliary and faecal with <1% recovered in urine. Grazoprevir is transported by P-gp and OATP1B1, while elbasvir is a substrate for P-gp. Both elbasvir (>99.9%) and grazoprevir (98.8%) are extensively bound to plasma proteins. The terminal half-life values are approximately 24 and 31 h, respectively [30].

No dose adjustment is required in patients with mild, moderate of severe renal impairment (including patients on HD or peritoneal dialysis). There is an increase in elbasvir (65%) and grazoprevir (86%) exposure in non-HCV infected subjects with an eGFR <30 ml/min/1.73 m2, but this is not considered to be clinically significant [30].

The safety of elbasvir/grazoprevir is based on Phase II and III clinical studies with the most commonly reported adverse reactions being fatigue and headache. Rare cases (0.8%) of substantial ALT level elevations were reported, slightly more frequently in female, Asian and elderly patients. Less than 1% of subjects treated with elbasvir/grazoprevir with or without RBV discontinued treatment due to adverse events.

Daclatasvir

July 24, 2015-FDA approved daclatasvir (daklinza) for the treatment of chronic HCV GT 3. Daklinza (daclatasvir), an NS5A replication complex inhibitor is indicated for use with sofosbuvir for the treatment of patients with chronic HCV GT 3 infection. SVR rates are reduced in HCV GT 3-infected patients with cirrhosis receiving this regimen. The recommended dosage of daklinza is 60 mg, taken orally, once daily in combination with sofosbuvir for 12 weeks. daklinza may be taken with or without food.The optimal duration of daklinza and sofosbuvir for patients with cirrhosis has not been established.

Daclatasvir should be administered at the dose of 60 mg (one tablet), or 30 mg (one tablet) when a reduced dose is needed, once per day with or without food. Approximately 90% of daclatasvir is eliminated in faeces (half as unchanged drug) and less than 10% is excreted in the urine (primarily as unchanged drug).

The pharmacokinetics of daclatasvir following a single 60 mg oral dose has been studied in non-HCV infected subjects with renal impairment. Daclatasvir unbound AUC was estimated to be 18%, 39% and 51% higher for subjects with creatinine clearance values of 60, 30 and 15 ml/min, respectively, relative to subjects.

With normal renal function. Subjects requiring HD had a 27% increase in daclatasvir AUC and a 20% increase in unbound AUC compared to subjects with normal renal function. Thus, no dose adjustment of daclatasvir is required for patients with any degree of renal impairment [30].

The most frequently reported side effects with daclatasvir were fatigue, headache and nausea.

Ribavirin (RBV)

The RBV dose should be 1000 or 1200 mg/day, based on body weight (<75 kg or >75kg, respectively), split in two administrations.

The main side effects associated with the administration of RBV are rash, cough, and haemolytic anaemia, which can be managed by stepwise dose reductions. RBV has a low potential for drug-drug interactions, and dose adjustment is needed in patients with severe renal insufficiency or ESRD who need ribavirin [30].

Approved HCV DAAs drugs in Europe in 2016 and ribavirin and IFN-free combination treatment regimens available as valuable options for each HCV genotype are shown in table 1 & 2.

New DAAs therapy in patients with renal impairment

A recent study (C-SURFER) evaluated the safety and efficacy of 12 weeks of a second-generation NS3/NS4A PI, grazoprevir (100 mg once daily) and an NS5A inhibitor; elbasvir (50 mg once daily) versus placebo for HCV GT 1 patients with CKD stages 4/5. The original study was designed to randomize eligible patients to either immediate or deferred treatment with elbasvir and grazoprevir. The delayed treatment arm received placebo and was treated with elbasvir and grazoprevir later. The data for the immediate treatment arm have been published [34]. The study participants were HCV GT1, CKD stages 4/5 (eGFR <30 mL/min/1.73 m^2), 75% on HD, 45% were African Americans. Small numbers of patients with compensated cirrhosis were allowed. The study reported an ITT and modified ITT of 94% and 99% for SVR12. There were no changes in hemoglobin or other adverse events or erythropoietin use in the treatment groups compared to placebo, while most patients in the treatment group normalized ALT and AST values compared to placebo. None of the GT 1a patients with baseline NS5A RAVs experienced viral relapse; the only reported relapse occurred in a patient with GT 1b. The basis for the lack of impact of NS5A RAVs on SVR rates in this population is unclear, but may relate to moderately increased AUCs of grazoprevir

Table 1: Approved HCV DAAs drugs in Europe in 2016 and ribavirin (adapted from reference 30).

