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REVIEW

Hepatitis C virus infection in maintenance hemodialysis patients: recommendations for diagnostics and treatment

Pavlina Dzekova-Vidimliski, Aleksandar Sikole

University Hospital of Nephrology, Skopje - Republic of Macedonia

ABSTRACT

Hepatitis C virus (HCV) infection is highly prevalent among patients treated with maintenance hemodialysis and is an important cause of morbidity and mortality. It is necessary to determine the HCV genotype and the viral load to monitor the clinical and laboratory features and to establish an optimal antiviral treatment strategy. Antiviral treatments are presented with a standard interferon-based regimen and new direct-acting antiviral agents. The advent of direct-acting antivirals has improved the efficacy and safety of HCV treatment for most patients, even in difficult-to-treat populations such as patients on hemodialysis. HCV treatment with direct-acting antivirals in hemodialysis patients is highly effective, with viral eradication rates similar to those seen in patients without chronic kidney disease and with acceptable adverse event profiles.

Keywords: Antiviral agents, Hepatitis C, Renal dialysis, Renal insufficiency

Epidemiology of HCV infection in hemodialysis patients

The prevalence of HCV infection in hemodialysis patients varies among geographical areas and dialysis centers, but it is higher than in the general population. HCV infection affects approximately 3% of the world population (1, 2). The prevalence of HCV infection in hemodialysis patients, estimated by the detection of antibodies against HCV (anti-HCV), varies between 3% and 10% in developed countries and from 15% to 75% in developing countries (3). The main risk factors for contracting HCV infection during hemodialysis include: the number of blood product transfusions, duration of hemodialysis treatment, prevalence of HCV infection in the dialysis unit and the lack of compliance with universal precautions (4, 5). Duration of hemodialysis treatment by year was associated with a 4% increased risk for contracting HCV infection ($p = 0.007$), ranging between 0.2% and 15% per year of hemodialysis treatment (6, 7). Despite the elimination of HCV transmission by the transfusion of blood products in developed countries, the vast majority of HCV infections were attributable to hand-borne nosocomial transmission or by the use of contaminated medication vials (8). Prospective trials have shown a reduction in HCV transmission within dialysis units where HCV positive patients had been isolated (9). However, the American Center for Disease Control and Prevention (CDC) and the Kidney Disease: Improving Global Outcomes (KDIGO) practice guidelines do not recommend dedicated machines or isolation of HCV positive patients. Instead, they recommend strict adherence to the universal precautions, careful attention to hygiene, sterilization of dialysis machines, and screening for anti-HCV at baseline, and then subsequently semiannually, as measures for reducing HCV transmission (3, 10).

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Corresponding author:
Aleksandar Sikole
University Hospital of Nephrology
Mother Theresa 17
1000 Skopje, R. Macedonia
asikole@hotmail.com

Natural history of HCV infection in hemodialysis patients

The natural history of HCV infection in hemodialysis patients is usually asymptomatic with an apparently indolent course. These patients have higher morbidity and mortality rates than the general population. The consequences of chronic hepatitis C are not as obvious in this population as they are present in patients with intact kidney function, because the HCV infection extends over decades rather than years. Chronic hepatitis C in hemodialysis patients is characterized by lower immunologic activity, the dominant pathophysiologic mechanism responsible for hepatocyte injury (11, 12). A case-control study included 36 HCV-positive patients on hemodialysis and 37 HCV-positive patients with intact kidney function matched for gender, age, and estimated time of infection. HCV-positive patients on hemodialysis had lower levels of alanine aminotransferase and a lower viral

load. Hepatic fibrosis and hepatic inflammatory activity were significantly higher in the patients with intact kidney function compared to the hemodialysis patients (73% and 47%, versus 60% and 28%, respectively) (13).

There is evidence that HCV infection was associated with a lower survival in hemodialysis population. A meta-analysis of 14 observational studies, with 145,608 dialysis patients, demonstrated that HCV antibody was an independent and significant risk factor for death. Compared to the HCV-antibody-negative patients on dialysis, the HCV-antibody-positive patients on dialysis have an increased risk for all-cause mortality (adjusted relative risk: 1.32) (14).

