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Hepatitis C in hemodialysis patients

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Abstract

Despite reduction of hepatitis C prevalence after recognition of the virus and testing of blood products, hemodialysis (HD) patients still comprise a high risk group. The natural history of hepatitis C virus (HCV) infection in dialysis is not fully understood while the clinical outcome differs from that of the general population. HD patients show a milder liver disease with lower aminotransferase and viral levels depicted by milder histological features on liver biopsy. Furthermore, the "silent" clinical course is consistent with a slower disease progression and a lower frequency of cirrhosis and hepatocellular carcinoma. Potential explanations for the "beneficial" impact of uremia and hemodialysis on chronic HCV infection are impaired immunosurveillance leading to a less aggressive host response to the virus and intradialytic release of "hepatoprotective" cytokines such as interferon (IFN)-α and hepatocyte growth factor. However, chronic hepatitis C is associated with a higher liver disease related cardiovascular and all-cause mortality of HD patients. Therapy is indicated in selected patients groups including younger patients with low comorbidity burden and especially renal transplant candidates, preferably after performance of a liver biopsy. According to current recommendations, choice of treatment is IFN or pegylated interferon with a reported sustained viral response at 30%-40% and a withdrawal rate ranging from 17% to 30%. New data regarding combination therapy with low doses of ribavirin which provide higher standard variable rates and good safety results, offer another therapeutic option. The new protease inhibitors may be the future for HCV infected HD patients, though data are still lacking.

Key words: Hemodialysis; Hepatitis C infection; Interferon; Ribavirin; Protease inhibitors

Core tip: Despite reduction of hepatitis C prevalence, hemodialysis (HD) patients still comprise a high risk group. HD individuals with chronic hepatitis C virus infection have lower aminotransferase and viral levels, milder histological features and a lower frequency of cirrhosis and hepatocellular carcinoma. However, liver disease is related to higher cardiovascular and all-cause mortality in this patient population. According to current recommendations, choice of treatment is interferon or pegylated interferon, whilst low doses of ribavirin also seem to have promising results. Data regarding new protease inhibitors are still lacking.

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EPIDEMIOLOGY OF HEPATITIS C: GENERAL POPULATION *VS* HAEMODIALYSIS PATIENTS

The prevalence of hepatitis C virus (HCV) infection worldwide is 3% and the infected people are estimated at 170 millions. Prevalence rates in Africa, America, Europe and South-East Asia are under 2.5%. In the Western Pacific regions the average ranges between 2.5% and 4.9% while in some parts of the Middle East HCV prevalence reaches 13%[1-3]. In Greece, a survey among 7016 hemodialysis (HD) patients conducted by the Hellenic Center for Infectious Diseases Control and the Hellenic Society of Nephrology in 2003, revealed a mean anti-HCV prevalence of 7.5%. Before 1990, the main routes of HCV transmission were blood product transfusions, intravenous drug use and unsafe medical procedures. Since the systematic screening of blood products, the risk of HCV infection related to transfusions is extremely low (1/20000000)[4]. Currently, the main sources of HCV infection are intravenous drug use, unsafe medical procedures, mother-to-child transmission and the use of unsterilized materials in activities such as acupuncture and tattooing. Household and sexual transmission is extremely low. The dialysis-related risk is estimated at 2% per year. There is a wide range in the prevalence of HCV infection among HD patients in different parts of the world, varying from 1% to 90%. In northern Europe the prevalence rate is less than 5%, in southern Europe and the United States around 10% and in many countries of northern Africa, Asia and South America ranges between 10%-70%[2]. With the systematic screening of blood products and the use of erythropoiesis-stimulating agents, the risk of transfusion related HCV infection in dialysis patients has dramatically decreased; however, they continue to comprise a "high-risk" group In several studies, the prevalence of HCV infection correlated strongly with time on dialysis, independently of the burden of transfusions and it was higher in HD than in peritoneal dialysis or home HD patients. These data strongly suggest that nosocomial transmission plays a crucial role[5]. Therefore, the Kidney Disease Improving Global Outcomes (KDIGO) workgroup for the prevention of HCV transmission in dialysis patients focused on the implementation of hygienic precautions concerning the staff of HD units and the sterilization of the dialysis machines. Of major importance is the fact that isolation of HCV infected patients does not seem to protect against HCV transmission in HD units and therefore it is not recommended[2].