Product	Presentation	Posology
Sofosbuvir	Tablets containing 400mg of sofosbuvir	One tablet once daily(morning)
Sofosbuvir/ledipasvir	Tablets containing 400mg of sofosbuvir and 90mg of ledipasvir	One tablet once daily(morning)
Sofosbuvir/velpatasvir	Tablets containing 400mg of sofosbuvir and 100mg of velpatasvir	One tablet once daily(morning)
Paritaprevir/ombitasvir/ritonavir	Tablets containing 75mg of Paritaprevir, 12.5mg of ombitasvir and 50mg of ritonavir	Two tablets once daily(morning)
Dasabuvir	Tablets containing 250mg of Dasabuvir	One tablet twice daily(morning and evening)
Grazoprevir/elbasvir	Tablets containing 100mg of Grazoprevir and 50mg of elbasvir	One tablet once daily(morning)
Daclatasvir	Tablets containing 30 or 60mg of Daclatasvir	One tablet once daily(morning)
Simeprevir	Capsules containing 150mg of Simeprevir	One capsule once daily(morning)
Ribavirin	Capsules containing 200mg of Ribavirin	Two capsules in the morning and 3 in the evening if body weight<75 kg Or Three capsules in the morning and 3 in the evening if body weight≥75 kg (or less if does reduction needed)

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Table 2: IFN-free combination treatment regimens available as valuable options for each HCV genotype (adapted from reference 20).

Combination regimen	Genotype 1	Genotype 2	Genotype 3	Genotype 4	Genotype 5 and 6
Sofosbuvir+ribavirin	No	Suboptimal	Suboptimal	No	No
Sofosbuvir/ledipasvir±ribavirin	Yes	No	No	Yes	Yes
Sofosbuvir/velpatasvir± ribavirin	Yes	Yes	Yes	Yes	Yes
Ombitasvir/paritaprevir/ritonavir+dasabuvir±ribavirin	Yes	No	No	No	No
Ombitasvir/ paritaprevir/ritonavir± ribavirin	No	No	No	Yes	No
Grazoprevir/elbasvir±ribavirin	Yes	No	No	Yes	No
Sofosbuvir+dadatasvir±ribavirin	Yes	Yes	Yes	Yes	Yes
Sofosbuvir+simeprevir±ribavirin	Suboptimal	No	No	Yes	No

or elbasvir observed in stage 4/5 CKD [35]. Based on these data, the fixed-dose combination elbasvir (50 mg) and grazoprevir (100 mg) (thereafter, elbasvir/grazoprevir) is recommended for the treatment of HCV GT 1 infection in patients with severely compromised renal function. No strong recommendation for NS5A RAV testing can be made in this population. While C-SURFER did not evaluate patients with GT 4 infection, it is likely that the high efficacy of elbasvir/grazoprevir in GT 1 and 4 infections in persons with normal renal function can be extrapolated to genotype 4-infected persons with CKD stage 4/5.

Sofosbuvir and RBV are renally eliminated. Safe and effective doses of sofosbuvir in those with eGFR less than 30 mL/min/1.73 m^2 have not been established. Though recommendations exist for reducing RBV dose and/or dosing frequency in those with renal impairment, this drug is poorly tolerated in this population. Daclatasvir, elbasvir/grazoprevir, ledipasvir, PrOD, and simeprevir are primarily hepatically metabolized and undergo minimal renal elimination. While exposures of many of these agents are higher in severe renal impairment presumably due to effects of uremic toxins, parathyroid hormone, and/or cytokines on hepatic metabolism, they do not require dose adjustments in renal impairment (Table 3&4).

The HCV-TARGET study is an ongoing prospective observational cohort study that evaluates the use of DAAs agents across clinical practices in North America and Europe. The study reported the safety and efficacy of sofosbuvir-containing regimens in patients with mild to severe renal dysfunction (eGFRs <30, 31-45, 46-60, and >60 mL/min) [36]. The patients received different regimens that included sofosbuvir (PEG-IFN, RBV, and sofosbuvir; simeprevir and sofosbuvir with or without RBV; or sofosbuvir and RBV). Overall, the regimens were well tolerated with no increased discontinuation among patients with low eGFRs. The rates of Sustained Virologic Response at 12 weeks (SVR12) were similar across the groups regardless of renal function. Notably, there was progressive deterioration of renal function and renal symptoms in the patients with eGFRs below 30 mL/min, suggesting the need for close monitoring of these patients. In summary, patients with low baseline renal function have a higher frequency of anemia, worsening renal dysfunction, and more severe adverse events, but treatment responses remain high and comparable to those without renal impairment.