Diagnosis of HCV infection in hemodialysis patients

Infection with HCV is characterized by increased serum levels of alanine aminotransferase (ALT). The laboratory blood testing for ALT is used to screen for liver disease in the general population. However, blood testing for ALT has weak diagnostic value in patients on dialysis, because their ALT levels are lower than in the general population (15, 16). The potential causes of lower serum ALT levels in the dialysis population are: vitamin B6 deficiency, suppression of ALT synthesis in hepatocytes, and defective release of ALT into the blood stream (17).

Detection of antibodies against HCV (anti-HCV) by the 3rd-generation enzyme immunoassay (EIA) is the most commonly used screening tool for HCV infection (18). Third-generation EIAs have high sensitivity (98.8%) and specificity (100%) (19). However, the time between HCV infection and the appearance of detectable antibodies (serological window period) is generally more than 40 days using third generation EIAs (20). In 2008, the 4th-generation EIA has become available, which was able to detect the HCV antibody significantly earlier than the other assays (21). Screening for anti-HCV should be repeated every 6 to 12 months in dialysis patients. A proportion of dialysis patients might test negative for anti-HCV, but test positive for persistence of viral particles (HCV-RNA) in the serum (22). Patients who are immunocompromised might either exhibit a delay in antibody production or an absence of specific antibodies following acute HCV infection. Dialysis units with a high prevalence of HCV infection were estimated to have an 18% false-negative, anti-HCV test rate (23).

When EIA reveals that a dialysis patient is anti-HCV positive, the next step is a quantitative determination of the viral load and genotype of HCV by polymerase chain reaction (PCR) molecular assays. The blood for HCV-RNA testing should be drawn prior to a hemodialysis session, because the presence of heparin in the blood could lead to a false-negative PCR result. Also, the viral load could decrease during the hemodialysis session. Adsorption of viral particles onto the dialysis membrane, the destruction of viral particles by the hydraulic pressure during the hemodialysis session, and the escape of the virus into the dialysate, could cause a transient decrease during the hemodialysis session with a gradual return to baseline level within 48 hours (24-26). To avoid false-negative results for HCV-RNA in patients on hemodialysis, it was recommended to test the persistence of HCV-RNA by highly sensitive reverse transcriptase-polymerase chain reaction assays (RT-PCR) or transcription-mediated amplification (27, 28).

HCV genotyping is also important, to predict treatment response and to specify the duration and dosage of the antiviral treatment. The study of Perez et al reported that HCV genotype 1a was the most prevalent in hemodialysis patients. The next most frequent genotype was 1b, followed by genotype 3, then 2, 4 and 5 (29).

Liver biopsy is the gold standard for assessment of liver fibrosis in patients with chronic hepatitis C. However, the use of liver biopsy is limited in hemodialysis patients because of its invasive nature, poor patient acceptance, and high risk of bleeding. Coagulopathy, thrombocytopenia, platelet dysfunction, and anticoagulation therapy given during the hemodialysis session are all risk factors for increased bleeding. In individuals with increased bleeding risk, the transjugular or transfemoral route for liver biopsy could be an option (30). Transient elastography, performed with a Fibroscan®, represents a noninvasive technique for assessment of liver fibrosis (31). It might be effective for evaluation of liver fibrosis in hemodialysis patients with chronic hepatitis C, but the predictive and cut-off values of this method should be optimized for this patient population (32).

Treatment of HCV infection in hemodialysis patients

A recent survey from the Dialysis Outcomes and Practice Patterns Study (DOPPS) demonstrated that only 1% of dialysis patients with HCV infection received antiviral medication. Among the subset on a waiting list for kidney transplantation, only 3.7% received antiviral treatment (33).

All HCV-positive kidney transplant candidates should be assessed to receive antiviral treatment prior to transplantation, to reduce the risk of post-transplant complications associated with HCV (34). The antiviral treatment of HCV infection is presented with the standard interferon treatment and the new direct-acting antiviral agents (DAAs).

Standard or pegylated interferon alpha

For more than a decade, standard treatment for HCV infection in hemodialysis patients was a monotherapy with standard or pegylated interferon alpha (35). The pharmacokinetics of interferon alpha is altered in hemodialysis patients because the kidney is the main site for degradation of the interferon molecule, while the liver plays only a minor role. The hemodialysis procedure has only a small effect on interferon alpha clearance (30). Pegylated interferon alpha has a very restricted volume of distribution, a longer half-life and reduced clearance compared to the standard interferon alpha. There are also differences in the pharmacokinetic profile of the 2 molecules of pegylated interferon alpha (PEGIFN alpha). The administration of PEGIFN alpha-2a is once weekly, independently of bodyweight. The PEGIFN alpha-2b has a shorter half-life in serum than PEGIFN alpha-2a and requires bodyweight based dosing (36).