HCV GENOTYPE DISTRIBUTION

A total of 6 different genotypes and multiple subtypes of HCV, each with a different geographic distribution have been identified. Genotype 1 is the most prevalent genotype worldwide. Subtype 1b is more frequent in Europe and Japan while subtype 1a in the United States. Genotype 2 is prevalent in North America, Europe, Japan (Subtypes a and b) and in northern Italy (subtype c). Genotype 3a is frequently seen in India and in European and American drug abusers while genotype 4 is encountered in North Africa, Middle East and among European drug abusers. Genotype 5 has been found in South Africa, genotype 6 in Hong Kong, genotypes 7, 8, 9 in Vietnam and genotypes 10 and 11 in Indonesia[6-8].

There are no firm data concerning the distribution of HCV genotype among HD patients. In studies conducted in the Netherlands, France, Morocco, Mexico and Turkey, there was a predominance of genotype 1b among patients on HD[9,10]. In a study from the United States, subtype 1a was the most frequent among dialysis patients while in Italian HD patients subtypes 2a and 3a predominated. Some of these studies showed a different genotype distribution in dialysis patients than in the general population, some others did not. In general, subtype 1a seems to be more frequent among HD patients than in the general population[9].

An interesting point is that dialysis patients are susceptible to mixed genotype infections attributed to multiple exposures in the dialysis environment. Mixed infections are not often identified due to their short duration and to the lack of sensitivity of the molecular techniques. When more sensitive techniques were applied, 13% of HCV infected HD patients were diagnosed with a mixed infection. In these patients, one of the transmitted subtypes usually prevails in the course of the disease and it is in general subtype 1a[9,11].

NATURAL HISTORY OF HEPATITIS C

In the general population, acute HCV infection affects 1/100000 subjects per year. In 50%-90% of the cases the infection is asymptomatic. In 30% of cases of acute hepatitis the resolution is spontaneous. Acute hepatitis resolves in 20%-30% of the cases spontaneously while in the vast majority it progresses to chronic hepatitis manifesting with variable, usually mild degrees of inflammation and fibrosis[12,13]. Liver damage is thought to be mediated by HCV-induced host cellular immune response rather by the cytopathic effect of the virus *per se*[3]. About 10%-40% (average 20%) of patients with chronic HCV infection will end up to cirrhosis in the second or third decade after infection while 1%-23% will develop hepatocellular carcinoma (HCC)[3,12,13]. The incidence of HCC in cirrhotic patients is 3% per year while the incidence

of death due to complications of cirrhosis is 4% per year. Factors that contribute to fibrosis progression are alcohol consumption, smoking, metabolic syndrome, co-infection with HIV or other hepatotropic viruses while older age at infection is considered as a major negative prognostic factor[14]. The role of viral load and genotype, as risk factors of progression, is debatable[3,12,13]. Chronic active HCV infection may also have extrahepatic impact, such as cryoglobulinemia-associated vasculitis, cutaneous manifestations, ocular lesions, sialadenitis and B-cell lymphoma[3].

The natural history of HCV in dialysis patients is difficult to assess due to inherent disadvantages. The infection in HD patients is usually asymptomatic and serum aminotransferase and Gamma-Glutamyl Transpeptidase levels are typically within the normal range. Moreover, there are concerns about performing liver biopsy in this group of patients because of platelet dysfunction and higher bleeding risk. Most of the studies show a milder HCV-associated liver disease in dialysis patients compared to the general population. In the study by Okuda *et al*[15], none of the dialysis patients with chronic HCV infection progressed to cirrhosis in contrast to more than ¼ of the infected patients in general population. In the study by Ishida *et al*[16], including patients from 314 hemodialysis units in Japan, the incidence rates of HCC and cirrhosis (1.8% and 8.6% respectively) in HCV (+) dialysis patients were much lower than in HCV (+) patients without renal disease (15%-20% for cirrhosis and 5%-28% for HCC). In the prospective study by Nakayama *et al*[17] among 1470 HD patients with follow up of 6 years, the incidence rate of HCC in dialysis patients was 0.6%, whereas in non-dialyzed patients it reached per year 1.2%. Interestingly, there is an inverse correlation with dialysis duration. In the study by Ishida *et al*[16], the incidence of cirrhosis and HCC in patients who were less than 10 years on dialysis, was higher than for those with dialysis duration of more than 10 years.

