HCV INFECTION AND CHRONIC RENAL DISEASE

Sofija Sekulic[1], Zeljko Mijailovic[1], Dejan Petrovic[2], Ruzica Lukic[3], Marina Jovanovic[4,5] and Ivan Jovanovic[5]

[1]Department of Infectious diseases, Faculty of Medical Sciences, University of Kragujevac, Serbia
[2] Department of Internal medicine, Faculty of Medical Sciences, University of Kragujevac, Serbia
[3]Department of Microbiology, Faculty of Medicine Foca, University of East Sarajevo, Bosnia and Herzegovina
[4]Department of Otorhinolaryngology, Faculty of Medical Sciences, University of Kragujevac, Serbia
[5]Center for Molecular Medicine and Stem Cell Research, Faculty of Medical Sciences, University of Kragujevac, Serbia

HCV INFEKCIJA I HRONIČNA BUBREŽNA BOLEST

Sofija Sekulić[1], Željko Mijailović[1], Dejan Petrović[2], Ružica Lukić[3], Marina Jovanović[4,5] i Ivan Jovanović[5]

[1]Katedra za zarazne bolesti, Fakultet medicinskih nauka, Univerzitet u Kragujevcu, Srbija
[2] Katedra za internu medicinu, Fakultet medicinskih nauka, Univerzitet u Kragujevcu, Srbija
[3] Katedra za mikrobiologiju, Medicinski fakultet Foča, Univerzitet u Istočnom Sarajevu, Bosna i Hercegovina
[4] Katedra za otorinolaringologiju, Fakultet medicinskih nauka, Univerzitet u Kragujevcu, Srbija
[5]Centar za molekularnu medicinu i istraživanje matičnih ćelija, Fakultet medicinskih nauka, Univerzitet u Kragujevcu, Srbija

ABSTRACT

Chronic Hepatitis C virus (HCV) infection is defined as persistence of HCV RNA in the blood for more than six months. HCV is a major cause of chronic liver disease and cirrhosis. It's serious public health problem, affects about 71 million people worldwide. HCV doesn't destroy hepatocytes directly. It activates the host's innate and acquired immune system and causes liver injury indirectly. Behind hepatic, HCV can cause extra-hepatic manifestations. One of them is renal disease which can lead to end-stage renal disease, ESRD. The prevalence of HCV infection in patients on hemodialysis is high, ranging from 5% to 60%. HCV infection is a significant cause of morbidity and mortality in patients with ESRD on hemodialysis. In this review, we discuss HCV infection and chronic renal disease as comorbidities, their severity and outcome.

Keywords: HCV, infection, chronic renal disease, comorbidity.

SAŽETAK

Hronična hepatitis C virusna (HCV) infekcija se definiše kao prisustvo HCV RNA u krvi duže od šest meseci. Glavni je uzrok hronične bolesti jetre i ciroze. Oko 71 milion ljudi širom sveta je inficirno ovim virusom koji predstavlja ozbiljan zdravstveni problem. HCV ne uništava hepatocite direktno. Aktivira urođeni i stečeni imunski sistem domaćina i indirektno oštećuje jetru. Osim oštećenja jetre, HCV izaziva i ekstrahepatične manifestacije. Jedna od njih je bubrežna bolest koja može da progredira do završnog stadijuma bubrežne bolesti (engl. end-stage renal disease, ESRD). Prevalencija HCV-a kod pacijenata na hemodijalizi je velika, kreće se od 5% do 60%, a HCV infekcija je značajan uzrok oboljevanja i smrtnosti kod pacijenata sa ESRD na hemodijalizi. U ovom preglednom članku, mi razmatramo HCV infekciju, hroničnu bubrežnu bolest kao komorbiditete, njihovu težinu i ishod.

Ključne reči: HCV, infekcija, hronična bubrežna bolest, komorbiditet.