Clinicians are advised to treat HCV-infected hemodialysis patients with standard or pegylated interferon, for 48 weeks with HCV genotypes 1 and 4, and for 24 weeks in genotypes 2 and 3. The standard interferon is administered subcutaneously, 3 times weekly after dialysis session. The pegylated interferon is administered subcutaneously, once weekly, after dialysis session (37).

There have been at least 4 meta-analyses demonstrating that interferon monotherapy is effective for HCV positive patients on dialysis, with overall sustained viral response (SVR) rates of 33% to 41% and treatment withdrawal rates of 17% to 30% (38-41). The discontinuation of treatment was more frequent in dialysis patients than in patients with intact kidney function. Flu-like symptoms, gastrointestinal, hematological and thyroid disorders, and severe depression were the most frequent adverse events, associated with discontinuation of the interferon therapy (38-42).

The interferon treatment should be discontinued in hemodialysis patients who do not achieve an early viral response (serum HCV-RNA negativity at week 12 of treatment). The nonresponders to interferon should be referred to a hepatologist, for further treatment options (43). Long-term viral negativity in patients who achieved SVR after interferon treatment was analyzed in the study of Gordon et al (44). Data for long-term HCV-RNA outcomes following SVR were available for 121 hemodialysis patients (20 studies). The probability of long-term viral negativity was 86% (95% CI, 77%-96%) 48 months after achievement of SVR. These findings were similar to the reports for patients with intact renal function, where over 90% of patients who achieved SVR remained persistently HCV-RNA negative after 5 years of follow-up (45).

Ribavirin

In patients with intact renal function, the addition of ribavirin (RBV) to interferon treatment is generally required to achieve an optimal SVR (46). The route of ribavirin elimination is mainly by the kidneys. There is a potential risk of ribavirin accumulation in hemodialysis patients, as a minimal amount of the drug is removed by the hemodialysis process. Therefore, a dose adjustment of ribavirin according to the renal function is necessary (17). It concentrates in circulating red blood cells, causing a relative adenosine triphosphate deficiency and increased susceptibility to oxidative damage, resulting in hemolytic anemia (47). The low dose of ribavirin (200 mg daily) was approved in 2011 in the USA for the treatment of HCV infection in patients on long-term hemodialysis (48). The treatment regimen for the combination therapy of interferon and ribavirin is 48 weeks for HCV genotypes 1 and 4, and 24 weeks for genotypes 2 and 3. Despite the fact that ribavirin was previously contraindicated in the setting of renal failure, this drug could be used at markedly reduced doses with careful monitoring of serum drug concentration and occurrence of anemia. The doses should be adjusted based on target serum level of 10 to 15 µmol/L in patients with intact kidney function. Erythropoiesis-stimulating agents can be used to counteract anemia and to help maintain an optimal ribavirin dose in hemodialysis patients (22, 36). An open-label, randomized, controlled trial compared the efficacy and safety between the combination therapy of pegylated interferon plus low-dose ribavirin and pegylated interferon monotherapy for treatment-naive patients with HCV on hemodialysis. The combination therapy with PEGIFN alpha-2a (135 µg/weekly) and RBV (200 mg/daily) was given to 103 hemodialysis patients for 48 weeks. The monotherapy with PEGIFN alpha-2a (135 µg/wk) was given to 102 hemodialysis patients for 48 weeks. Compared to monotherapy, combination therapy had a higher SVR rate (64% vs. 33%, p = 0.001). The anemia was significantly more frequent in patients receiving combination therapy than in those receiving monotherapy (72% vs. 6%, p = 0.001). The adverse event-related withdrawal rates were 7% in the combination therapy group and 4% in the monotherapy group (49).

The American Association for the Study of Liver Diseases (AASLD) current guidelines recommend standard treatment with PEGIFN alpha and dose-adjusted ribavirin (200 mg daily) for patients infected with HCV genotype 2, 3, 5, or 6 on maintenance hemodialysis. Ribavirin should be restricted to hemodialysis patients with a baseline hemoglobin concentration above 10 g/dL. Ribavirin should be discontinued if hemoglobin levels decline by more than 2 g/dL despite the use of erythropoietin (48).