Risk factors for progression of liver disease in HCV-positive dialysis patients

Several factors have been associated with a more rapid progression of liver disease in the HD population. These include alcohol abuse, tobacco consumption, older age of HCV acquisition, duration of infection as well as co-infection with HIV or other hepatotropic viruses[18]. There is no universal agreement among authors regarding the role of genotype (especially 1b), viral load, metabolic syndrome and AST levels as risk factors for progression of HCV-related liver disease. On the other hand, male gender and liver siderosis, which are established risk factors for hepatitis progression in HCV (+) non uremic patients, did not correlate with a more severe liver disease in HD patients[8,19,20].

In some studies, genotype 1b correlated with a higher rate of evolution to chronicity, a more severe liver disease and a more aggressive course. Some others suggest that genotype 1b is just a marker of more severe disease reflecting a longer duration of infection, since patients affected with genotype 1b are usually older[8].

DIAGNOSIS OF HEPATITIS C IN CHRONIC KIDNEY DISEASE AND HEMODIALYSIS

Initial testing for HCV

According to the KDIGO hepatitis C guidelilnes of 2009, it is recommended that "patients on haemodialysis should be tested when they first start haemodialysis or when they transfer from another haemodialysis facility" while for predialysis patients with chronic kidney disease the recommendation to test for hepatitis C is weak. Especially dialysis patients who are candidates for kidney transplantation should be screened, evaluated and if necessary treated for hepatitis C before entering the waiting list[21].

Which is the preferable method for initial HCV testing in dialysis patients?

According to the KDIGO guidelines, either initial testing with enzyme immunoassay (EIA) or with nucleic acid testing (NAT) is suggested, depending on the low or high prevalence of the virus in the country and in the particular haemodialysis unit. Currently, 3rd generation EIA is used as the preferable immunologic assay and has proven high sensitivity also in dialysis patients[22]. As in the general population, detection of the HCV antibody by EIA in HD patients may be indicative of acute, chronic or even resolved infection. So, it is reasonable to perform initial screening for hepatitis C in HD patients with 3rd generation EIA while the use of recombinant immunoblotting assay (RIBA), as the confirmatory assay in case of positive EIA, has been largely replaced by NAT[23]. On the other hand, an unknown but substantial number of hemodialysis patients will test negative for anti-HCV antibodies while having detectable HCV viraemia. In a large multicentre German study by Hinrichsen *et al*[24] including 2796 dialysis patients, 0.8% of the entire study population was HCV-RNA positive but anti-HCV negative.There is no doubt that detection of HCV-RNA by RT-PCR is the most sensitive and specific assay for HCV detection. Given the proportion of false negative results and the higher prevalence of the virus in dialysis patients, the preferential test for initial screening is NAT, but the final decision is up to every dialysis unit and depends on the prevalence of HCV infection and the financial status of the particular country[21].

Retesting for HCV in dialysis patients

In initially anti-HCV negative HD patients, retesting with EIA should be considered every 6-12 mo. Retesting with NAT is suggested in patients with unexplained elevation of aminotransferase levels, if there is suspicion of an outbreak of HCV in a HD unit,

in patients on the waiting list for transplantation and for the monitoring of therapy in those who are treated[21].

Liver biopsy

Of major importance in clinical practice is the identification of CHC severity in all patients settings including patients on dialysis.

Besides liver biopsy, novel non-invasive techniques are used to validate hepatic fibrosis. Transient elastography (TE, Fibroscan) evaluates the degree of fibrosis by liver stiffness measurement. It has been used in non-uraemic patients with CHC with good results[25]. The other non-invasive method is the AST-to-platelet-index (APRI). In HD patients, despite promising results reported in one study[26], TE needs to be validated in larger cohorts, whereas APRI has shown low diagnostic accuracy[27]. Thus, liver biopsy still remains the gold standard in the evaluation of CHC and, besides concerns regarding higher bleeding risk due to uremic platelet dysfunction, it has been shown that it can be safely performed also in HD patients[28].