Corresponding author:
Sofija Sekulic, MD
Department of infectious diseases
Faculty of Medical Sciences University of Kragujevac
Svetozara Markovica 69, 34000 Kragujevac, Serbia
Tel +38134306800, Fax. +38134306800112
E-mail: sofija.sekulic91@gmail.com

ETIOLGY, EPIDEMIOLOGY AND IMMUNO-PATHOGENESIS OF HCV INFECTION

Hepatitis C virus (HCV) is a positive single-stranded RNA virus with 9.6 kb in length, belongs to the genus *Hepacivirus* in the family *Flaviviridae (1).* HCV genome encodes seven non-structural (NS) proteins (NS1 or P7, NS2, NS3, NS4A, NS4B, NS5A and NS5B) and three structural proteins (Core, E1 and E2) (2). They are the host's target of the innate and adaptive immune response (2, 3). Hepatitis C virus (HCV) transmission occurs on parenteral way (by intravenous drug injection, by parenteral exposure of blood through the use of contaminated or inadequately sterilized instruments and needles used in medical and dental interventions, organ transplantation, hemodialysis), or by other activities that disrupt the integrity of the skin (e.g. tattooing, piercing), sexual way, vertical way (prenatal, perinatal and postnatal) (4, 5, 6). Number of chronically infected patients with HCV is about 71 million worldwide (7).

HCV has a high genomic variability, 7 genotypes and at least 67 subtypes (8). Determination of HCV genotypes and subtypes is important for the definition of epidemiological patterns and effective treatment (8). The most frequently genotypes in world are genotype 1, 2, 3 (8). Genotype 4 is one of the more difficult genotypes to treat (9). Although association between HCV genotype and fibrosis progression appears inconclusive, some studies revealed that infection with genotype 3 has higher risk of severe hepatic steatosis, fibrosis progression and increased oncogenesis (9, 10, 11, 12, 13).

Hepatocytes are the main place of HCV replication. Cell-mediated immune reaction against infected liver cells causes the most injury in the liver (14). Host's first-line antiviral defense mechanism is innate immunity, characterized by production of interferons (IFNs) and pro-inflammatory cytokines (1). Interferon type I in infected cells induces accumulation of double-stranded RNA-dependent protein kinase (PKR), expression of genes which induce the apoptosis of infected hepatocytes and inhibition of viral replication (3, 15). Parenchymal cells (hepatocytes), non-parenchymal liver cells (Kupffer cells (KCs), hepatic stellate cells (HSCs)) and immune cells (dendritic cells and NK cells, mast cells, macrophages) recruited to the liver are enrolled in anti-viral immune response, so these cells play a key role in the elimination of acute HCV infection within 6 months from onset (1, 16, 17). Retinoic acid-inducible gene-I (RIG-I)-like receptors and Toll-like receptors are the main pattern recognition receptors that recognize HCV pathogen-associated molecular patterns (3). During HCV infection, TLR3 and RIG-I on infected hepatocytes, TLR7 on Plasmacytoid *dendritic* cells (pDC) are engaged by HCV RNA to induce the secretion interferons type I and III which further inhibit HCV replication and activate NK cells (3). Activated NK cells produce IFN-γ and TNFα, which inhibit HCV replication and induce DC maturation. Activation and differentiation of CD4^{+} T cells and CD8^{+} T cells into Th1 cells and Cytotoxic T cells (CTL) is facilitated by IL-12, produced mainly by matured DCs (3).