Direct-acting antiviral agents

The introduction of direct-acting antiviral agents (DAAs) has revolutionized HCV treatment with impressive SVR rates, rare adverse events, 12 weeks duration of therapy, and daily oral drug dosage. The DAAs target viral nonstructural proteins to prevent viral replication. The first 2 drugs, approved in 2011 as 1st-generation NS3/4A protease inhibitors, were telaprevir and boceprevir. Another 3 DAAs were approved in 2013-2014 as 2nd-generation NS3/NS4A protease inhibitors: simeprevir and daclatasvir; and sofosbuvir as a NS5B nucleotide polymerase inhibitor. Ledipasvir, 3D regimen and Grazoprevir/Elbasvir are the newest DAAs, approved in 2015-2016. Treatment guidelines are constantly evolving due to emerging regimens and real-world treatment data. Before the era of DAAs, HCV treatment efficacy was assessed 24 weeks after completion (SVR24) of the standard therapy. Considering that assessment at 12 weeks after treatment completion has been shown to be equally relevant, since many new treatment regimens are only 8 to 12 weeks in duration, SVR12 became the current standard for HCV treatment efficacy (50-52).

Telaprevir/boceprevir

The first-generation NS3/4A protease inhibitors are metabolized primarily by the liver and dose adjustments were not required for patients with renal impairment, although patients with glomerular filtration rate (GFR) less than 50 mL/min were excluded from their registration trials. Telaprevir or boceprevir was administered together with pegylated interferon and ribavirin, as a triple therapy. Anemia was the main adverse event in patients with intact kidney function, and it would also be expected in patients with renal impairment (53). Despite the lack of data for the required dose adjustments, there have been a few small case series evaluating the safety and efficacy of these protease inhibitors in patients on hemodialysis (54). However, the use of telaprevir/boceprevir-based triple therapy for the treatment of HCV infection in hemodialysis patients is not recommended by the current AASLD guidelines (48).

Simeprevir

Dose adjustments for this 2nd-generation protease inhibitor was not required in the setting of mild to severe renal

impairment, because renal elimination of this agent was negligible (<1%). The efficacy and safety of simeprevir has not been adequately studied in patients requiring hemodialysis (55). The current AASLD guidelines do not recommend simeprevir for the treatment of HCV infection in hemodialysis patients, due to lack of sufficient evidence (48).

Sofosbuvir

The HCV NS5B nucleotide inhibitor is eliminated mainly by the kidneys (~81%). A single dose (400 mg) of sofosbuvir resulted in 56%, 90%, and 456% higher levels of the active metabolite of sofosbuvir among individuals with mild, moderate, and severe renal impariment, respectively, compared to individuals with normal renal function (55). A multicenter retrospective study was conducted to assess efficacy and safety of sofosbuvir in 50 HCV infected patients with severe renal impairment (GFR <35 mL/min) (56). Seventy percent of the study patients were on maintenance hemodialysis. Antiviral treatment consisted of SOF/RBV in 7 patients, SOF/RBV/PEGIFN in 2 patients, SOF/daclatasvir ± RBV in 30 patients and SOF/simeprevir ± RBV in 11 patients. A reduced dose of sofosbuvir (400 mg 3 times a week or 400 mg every other day) was given to all hemodialysis patients. SVR12 was 86%.

Sofosbuvir, the cornerstone of most HCV treatment regimens, should not be administered to patients with severe renal impairment (GFR <30 mL/min) or in those who require hemodialysis, until more data are available, according to the current AASLD guidelines (48).

Ledipasvir

The HCV NS5A inhibitor is excreted in the feces (~86%), with 1% elimination by the kidneys (55). No dose adjustments were required for patients with mild to severe renal impairment. However, there are no data on the efficacy and safety of ledipasvir for the treatment of HCV infection in hemodialysis patients, according to the current AASLD guidelines (48).

Fixed-dose ombitasvir, paritaprevir, ritonavir and dasabuvir (3D regimen)

The 3D regimen is an oral regimen that consists of ombitasvir (NS5A inhibitor), paritaprevir (NS3/4A protease inhibitor), and ritonavir, a booster to increase the exposure of paritaprevir, coformulated into 1 tablet, and dasabuvir (non-nucleoside NS5B inhibitor) as a separate tablet. All components of this regimen are primarily excreted in the feces (~86%), with less than 11% elimination by the kidneys (57).