The question concerning the indications of liver biopsy performance remains largely unanswered. Ideally, liver biopsy would be useful, at least initially, in all HCV positive HD patients with sustained viremia in order to evaluate the severity of liver disease, the necessity of therapy and the long term prognosis. In fact, according to the KDIGO guidelines, the only clearly defined subgroup of HD patients in whom a baseline liver biopsy is recommended is this of kidney transplant candidates[2]. The rationale for this recommendation is that a substantial percentage of renal transplant candidates (up to 25%) may have subclinical pre-cirrhotic disease which precludes kidney transplantation. Moreover, kidney transplant candidates with persistent viremia should be treated in order to achieve sustained virological response (SVR) or at least low viremic load before transplantation. Within this context liver biopsy may guide therapy and determine prognosis.

PRINCIPAL DIFFERENCES IN CLINICAL, LABORATORY AND HISTOLOGICAL PARAMETERS IN HEMODIALYSIS PATIENTS WITH HCV INFECTION

Lower viral load in dialysis patients

Based on literature data, HCV load in HD patients is usually low. However, in a few studies similar or even higher viral loads were found compared to non-uremic patients[29-31] while fluctuation of HCV-RNA as well as intermittent viremia have also been reported[32].

Two prospective trials with intermediate to long term follow up have both shown a decrease in HCV-RNA levels and even clearance of the virus in some instances over time in HD patients but not in non-uremic controls[15,33].

Impact of hemodialysis procedure on viral load: A number of studies have investigated HCV viral kinetics before, during and after a regular 4-h hemodialysis session. Most studies revealed a significant decrease in HCV viral load during HD session with a return to basal levels after 48 h, prior to the next dialysis session[33,34].

When the effect of the type of dialysis membrane on viral load kinetics was examined, there was a decrease with hemophan and polysulfone membranes but not with cuprophan[35]. The main mechanisms for the explanation of the intradialytic reduction of HCV are the following.

Passage of the virus through the membrane into the dialysate or the ultrafiltrate

This mechanism seems rather insufficient to explain viral load reduction during HD, since HCV virions are larger (30-40 nm) than the pores of the dialysis membrane (10-20 nm). Three studies failed to detect HCV-RNA in the dialysis ultrafiltrate[36-38].

Adsorption of the virus or viral particles by the dialysis membrane

In vitro and *in vivo* studies evaluating this potential mechanism of HCV reduction have revealed rather conflicting results. The negative findings from *in vitro* investigations render this mechanism unlikely[39,40].

HCV reduction via host-mediated factors

The basis of this interesting concept is that the contact of patients blood with extracorporeal circulation leads to the release of pro-inflammatory cytokines such as IL-6 and TNF-α as well as IFN-α and hepatocyte growth factor (HGF), factors with potentially antiviral properties[34].

Nevertheless, the impact of the dialysis membrane or the dialysis procedure (hemofiltration, hemodiafiltration) on HCV viral kinetics requires further investigation.

Lower aminotransferase levels

Several studies have shown that aminotransferase (AST, ALT) levels are low in patients on dialysis and this reduction appears to occur already in patients with advanced chronic kidney disease even before the initiation of renal replacement treatment[41,42]. HD patients with CHC have serum aminotransferase levels which are at the upper limit but still within the normal range, although higher compared to HCV (-) HD patients.

The diminished values of liver enzymes restrict their diagnostic significance while their use as a tool for hepatitis surveillance and follow-up is unreliable. There is no definite explanation regarding the lower transaminase levels observed in HD patients, although several aetiologies have been postulated.

Vitamin B6 (co-factor for aminotransferase syn-

Table 1 Histological features in hepatitis C virus infected hemodialysis patients