These cells secrete IL-12 and IL-15 and activate NK cells (3). CTL and activated NK cells produce perforin and granzyme B that induce the cytolysis of HCV-infected cells (3). Th1 cells secrete IL-2 which induce the proliferation of CD8 T cells, as well as TNFα which inhibits HCV replication inducing a cytolysis of HCV-infected cells (3). Th1 cells produce IFN-γ and induce the differentiation of B cells into plasma cells which produce neutralizing antibodies (3). Targets of neutralizing antibodies are HCV E1 and E2 molecules (18). The effect of humoral anti-viral response is neutralization of viral and cellular factors which promote HCV entry into host cells. Neutralizing antibodies inhibit the binding of HCV to host cellular receptors (3, 18). In more than 80% of infected patients acute phase progrediates to chronic infection because of limitation of immune responses to eliminate the virus (2, 3, 4, 19). Persistence of Hepatitis C viral infection in the host can be explained with virus ability to evade immune surveillance thanks to viral mutation and inhibition of innate immune cells such as dendritic cell (DC) and natural killer (NK) cells by HCV viral proteins (3). Additionally, virus has ability to alter innate and adaptive immune response, by involvement of Regulatory T cells (Tregs) (3). There are opinions that Tregs have a central role for HCV persistence (20). Tregs suppress activation and differentiation of many immuno-competent cells, block co-stimulation by DCs and induce apoptosis of activated effector T cells (20). Treg subsets produce TGF-β and subsequently stimulate fibrosis (20). Some studies showed increased number of regulatory T cells in peripheral blood and in liver tissue of chronic HCV patients (20). Constant inflammatory response in liver mediated by pro-inflammatory cytokines/ chemokines (IL-6, TGF-β1, IL-1β, IL-18 and CCL5) released from HCV-infected hepatocytes and liver macrophages, may lead to the activation of quiescent hepatic stellate cells (HSCs) which develop a myofibroblastic phenotype to secrete and deposit the extracellular matrix (ECM) proteins such as collagen type I, resulting in development of fibrosis and cirrhosis. (21, 22). HCV induce fibrosis by upregulating miR-192 expression via HCV core protein and enhancing expression of mayor potent profibrogenic cytokine, TGF-β1(21). TGF-β1 is a main potent profibrogenic cytokine and plays a key role in pathogenesis of liver fibrosis (21). Activation and proliferation of hepatic myofibroblasts is the main mechanism in liver cirrhosis development (22). Perforin/granzyme pathway, Fas ligand released from inflammatory cells with its receptor Fas on hepatocytes, is other candidate mechanism to enhance liver damage (23).

OUTCOME AND CLINICAL MANIFESTATIONS OF HCV INFECTION

Acute HCV infection leads to chronic hepatitis and eventually causes fibrosis, cirrhosis (in 20-30% of cases) and hepatocellular carcinoma (HCC in 1-5% of cases) (5). Hepatitis C is resolved spontaneously by involving innate and adaptive immunity in less than 20% of patients (4, 5, 6, 17). Chronic HCV infection is defined as viral replication which persists for more than six months (24). Patients in this stage are usually asymptomatic, and transaminases are increased or

in normal range (24). Only 15% of infected patients have symptoms (17). The most frequent manifestations include unspecific signs like fatigue, fever, myalgia, nausea, arthralgia, abdominal pain, pruritus and anorexia (17, 25). Other symptoms include jaundice, bilirubinuria and very rarely light colored stools (17, 25, 26, 27, 28). Chronic HCV infection causes hepatic and extrahepatic manifestations (29, 30, 31, 32, 33, 34, 35, 36). Infected HCV patients can develop extrahepatic manifestations caused by immune abnormalities which result in autoimmunity (26). At least one extrahepatic manifestation occurs in 38% to 76% patients with chronic HCV infection (26, 37). Extrahepatic manifestations include mixed cryoglobulinemia-the most frequent 60%-75%, chronic kidney disease or end-stage renal disease, membranoproliferative glomerulonephritis type 1, type 2 diabetes, B-cell lymphoma, lichen planus, porphyria cutanea tarda, Sjögren's syndrome, rheumatoid-like arthritis, SLE, depression, autoimmune thyroiditis, idiopathic pulmonary fibrosis, antiphospholipid syndrome, sarcoidosis, sysitemic slerosis, Behcet disease, xerophthalmia; cardiovascular manifestations as carotid atherosclerosis, coronary heart disease; neurological conditions as peripheral neuropathy, cognitive impairment and cerebrovascular accidents; (26, 29, 30, 31, 32, 33, 34, 35, 36, 38).

DIAGNOSIS AND THERAPY OF CHRONIC HCV INFECTION

Diagnostic criteria for HCV infection is presence of anti HCV antibody and HCV RNA (39). HCV RNA is the first detectable virus marker that appears one to two weeks after exposure (17). The anti-HCV IgG response can be detected seven-eight weeks later, and standard test to detect anti-HCV antibodies in serum and plasma is an immunoassay or enzyme-linked immunosorbent assay (EIA) (17, 40, 41). Quantitative HCV RNA assays are used to confirm the presence of infection, to quantify the amount of HCV RNA, and to guide decisions for antiviral therapy (41). Real-time PCR methods despite standard PCR methods have better sensitivity for HCV level testing (41).