Data on patients treated with a regimen of simeprevir and low-dose sofosbuvir without RBV have been reported. In one study, 18 HCV-infected patients (11 requiring HD, 3 with a mean eGFR of 16 mL/min) underwent open-label treatment with simeprevir and sofosbuvir. All patients received full-dose simeprevir (150 mg) daily. Sofosbuvir dose was reduced to 200 mg daily in 15 patients and 400 mg every other day in 3 patients. The length of therapy was 12 weeks in 17 patients and 24 weeks in 1 patient with cirrhosis. One patient developed new onset hepatic encephalopathy and another developed uncontrolled diarrhea, both requiring hospitalizations during treatment. Minor adverse events were fatigue (28%), anemia (11%), rash or itching (11%), and nausea (5%), and were managed medically; there were no treatment discontinuations. Of the 16

Table 3: Dose adjustments needed for patients with mild and moderate renal Impairment (adapted from reference 31).

Renal Impairment	eGFR/ CrCl Level (mL/ min)	PEG-IFN	Ribavirin	Sofosbuvir	Ledipasvir	Daclatasvir	Ombitasvir	Dasabuvir	Paritaprevir	Simeprevir	Velpatasvir	Elbasvir	Grazoprevir
Mild	50-80	PEG-IFN (2a) 180 µg: PEG-IFN (2b) 1.5 µg/kg	Standard	Standard	Standard	Standard	Standard	Standard	Standard	Standard	Standard	Standard	Standard
Moderate	30-50	PEG-IFN (2a) 180 µg: PEG-IFN (2b) 1 µg/kg (25% reduction)	Alternating Doses 200 mg and 400mg Every other day	Standard	Standard	Standard	Standard	Standard	Standard	Standard	Standard	Standard	Standard

Abbreviations: CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HD, hemodialysis.

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patients who completed treatment, only 9 patients reached relevant milestones. Per the current per-protocol analysis, SVR4 was seen in 91% and SVR12 in 89%. One patient with cirrhosis (who had a prior HCV PI-containing treatment failure) relapsed within 4 weeks after completion of treatment. In summary, the regimen of simeprevir and reduced-dose sofosbuvir is safe and well tolerated. In another study, 12 patients with eGFRs below 30 mL/min received sofosbuvir (400 mg) and simeprevir (150 mg). The regimen was well tolerated and resulted in viral suppression in all patients [37].

Twenty patients with HCV GT 1 infection and stage 4 or 5 (eGFR <30 mL/min/1.73 m^2) CKD without cirrhosis were treated with daily fixed-dose combination of paritaprevir (150 mg), ritonavir (100 mg), and ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) (PrOD) with or without RBV in a multicenter, open-label phase IIb study (RUBY-1 study) [38]. Notably, 70% of patients were black and 65% had CKD requiring HD. RBV (in those with HCV GT 1a only) was dosed 4 hours before HD and monitored with weekly hemoglobin assessments. RBV doses were suspended for a 2 g/dL or more drops in hemoglobin level and resumed when the hemoglobin level normalized. All patients (10/10) achieved SVR4 [38]. Interestingly, the use of RBV was associated with more of a drop in hemoglobin level, and 8 of 13 patients required interruption of RBV dosing. Four of 8 patients also required erythropoietin treatment during the first 7 weeks of therapy. Mean drug concentrations (C_{trough}) of all drugs were measured and levels were within the range that was observed with previous pharmacokinetic studies in healthy volunteers. In summary, most patients with HCV GT 1 with or without cirrhosis who were treated with PrOD with or without RBV achieved viral suppression. However, RBV-induced anemia can occur frequently, and close monitoring of all patients and judicious dose reductions of RBV are required. As described in other sections, PrOD should be used with caution in patients with Child Turcotte Pugh A cirrhosis and avoided in patients with CTP B or C.