Ref.	Study design/ country	No. of patients	Control group	Histological features	Milder histology in HD as conclusion
Barril[50]	Multicenter observational/ Spain	*n* = 218 HD pts Rebiopsy after 7 yr (*n* = 181)	None	70% chronic hepatitis 3% steatosis 15% cirrhosis 74% stable disease 11% progression	(+/-)
Trevizoli *et al*[48]	Case-control study/Brasil	*n* = 36 aHCV(+) HD pts	*n* = 37 aHCV(+) with normal renal function	HD pts *vs* control group: Hepatic fibrosis 47.2% *vs* 73% ($P < 0.025$) Inflammatory activity 27.7% *vs* 59.5 % ($P = 0.003$)	(++)
Mysorekar *et al*[51]	Observational/ India	*n* = 45 aHCV(+) HD pts	None	67% (*n* = 30/45) mild inflammatory activity+mild fibrosis (stage 0, 1, 2)	(+/-)
Sterling *et al*[31]	Prospective case-contrrol study/United States	*n* = 50 aHCV(+) HD pts (transplant candidates)	Two A.Normal renal function, normal ALT (*n* = 43) B.Normal renal function, ↑ ALT (*n* = 43)	Advanced liver disease (bridging fibrosis/ cirrhosis) in 22% of HD pts *vs* 12% in group A (NS) and 48% in group B ($P < 0.001$) Mild hepatic inflammation in 62% of HD pts (score1-3) *vs* 36% in control groups A and B ($P < 0.0001$)	(++)
Cotler *et al*[30]	Case-control study/United States	*n* = 46 aHCV(+) HD pts	*n* = 46 aHCV (+) with normal renal function	HD pts *vs* control group: Less inflammatory activity ($P < 0.001$) Less bridging fibrosis/cirrhosis (13% *vs* 30%, $P = 0.043$)	(++)
Aslinia *et al*[49]	Cross sectional/ United States	*n* = 156 aHCV(+) HD pts	*n* = 138 aHCV(+) with normal renal function	HD pts *vs* control group: Less necroinflammation ($P < 0.05$) Less fibrosis ($P < 0.0001$)	(++)
Becker *et al*[19]	Brasil	*n* = 216 aHCV(+) HD pts	None	77% absence of septal fibrosis (F0, F1) 12% F2 7% F3	(+)
Sakellariou *et al*[18]	Comparative analysis/Greece	*n* = 61 aHCV(+) HD pts	*n* = 326 non-HD, aHCV(+) pts	4% cirrhosis HD pts vs control group: Milder stage ($P = 0.033$) Lower grade (periportal activity, portal inflammation, lobular activity) ($P < 0.001$) Lower frequency of: Lymphoid aggregates (10.2% *vs* 50%, $P < 0.001$) Bile duct lesions (1.7% *vs* 22.1%, $P < 0.001$) Less extent of steatosis in HD pts ($P = 0.022$)	(++)

HD: Hemodialysis; HCV: Hepatitis C virus; ALT: Aminotransferase.

thesis) deficiency could not be verified as a causative factor due to controversial and limited data[42-44].

In the study by Huang *et al*[45] it was hypothesized that AST levels reflect the high metabolic activity of homocysteine due to its high values observed in HD patients and their correlation with low AST.

The contribution of hemodilution in the decrease of aminotransferases has also been examined by several investigators. Yasuda *et al*[42] observed a 15-35% increase in serum ALT/AST after dialysis compared to the pre-dialysis values. Sombolos *et al*[46] showed that in patients who underwent euvolemic HD, there were no differences in ALT/AST levels prior to and after the procedure. On the other hand, when HD with fluid removal or isolated ultrafiltration was performed, there was an increase in aminotransferase levels after the procedure, indicating that the aminotransferase reduction during dialysis could not be attributed to removal of enzyme inhibitors.

Low aminotransferase levels may also be ascribed to factors related with dialysis procedure, and to the impact of dialysis on disease severity through reduction of viremia, increased production of HGF and IFN-α and lymphocyte activation[47].

Milder histology

There are only a few studies referring to histological data of CHC in HD patients. Mild CHC has been recorded in the majority of previous studies of HCV-infected HD patients with a low incidence of severe fibrosis and cirrhosis (5.5%-13%)[19,48,49]. In a recent comparative study of our group, hepatitis activity (including portal inflammation, interface hepatitis and lobular activity) was minimal or mild in 90% of HD patients. In the same series, fibrosis was usually minimal/mild (60%) or absent (26%) while severe fibrosis and cirrhosis was found in 5% and 3.5% of the cases respectively. A significant lower frequency compared to non-uremic patients was also demonstrated regarding the specific CHC features such as lymphoid aggregates (10.2% *vs* 50%), bile duct lesions (1.7% *vs* 22.1%) and steatosis[18] (Table 1).

PATHOGENETIC BACKGROUND OF CHRONIC HEPATITIS C IN HEMODIALYSIS PATIENTS

As already mentioned, in HD patients setting HCV-induced liver disease runs a more benign course showing a lower incidence of cirrhosis compared to non-uremic patients[16].

Histological findings are strongly supportive of a particularly mild chronic hepatitis type while the demonstration of minimal and mild necroinflammatory activity and lack of immune-related specific features such as lymphoid aggregates and "hepatitic" bile duct lesions, speak in favor of a deficient immune reaction.