Treatment of chronic HCV⁺ patients is based first of all on genotype, extent of fibrosis or cirrhosis and comorbidities (4). Treatment of HCV infection has been changed for years and it has evolved from using nonspecific antiviral therapy, interferon, to interferon and nucleoside analog, ribavirin (4, 8). Later, is showed that pegylated interferon (peg-IFN) is more effective than non-pegylated one, and combination of PegIFNα and ribavirin had been the standard of care before using DAAs (Direct-acting antiviral agents) (8). Interferon/Ribavirin therapy combination, for 24–48 weeks, eradicated the virus in approximately 50% of treated patients (42, 43). Each genotype has different response to antiviral therapy (8). HCV genotype with HCV-RNA baseline level is the major predictor of sustained virological response (SVR) to antiviral therapy (8).

HCV infected patients with genotype 2-and 3 reach sustained virological response (SVR) using pegylated-interferon in combination with ribavirin (pegIFN/RBV) in 80%; genotype 1 and 4 infections leads to an SVR only for about 50%; genotypes 5 and 6 have intermediate response rates, while infected patients with genotype 3 with dual pegIFN/RBV therapy have SVR rates worse than infected patients with genotype 2 (8, 13, 43). Since 2011. Direct-acting antivirals (DAAs) are being used for treatment of chronic hepatitis and their targets are viral proteins NS3, NS5A, and NS5B (43, 44). The first-generation NS3/4A protease inhibitors, boceprevir and telaprevir, used in combination with PEG-IFN-α and Ribavirin leads to SVRs in approximately 70% of HCV genotype 1-infected patients (44). As this triple therapy showed some bad effects and led to the generation of drug-resistant HCV, they are no longer recommended (44). The protease inhibitors (simeprevir, paritaprevir, grazoprevir, glecaprevir, and voxilaprevir), the NS5A inhibitors (velpatasvir, pibrentasvir, and daclatasvir), and the NS5B inhibitors (sofosbuvir and MIV-802) present higher barrier to viral resistance, cover more of the viral genotypes, have better pharmacokinetics, have high SVRs and an excellent tolerability profile also in patients with renal impairment (9, 43, 44, 45). Success of therapy is increased from the 15% to 20% by the IFNα monotherapy (which has a high relapse rate) to over 90% by the DAA treatments (43, 46, 47). The goal of treatment in HCV infection is achievement of a SVR (41). SVR is defined as undetectable HCV RNA in peripheral blood 12 weeks after the end of the treatment (41). Limiting factor, first of all in developing countries, for usement of DAA, is high cost (48).

CHRONIC KIDNEY DISEASE (CKD)

Chronic kidney disease (CKD) is defined as a renal parenchyma damage leading to chronic deterioration of renal function that may progress to end-stage renal disease (ESRD) gradually (49). The term CKD has replaced previously used terms "chronic renal insufficiency" and "chronic renal failure" (49). CKD is characterized by abnormal albumin excretion or decreased kidney function, quantified by glomerular filtration rate (GFR), of less than 60 mL/min per 1.73 m² that persists for more than three months. (49, 50, 51) Most often used equation for estimating glomerular filtration rate (GFR) from serum creatinine is Cockcroft-Gault equation. (49, 50, 51) The Kidney Disease Improving Global Outcomes (KDIGO) organization classified the stages of CKD using a "traffic light" staging system based on eGFR(G1-G5) and albuminuria (A1-A3) (52).

Table 1. Chronic kidney disease stages

Stage	eGFR value
I	normal or high eGFR ≥ 90 mL/min per 1.73 m²
II	eGFR between 60 to 89 mL/min per 1.73 m²
IIIa	eGFR between 45 to 59 mL/min per 1.73 m²
IIIb	eGFR between 30 to 44 mL/min per 1.73 m²

Stage	eGFR value
IV	eGFR between 15 to 29 mL/min per 1.73 m^2
V	eGFR of < 15 mL/min per 1.73 m^2 or end-stage renal disease
Stage	**albuminuria**(usually measured by urinary albumin-to-creatinine ratio)
A1	< 30 mg/g
A2	30-300 mg/g
A3	>300 mg/g