For patients infected with HCV genotypes 2, 3, 5, or 6 with GFR ≤ 30 mL/min for whom the urgency to treat is high, and for whom treatment has been elected before KTx, standard treatment remains PEG-IFN plus dose-adjusted RBV (200 mg daily). However, caution is recommended in this group, owing to the potential for hemolytic anemia due to impaired renal clearance in this population, and RBV should be restricted to those with a baseline hemoglobin concentration above 10 g/dL. RBV should be discontinued if hemoglobin level declines by more than 2 g/dL despite the use of erythropoietin. Few data exist to guide treatment with current IFN-free regimens. Consideration may be given on an individualized basis to a sofosbuvir-based regimen, with careful attention paid to patient comorbidities and toxicities while on therapy.

AASL/IDAA Recommendations for Patients with Renal Impairment, Including Severe Renal Impairment (CrCl <30 mL/min) or ESRD Requiring Hemodialysis or Peritoneal Dialysis [31]

Recommended Dosage Adjustments for Patients with Mild to Moderate Renal Impairment

1. For patients with mild to moderate renal impairment (CrCl 30 mL/min-80 mL/min), no dosage adjustment is required when using daclatasvir (60mg*), fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg), fixed-dose combination of sofosbuvir (400mg)/velpatasvir (100mg), or fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with (or without for HCV genotype 4 infection) twice-daily dosed dasabuvir (250 mg), simeprevir (150 mg), or sofosbuvir (400 mg) to treat or retreat HCV infection in patients with appropriate genotypes.

   Rating: Class I, Level A

Recommended Regimens for Patients with Severe Renal Impairment, Including Severe Renal Impairment (Creatinine Clearance [CrCl] <30 mL/min) or End-Stage Renal Disease (ESRD)

Recommended regimens are listed in groups by level of evidence, then alphabetically.

2. For patients with genotype 1a, or 1b, or 4 infection and CrCl below 30 mL/min, for whom treatment has been elected before kidney transplantation, daily fixed-dose combination of elbasvir (50 mg)/grazoprevir(100mg) for 12 weeks is a Recommended regimen.

   Rating: Class IIa, Level B

Table 4: Dose adjustments needed for patients with severe renal Impairment and ESRD on HD (adapted from reference 31).

Severe <30	PEG-IFN 200 mg/d (2a) 135 µg: PEG-IFN (2b) 1 µg/kg (50% Reduction)	Limited data available	Data not available	Limited data available	Limited data available	Limited data available	Limited data available	Standard	Data not available	Standard	Standard
ESRD with HD	PEG-IFN 200 mg/d (2a) 135 µg/wk or PEG-IFN (2b) 1 µg/kg/wk or Standard IFN 3 mU 3x/wk	Limited data available	Data not available	Limited data available	Limited data available	Limited data available	Limited data available	Limited data available	Data not available	Standard	Standard

Abbreviations: CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HD, hemodialysis.

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3. For patients with genotype 1b infection and CrCl below 30 mL/min for whom the urgency to treat is high and treatment has been elected before kidney transplantation, daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) for 12 weeks is a Recommended regimen.

   Rating: Class IIb, Level B

4. For patients with HCV genotype 2, 3, 5, or 6 infection and CrCl below 30 mL/min for whom the urgency to treat is high and treatment has been elected before kidney transplantation, PEG-IFN and dose-adjusted ribavirin** (200 mg daily) is a Recommended regimen.

   Rating: Class IIb, Level B

*The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

**Caution is recommended in this group, owing to the potential for hemolytic anemia due to impaired renal clearance in this population, and ribavirin should be restricted to those with a baseline hemoglobin concentration above 10 g/dL.

Alternative Regimen for Genotype 1a-infected Patients with CrCl below 30 mL/min

5. For HCV genotype 1a infection, daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) and dose-adjusted ribavirin** (200 mg daily) for 12 weeks is an Alternative regimen.

   Rating: Class IIb, Level B

**Caution is recommended in this group, owing to the potential for hemolytic anemia due to impaired renal clearance in this population, and ribavirin should be restricted to those with a baseline hemoglobin concentration above 10 g/dL.