Although the factors that "protect" uremic patients from immune mediated liver injury are not very well known, there are some interesting theories for this apparently paradox. Alterations in acquired immunity leading to impaired immune response against pathogens and to inadequate response to vaccinations have been recorded in HD patients[52]. This deficient immune response seems to be multifactorial. There is a defective function of antigen presenting cells (APC's) in means of co-stimulation *via* B7-2(CD86) on monocytes leading to ineffective T-cell proliferation and activation[53]. Most studies dealing with uremia and dialysis have focused on T-cell immunity, however B-cell function is also affected in patients with end-stage renal disease. Altered B-cell subpopulations with an imbalance between immature and memory B-cells as well as reduced expression and signaling *via* the BAFF receptor resulting in reduced B-cell survival and differentiation, have been reported[54,55]. This status of "reduced immunosurveillance" rather than overt "immunosuppression" seems to exert an anti-inflammatory protective effect on dialysis patients with chronic HCV infection.

Another possible pathogenetic mechanism explaining the milder disease profile of hepatitis C in HD patients is that hemodialysis procedure increases the levels of HGF. HGF is a potent mitogen for hepatocytes that promotes liver regeneration and restitution of liver cell loss[56,57]. In a study by Rampino *et al*[58] in 1999, a marked and sustained release of HGF was observed in HD compared to non-HD patients and this was further associated with milder histological findings and a lower degree of fibrosis. The low viral load as triggering factor of a weak immune reaction has also to be taken into consideration.

IMPACT OF HCV INFECTION ON SURVIVAL OF HD PATIENTS

Impact on overall survival

HCV-associated mortality in HD patients is attributed to cirrhosis complications, the development of HCC or to the additive effect of uremia and HCV predisposing to infections and sepsis. The true impact of HCV infection on survival is difficult to assess in HD population, so that longitudinal studies with sufficient numbers of patients, meta-analyses and multicenter cohorts or national surveys are needed. It has to be stressed that HD patients have a 4 to 5 times higher age-adjusted death rate compared to non-uremic patients and a 30-fold increase in cardiovascular deaths, whereas liver-related mortality is usually low[59,60]. This means that HD patients may die from other causes, mainly cardiovascular, before developing cirrhosis or HCC. However, cumulative literature data in this field point towards an increased mortality of anti-HCV(+) HD patients compared to their anti-HCV (-) counterparts.

In a meta-analysis by Fabrizi *et al*[61], that included four studies with a total of 2341 patients and a mean follow up of 37-96 mo, the summary estimate for adjusted relative risk (aRR) of all-cause mortality in HCV(+) HD patients was 1.57 (95%CI: 1.33-1.86) compared to their non-infected counterparts.

As shown in Table 2, data from four national surveys confirm the higher HCV-associated mortality in HD patients[62-65].

Impact of HCV infection on cardiovascular mortality

An increased cardiovascular risk among HD patients with HCV infection has been reported in several studies. Kalantar-Zadeh *et al*[66] studied 2.778 HCV (+) dialysis patients and found that hazard ratio (HR) for cardiovascular death was 1.48 (95%CI: 1.05-2.08, P = 0.02) and persisted after adjustment for several case-mix parameters and for available surrogates of the "malnutrition-inflammation syndrome".

It has been observed that HCV infected patients on dialysis have a greater prevalence of hypoalbuminemia when compared to non-infected patients. In the study of Kalantar-Zadeh *et al*[67] serum levels of albumin were significantly lower in HCV-positive dialysis patients (3.68 ± 0.45 *vs* 3.76 ± 0.41 g/dL). The authors suggested that the impact of HCV infection on nutritional status and inflammation may be a main cause of cardiovascular mortality in the dialysis population. In another study conducted by Petit *et al*[68], HCV infection was associated with liver steatosis, insulin resistance and hypoadiponectinemia, factors related to the metabolic syndrome as well as independent risk factors for cardiovascular mortality. Oyake *et al*[69] evaluated 94 dialysis patients with measurements of aortic stiffness by carotid-femoral pulse wave velocity (PWV). They found that mean blood pressure and HCV viremia were significantly and independently associated with high PWV. Cerebrovascular and cardiovascular event rates were significantly higher in HCV-positive dialysis patients. The authors suggested that HCV infection plays an atherogenic role through aggravation of the metabolic syndrome and dyslipidemia.