Twenty patients with HCV genotype 1 infection with GFR <30 mL/min (65% hemodialysis-dependent) 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) for 12 weeks. Patients with HCV genotype 1a infection also received ribavirin (n = 13). SVR12 was 90% (58).

The current AASLD guidelines recommend the 3D regimen treatment (12 weeks) for hemodialysis patients infected with HCV genotype 1b. The 3D regimen plus dose-adjusted ribavirin (200 mg daily) was recommended for hemodialysis patients with HCV genotype 1a infection (48).

Grazoprevir/elbasvir

Grazoprevir is a 2nd-generation NS3/4A protease inhibitor while elbasvir is an NS5A inhibitor. Less than 1% of both drugs are eliminated by the kidneys. In a phase 3 randomized study on the safety and efficacy of grazoprevir/elbasvir, 224 patients with HCV genotype 1 infection and GFR less than 30 mL/min (75% hemodialysis-dependent) were randomly assigned to receive grazoprevir/elbasvir 100 mg/50 mg, once daily for 12 weeks (n = 111), or placebo (n = 113). After 4 weeks of follow-up (study week 16), unmasking occurred and patients in the placebo group received grazoprevir/elbasvir. The most common adverse events were headache, nausea, and fatigue, occurring at similar frequencies in both groups. The primary end point was SVR12, achieved in 99% of patients who completed treatment. One patient relapsed 12 weeks after treatment completion (59). Based on this data, current AASLD guidelines recommend the fixed-dose combination grazoprevir/elbasvir (100 mg/50 mg) for the treatment of HCV genotype 1 infection in hemodialysis patients. Although the study did not evaluate patients with HCV genotype 4 infection, it is likely that the high efficacy of elbasvir/grazoprevir could be expected in genotype 4 infected individuals on hemodialysis as well (48).

A very recent multicenter study was presented at the AASLD Liver Meeting 2016. A combination of 2 new DAAs, glecaprevir (NS3/4A protease inhibitor) and pibrentasvir (NS5A protease inhibitor) were used to treat HCV genotype 1-6 in 104 patients with GFR <30 mL/min/1.73 m^2. The dose of GLE/PIB was 300 mg/120 mg once daily for 12 weeks. SVR4 was achieved in 103/104 patients. Adverse events were noted in 24% of the patients, none related to the study drug. The results suggest that a fixed combination of GLE/PIB was a suitable option for patients with severe renal impairment (60).

The American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) recommended the treatment regimens for patients with severe renal impairment (GFR <30 mL/min), presented in Table I. (48).

Conclusions

Hepatitis C virus infection is highly prevalent among hemodialysis patients and is associated with a lower patient survival. All HCV-positive hemodialysis patients should be assessed to receive antiviral treatment, and should certainly be candidates for kidney transplantation.

The antiviral treatment is presented with standard interferon-based regimen reserved for HCV genotype 2, 3, 5 or 6, and the new direct-acting antiviral agents. The daily fixed-dose combination of elbasvir/grazoprevir is recommended for patients on hemodialysis with HCV infection genotype 1a, 1b or 4, as well as the combination of paritaprevir/ritonavir/ombitasvir/dasabuvir for HCV genotype 1b. The SVR12 rates varied between 90% and 100%, with acceptable adverse

TABLE I - Summary of recommendations for the treatment of HCV infection in patients with severe renal impairment

HCV treatment drug	HCV genotype	Duration of treatment
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) (*Rating: Class IIa, Level B*)	1a, 1b, 4	12 weeks
Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) (*Rating: Class IIb, Level B*)	1b	12 weeks
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) (*Rating: Class IIb, Level B*)	1a alternative regimen	12 weeks
PEGIFN (PEGIFN alpha-2a: 135 µg/weekly or PEGIFN alpha-2b:1 µg/kg/weekly) and dose-adjusted ribavirin* (200 mg daily) (Rating: *Class IIb, Level B*)	2, 3, 5, 6	24 weeks

* Ribavirin should be restricted to patients with a baseline hemoglobin concentration above 10 g/dL.

event profiles. Prospective clinical trials are being conducted to define new DAA treatment regimens associated with high rates of viral eradication and minimal side-effects.

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