DAAs Therapy in Renal Transplant Patients

Several recent reports have described successful outcomes with DAAs combination therapy in renal-transplant patients [39,40]. (Sawinski, 2016); (Kamar, 2016) Sawinski et al [39] treated 20 HCV-infected KT recipients (88% genotype 1, half with advanced fibrosis, and 60% treatment-experienced) with sofosbuvir-based regimens and reported resulted 100% SVR [39]. (Sawinski, 2016) Various sofosbuvir-based DAAs combinations were used, including simeprevir plus sofosbuvir (n=9), ledipasvir/sofosbuvir (n=7), sofosbuvir plus RBV (n=3), and daclatasvir plus sofosbuvir (n=1). Two patients required dose reductions due to anemia (associated with RBV use), however no significant changes in serum creatinine, proteinuria, or graft rejection were seen before or after treatment. Forty-five percent of patients required dose reduction of immunosuppressive agents while on therapy [39]. (Sawinski, 2016)

A second study of 25 KT recipients with chronic HCV infection, treated with sofosbuvir-based regimens reported a 100% SVR [40]. (Kamar, 2016) Patients included were infected with GT 1 (76%), had eGFR >30 mL/min (100%), and had advanced fibrosis (44%). Treatment regimens included ledipasvir/sofosbuvir (n=9), daclatasvir plus sofosbuvir (n=4), sofosbuvir plus RBV (n=3), ledipasvir/sofosbuvir plus RBV (n=1), simeprevir plus sofosbuvir plus ribavirin (n=1), simeprevir plus sofosbuvir (n=6), and sofosbuvir plus PEG-

IFN/RBV (n=1). Treatment was well tolerated without any discontinuations, dose reductions, graft rejections, or changes in serum creatinine levels, and no drug interactions with calcineurin inhibitors were observed [40] (Kamar, 2016).

A third study specifically treated three HCV GT 4 renal transplant patients with sofosbuvir (400 mg) plus RBV (1000 mg) for 24 weeks with 100% SVR [41]. (Hussein, 2016) Anemia was reported in two patients related to concomitant RBV use. No other adverse events were reported [41].

Finally, a recent clinical trial described the safety and efficacy of ledipasvir/sofosbuvir in KT recipients (N=114) who were more than 6 months posttransplant [42]. (Colombo, 2016) The patients were mainly infected with genotype 1 or 4, with or without cirrhosis, and with or without prior treatment experience. Patients were randomized to receive ledipasvir/sofosbuvir for 12 or 24 weeks. Prior to treatment, median eGFR was 50 mL/min for those who were treated for 12 weeks and 60 mL/min for those who were treated 24 weeks. 96% achieved SVR12. Adverse events were common (64%) and 11% had a serious adverse event, but less than 1% discontinued treatment due to adverse effects [42].

European association for the study of the liver (EASL) recommendations for DAAs Therapy in Renal Transplant Patients [30]

1. Solid organ transplant recipients, including kidney, heart, lung, pancreas or small bowel recipients should be treated for their HCV infection after transplantation, provided that their life expectancy exceeds one year (A1).

2. Patients infected with HCV genotype 1, 4, 5 or 6 infection should be treated with the fixed-dose combination of sofosbuvir and ledipasvir, the fixed-dose combination of sofosbuvir and velpatasvir (if the drugdrug interaction profile with immunosuppressants is favourable in on-going studies), or the combination of sofosbuvir and daclatasvir according to the general recommendations, without the need for immunosuppressant drug dose adjustments (with the probable exception of everolimus) (B1).

3. Patients infected with HCV genotype 2 should be treated with the on-going studies) or the combination of sofosbuvir and daclatasvir according to the general recommendations, without the need for immunosuppressant drug dose adjustments (with the probable exception of everolimus) (B1).

4. Patients infected with HCV genotype 3 should be treated with the on-going studies) or the combination of sofosbuvir and daclatasvir according to the general recommendations, without the need for immunosuppressant drug dose adjustments (with the probable exception of everolimus) (B1).

Summary and Future treatment

1. The new DAAs treatments for HCV are more effective, easier to take and have fewer side-effects than older treatments.

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2. The treatment of HCV in patients with CKD including dialysis patients and KT recepient with the new DAAs can be done with sustained virologic response (SVR) more 90%.

3. The goals of future therapy will include 1) Pan-genotypic activity with high barrier to resistance 2) Simplified dosing 3) RBV free and 4) Shorter duration of treatment. Many current regimens still require RBV which can cause significant anemia and fatigue in sensitive populations. Several investigational agents have been presented with impressive pan-genotypic activity without RBV.

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