In a meta-analysis of fourteen observational studies, the adjusted relative risk for cardiovascular mortality in HCV infected dialysis patients was 1.26 (95%CI: 1.10-1.45)[70]. In a national wide survey

Table 2 Hepatitis C virus-associated mortality in hemodialysis patients: National surveys

National survey	Ref.	No. of HD patients	Outcome	Relative risk
Australia New Zealand Dialysis and Transplant Registry	Scott *et al*[62]	23046 (10-yr follow up)	Independent and significant association between a HCV(+) and all-cause mortality	HR = 1.25 (95%CI: 1.07-1.46, P = 0.004)
National or regional dialysis registries of 10 Asia-Pacific countries/areas (Australia, New Zealand, Japan, China, Taiwan, Korea, Thailand, Hong-Kong, Malaysia, India)	Johnson *et al*[63]	173788	Data available for Australia, New Zealand and Japan	HR = 1.25 (95%CI: 1.07-1.46, P = 0.004)
Dialysis Outcomes and Practice Patterns Study (DOPPS) from the United States (in three continents: Europe, Japan, United States)	Goodkin *et al*[64]	206134	a HCV(+) is an independent predictor of all-cause mortality	RR = 1.17 (P < 0.0159)
The Japanese cohort	Japanese Society of Dialysis[65]	76201	a HCV(+) is an independent predictor of all-cause mortality	RR = 1.37 (95%CI: 1.15-1.62, P = 0.003)

HD: Hemodialysis; HCV: Hepatitis C virus.

Table 3 Meta-analyses of trials with convetional and pegylated interferon-α in hepatitis C virus infected hemodialysis patients

Conventional IFN/Peg IFN therapy	Ref.	No. of patients	Dose	Duration	SVR (%)	Withdrawal rate (%)
Two metaanalysis studies (IFN-α)	Fabrizi *et al*[73]	269	1.5-6.0 MU/d to 3 times per week	24-48 wk	37	17
IFN-α	Russo *et al*[74]	213	3.0-5.0 MU/d to 3 times per week	24-48 wk	33	30
Two head-to-head comparisons (IFN-α *vs* PegIFN-α)	Fabrizi *et al*[75]	645	1.0-6.0 MU/d to 3 times per week (n = 529)	8-48 wk	39	19
			135-180 μg/wk (a-2a) or 0.5-1.0 μg/kg per week (a-2b) (n = 116)	48 wk	31	27
IFN-α *vs* PegIFNα + ribavirin	Gordon *et al*[76]	546	1.0-6.0 MU/d to 3 times per week (n = 459)	16-48 wk	41	26
			135-180 μg/wk (a-2a) or 0.5-1.0 μg/kg per week (a-2b) (n = 87)	24-48 wk	37	28
PegIFN-α	Fabrizi *et al*[77]	254	135-180 μg/wk (a-2a) or 0.5-1.1 μg/kg per week (a-2b)	24-48 wk	33	23

HD: Hemodialysis; HCV: Hepatitis C virus; IFN-α: Interferon-α; PegIFN-α: Pegylated interferon-α; RBV: Ribavirin.

from Autralia-New Zealand within a total of 23046 HD patients, a significantly increased cardiovascular risk was found among HCV infected dialysis patients which persisted after adjustment for age and pre-existing cardiovascular disease (HR = 1.34, 95%CI: 1.08-1.67, P = 0.007)[62].

TREATMENT OF HEPATITIS C IN HD PATIENT

Although difficult to establish, there is a true impact of HCV infection on mortality in HD patients. The principal goal of HCV treatment is to decrease liver related mortality. In most studies surrogate endpoint of therapeutic success is virological response. Among virological responses, the most important is SVR defined as undetectable HCV-RNA, measured by a sensitive assay after the completion of 24 wk of therapy.

The currently recommended therapy for CHC in the general population is a combination of pegylated interferon-α (PegIFN-α) and ribavirin (RBV) for 24 wk (genotypes 2 and 3) and 48 wk (genotype1) with achievement of SVR in about 50% of patients[71].

Unfortunately, treatment-related toxicity with IFN-α (influenza-like symptoms, fever, anemia, neutropenia, neuropsychiatric disorders) and with RBV (severe hemolysis) represent a major barrier to successful therapy. Even in the general population a need for dose reduction has been reported in 35%-42% of patients and treatment discontinuation in about 30%[72].