CKD presents a serious public health problem, affecting 8–16% of the adult population worldwide (53). Risk factors for kidney damage are: diabetes and high blood pressure, high cholesterol, female sex, age >60 years, African American ethnicity, obesity, smoking, inflammatory kidney diseases (54). As kidneys in CKD become affected by tubulointerstitial fibrosis and exhibit nephron loss, they aren't able to remove metabolic "waste", including end-products of protein metabolism (49). Impaired renal clearance leads to accumulation of "uremic toxins" and have negative impact on different biological functions, especially on the inflammatory, cardiovascular and fibrogenic systems (49). There are no obvious clinical symptoms in early stage disease but as time goes, some of the manifestations appear: loss of appetite, nausea and vomiting, itching, muscle cramps, anemia, hemathuria, proteinuria, decreased urine output or more frequent urination, especially at night, hypertension, edema (55). As people with CKD can be asymptomatic, diagnostic tests which include the measurement of the creatinine level in the blood and protein in the urine, are the only way to find out for disease (54). Diagnostic critera for CKD are: decreased eGFR (<90 mL/min/1.73 m2) and one or more marker of kidney demage (albuminuria, urinary albumin to creatinine ratio (ACR) ≥30 mg/g (3 mg/mmol), structural and histological abnormalities, electrolyte and other abnormalities due to tubular disorders, urine sediment abnormalities (hematuria, red or white blood cell casts, oval fat bodies or fatty casts, granular casts, and renal tubular epithelial cells) present for at least 3 months (52, 54). High blood pressure may also point to underlying chronic kidney disease (52, 54). As there is no current medicament for CKD, in usement are some which can help control the signs and symptoms, reduce the risk of complications, and slow the progression of the disease (56). Some of mediacaments which can be used for treatment of CKD, include mineralocorticoid-receptor antagonists, ACE inhibitors, sodium/glucose cotransporter 2 inhibitors, anti-inflammatory drugs, drugs that mitigate oxidative injury, and at the end hemodialysis which is reserved for those patients with ESRD (56).Chronic kidney disease is associated with some complications, usually when GFR declines below 60 mL/min/1.73m2, including increased incidence of cardiovascular disease, hyperlipidemia, anemia and metabolic bone disease, neurogical, infectious disease (50, 53, 57).

CHRONIC KIDNEY DISEASE AND COMORBIDITIES

Comorbidities in CKD include first of all hypertension, diabetes, hyperlipidemia, cerebrovascular disease, malignancy, liver disease, anemia, ischemic heart disease, gout, connective tissue disease, congestive heart failure, thyroid disorder, tuberculosis (58). Hypertension as one of main comorbidity in CKD patients, increased death by nearly 20% for every 10 mmHg higher diastolic blood pressure, and 45% of the patients with ESRD already have advanced manifestations of cardiovascular disease (59). Diabetes Mellitus is present in about 30-40% of all patients with ESRD (59). Patients with three or more comorbidities, male sex, lower baseline eGFR were associated with faster CKD progression, increased risk for dialyzing (58, 59).

CHRONIC KIDNEY DISEASE AND HCV

As we know, chronic HCV infection, which can lead to cirrhosis and hepatocellular carcinoma, also results in numerous other complications, including impairment of renal function (14). Chronic kidney disease (CKD) is one of the most common extrahepatic manifestations in patients with chronic HCV (38). In some study it was showed that HCV-infected patients had a 27% increased risk of CKD, compared with non-HCV patients (14, 38). There are some suggested pathogenic mechanisms of HCV-mediated renal syndromes: direct viral invasion of the renal parenchyma; deposition of immune complex in glomeruls, renal complications of HCV infection; and nephrotoxicity of antiviral drugs (14). We can say that HCV infection is associated with renal disease, as both the cause and the consequence (14, 35). On the other side, patients with end-stage renal disease (ESRD) treated with hemodialysis are at particular risk of acquiring HCV because of permanent vascular access, frequent exposure to possibly contaminated equipment (60, 61). The prevalence of HCV in patients on hemodialysis is high, ranging from 5% to 60% (62). The most represented genotypes in dialysis patients are 1a, 1b, 3 (49). In hemodialysis centers, the most frequent contamination is inappropriate handling of equipment by hemodialysis (HD) center staff, inappropriate disinfection and cleaning of surfaces, inappropriate parenteral administration of drugs (63). In one study revealed that patients with HCV and ESRD have less progression of liver injury, decreased level of AST, ALT and LDH, increased systemic level of IL-6 and Gal-3, and no significant differences in the concentrations of IL-1β, IL-4, and IL-23 and anti-HCV antibodies in comparison with HCV+ patients without ESRD (61). It was noticed that increased systemic level of IL-6 and Gal-3 in ESRD HCV$^+$ patients have hepatoprotective role (61). Gal-3 has hepatoprotective activity in ESRD HCV+ patients on two ways: inhibits local inflammation and consequent destruction of hepatocytes, and inhibits apoptosis (protects mitochondrial membrane integrity, inhibits caspase activation, inhibits releasing of cytochrome C) (61). IL-6 stimulates proliferation of hepatocytes and nonparenchymal cells in the liver, during infection IL-6 induces acute phase protein production in the liver and helps expression of many protective genes in the