In end stage renal disease patients, although SVR is even slightly better than for non-uremic patients, all treatment options are associated with increased toxicity and higher withdrawal rates[73]. On the other hand, given the enhanced treatment-related toxicity, the high comorbidity and the slow progression of liver disease, there is no rationale to treat all HD patients with HCV viremia. According to the KDIGO Guidelines, the ERBP Work Group considers that "treatment should be mainly considered for younger patients without major comorbidities and that "the decision to treat should be thoroughly discussed with the patients, particularly if they are infected with genotype 1". They also suggest to "try to clear HCV in transplant candidates by appropriate treatment".

Treatment options are the same as for the general population. Conventional IFN-α, pegylated IFN-α (α-2α or α-2β) or combination of IFN with RBV. Given the altered pharmacokinetics in HD and the high treatment related toxicity, the recommended doses in HD are: conventional IFN (2α or 2β) 3MU three times

Table 4 Studies with combined Ribavirin plus Interferon-α therapy in hepatitis C virus infected hemodialysis patients (n > 10)

Combination therapy	Ref.	No. of patients	Dose	Duration	SVR (%)	Withdrawal rate (%)
IFN-α + RBV	Mousa *et al*[78]	20	3 MU (IFN) + 200 mg (RBV) 3 times per week	24 wk (n = 9)	67	0
			3 MU (IFN) + 200 mg (RBV) 3 times per week	48 wk (n = 11)	36	0
PegIFN-α + RBV	Rendina *et al*[79]	35	135 μg/wk (Peg-IFN-a-2a) + 200 mg/qd (RBV)	48 wk (gtp 1) 24 wk (non-gtp 1)	97	14
PegIFN-α + RBV	Carriero *et al*[80]	14	135 μg/wk (Peg-IFN-a-2a) + 200 mg/qd(RBV)	48 wk	29	71
PegIFN-α + RBV	Hakim *et al*[81]	15	135 μg/wk (Peg-IFN-a-2a) + 200 mg/wk to 3 times per week (RBV)	48 wk	7	33
PegIFN-α + RBV	Liu *et al*[82]	35	135 μg/wk (Peg-IFN-a-2a) + 200 mg/qd (RBV)	48 wk (gtp 1) 24 wk (non-gtp 1)	60	17

IFN-α: Interferon-α; PegIFN-α: Pegylated interferon-α; RBV: Ribavirin.

weekly or reduced doses of pegIFN2α 135 μg/wk or 2β 1 μg/kg weekly whereas RBV is not recommended, but it has been used in clinical trials under strict monitoring of anemia in combination with high doses of erythropoietin. Results from five meta-analyses with IFN therapy and from studies with more than 10 patients which received combined therapy with RBV, are summarized in Table 3. Conventional IFN treatment monotherapy resulted in SVR in 33%-45% of HD patients, though with a withdrawal rate from 17%-30%. As shown in Table 3 the response to PegIFN monotherapy is comparable to slightly better than to conventional IFN with a reported discontinuation rate of 23%-28% in three studies and 0%-20% in one. Combination therapy leads to SVR in 40%-50% of patients with genotype 1 and in 80% of patients with genotypes 2 and 3 while the discontinuation rate is about 33% (Tables 3 and 4)[73-82].

A better understanding of the viral cycle of HCV has resulted in the development of new antiviral drugs, targeting specific enzymes of HCV as protease inhibitors (telaprevir and borceprevir) entry inhibitors, nucleosides and non-nucleosides polymerase inhibitors.

The results of phase Ⅱ and Ⅲ trials of the first generation of protease inhibitors (telaprevir and borceprevir) in combination with standard therapy in the general population of HCV infected patients have been very promising including relapsers and partial or null responders[83,84].

In patients with renal failure and hemodialysis, data regarding these new oral antiviral drugs are not available, though they apparently not require dose adjustments to renal function.

Trials with combinations of the new oral antivirals should be the next step in the improvement of care in hemodialysis patients with HCV.

CONCLUSION

HCV infection remains the major cause of chronic liver disease in HD patients. Although it presents a histologically and clinically milder hepatitis than in the general population -probably related to immunocompromised status and HD procedure- it negatively impacts survival on dialysis. Therapy is indicated in selected cases with acceptable tolerability and clearance of the virus in about one third of the treated patients.

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