hepatocytes stimulating hepatocyte proliferation and their survival (51). Gal-3 and IL-6 protect the liver from virus destruction, subsequently decreasing systemic level of AST and ALT and also stimulates liver regeneration (61). In one study was tested IL-33/sST2 pathway in ESRD HCV+ patients and HCV+ patients without ESRD (64). They found positive correlation between serum level of sST2 and urea and creatinine, and no effect of viral activity on systemic value of sST2 (64). For the first time it was noticed increased level of sST2, significantly increased sST2/IL-1, sST2/IL-4 and sST2/IL-23 ratio in ESRD HCV+ patients in comparison with HCV+ patients (64). Soluble form of ST2 is a decoy receptor for IL-33, which blocks IL-33/ST2 signaling and inhibit inflammation, so ST2 can be considered as an immunosuppresive molecule targeting innate and aquired anti HCV immune response. (64). This implicate less liver damage and its protective role of sST2 in ESRD HCV+ patients (64).

Patients on hemodialysis should be tested on HCV every 6 months and repeat ALT monthly which is increased in those patients (65). Very careful treatment of HCV is necessary for patients with ESRD (66). It was shown that usement of ribavirin for HCV infection in ESRD patients can cause hemolytic anemia (66).

Glecaprevir/pibrentasvir, or paritaprevir/ritonavir/ombitasvir/dasabuvir combination or grazoprevir plus elbasvir regimen can be given to patients with GFR <60 and >30 ml/min/1.73 m^2. Sofosbuvir also can be used but only if there are no other options (66). When patients have a GFR of <30 and >15 ml/min/1.73 m^2, only paritaprevir/ritonavir/ombitasvir/dasabuvir or grazoprevir plus elbasvir regimen can be used (66). The active metabolite of sofosbuvir is eliminated by the kidneys and its use is restricted to patients who have eGFR of ≥30 ml/min per 1.73 m^2(66). For patients with ESRD (GFR <15 ml/min/1.73 m^2 or dialysis patients), glecaprevir/pibrentasvir or grazoprevir plus elbasvir combination may be given (66). Some DAA regimens have been demonstrated to have high safety and efficacy for patients with advanced CKD and ESRD, including glecaprevir/pibrentasvir, which effectively treatsall genotypes of HCV; elbasvir/ grazoprevir for HCV genotypes 1 and 4; ombitsavir/dasabuvir/paritaprevir/ritonavir for genotype 1(67).

CONCLUSION

HCV infection and renal disease are strongly linked. On the one side HCV infection increases the risk of CKD and its progression to ESRD, at the other side patients who are on hemodialysis are in big risk to get HCV infection. Recent studies revealed that ESRD patients have increased systemic level of some cytokines and immunomodulatory mediators that play hepatoprotective role which correlate with less progression of liver injury in comparison with HCV+ patients without ESRD. Several direct-acting antivirals (DAAs) have been approved for clinical use, including NS3/4A, NS5A and NS5B inhibitors The combination of these DAAs has become the standard treatment for patients with HCV infection, which greatly improves sustained virologic response (SVR)

rates to over 90%, and for patients with HCV infection CKD / ESRD.

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CONFLICT OF INTEREST

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