Review

Hepatitis C Infection in Hemodialysis Patients

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ABSTRACT: Three centuries after the identification of hepatitis C virus (HCV), specialized literature has outlined the epidemiology, viral kinetics and clinical manifestations of this infection. A major cause of morbidity-mortality in patients with renal transplantation and in hemodialysis patients is HCV infection. In high seroprevalence countries, internal accounts are not uniform. The European trend is to decrease the incidence and prevalence of HCV in hemodialysis patients. In Europe, the prevalence of HCV infection among hemodialysis patients tends to be higher than that of the general population, but it is variable by region. Some studies indicate a decrease in incidence in parallel with prevalence in dialysis centers over the last 10 years, while others maintain a high incidence. In some countries, as is the case with Romania, both prevalence and incidence remain high, with the major route of transmission being nosocomial, probably due to limited resources for a rapidly growing dialyzed population. Some authors recommend more isolation measures to be taken in centers with high prevalence of infection.

KEY WORDS: *hepatitis C virus, hemodialysis, general data*

Introduction

HCV is a small virus (50nm), isolated and cloned for the first time in 1989 [1]. It consists of a ribonucleotide (RNA) positive single strand with approximately 9600 nucleotides [2] and a genome composed of both structural and non-structural proteins.

Seven genotypes have been identified, each of which is divided into several subtypes and strains [3,4].

Of these, genotypes 1-3 are the fastest on the global scale, 1a and 1b being the most common (responsible for 60% infections around the world).

Epidemiology of HCV infection

Numerous laboratory tests have shown with certainty that HCV infection is widespread among patients with chronic kidney disease undergoing hemodialysis. Moreover, they have also shown that HCV infection is a clear cause of morbidity in these patients. Lack of screening tests, contact with blood and blood products, nosocomial transmission and long hemodialysis are the main risk factors for HCV infection [5].

Worldwide, chronic hepatitis C virus has a prevalence between 5% and 60% depending on the geographical region [6-9].

In the US in 2002 HCV infection in hemodialysis centers was estimated at about 8%, about 5 times higher than among the general population [10-11].

In Europe, the incidence of HCV infection among hemodialysis patients is higher than that of the general population, varying from one region to another: lower in the north (England 2%, Sweden 8.8%), and higher in the south (Spain 25%, Italy 27%, Turkey 30%) [12,13].

At national level in 1999, Adrian Covic et. al [14] conducted a study on patients in the region of Moldova. The test concluded that the HCV community prevalence is 7 times higher in Moldova than in Western Europe (4.6% for volunteer blood donors in this region compared to 0.6% in France-RIBA III), suggesting the importance of intra-community transmission. In the region of Moldova, HCV infection was present in 75% of hemodialysis patients, HBV in 17%, and coinfection B+C in 10%. Anti-HCV antibodies were found positive in 47% of patients tested on entry and prior to hemodialysis initiation.

This article also mentions a higher incidence (80.6%) in the dialysis center of Carol Davila Hospital from Bucharest. Apart from the information from Carol Davila Hospital, which is the oldest dialysis center in Bucharest, other data on HCV infection incidence in Bucharest is almost non-existent. Furthermore, the data from the Bucharest University Emergency Hospital does not seem as bleak as the aforementioned.

At the regional level, in Olt County, the results of the epidemiological study on the incidence and prevalence of hepatitis C virus among dialysis patients has revealed an increase in the incidence of declining prevalence among hemodialysis patients over the past 3 years, which is still a real public health problem. The epidemiological study was carried out from 2015 to 2018 with data collected from the three hemodialysis centers in the county (two private centers and one state center).

However, the total positive HCV hemodialysis has been decreasing since 2015. Although there has been an increase in the number of new cases, respectively an increase in incidence, the number of HCV+ excluded from the study (deaths, transfers to another center or peritoneal dialysis, kidney transplantation, or loss of evidence) was even greater, so the difference between the two categories, the prevalence, is decreasing. (Table 1)

Table 1. Current trend of HCV infections among dialysis patients, in the Olt County, Romania

Period	Entrants	Exit	Balance	Incidence	Prevalence	Total	Incidence %	Prevalence %
2015	38*	8	30	4	34	187	2.13	18.18
2016	21	3	18	6	42	187	3.20	22.46
2017	12	13	-1	7	36	194	3.60	18.56
June 2018	9	14	-5	15	28	194	7.73	14.43

Prevention of HCV infection

Chronic hepatitis C virus represents a major cause of morbidity-mortality in transplant and hemodialysis patients. In developed countries, there is a prevalence ranging between 5% and 60% of HCV among patients with end stage chronic renal disease. It is known that the risk of HCV infection is several times higher in chronic kidney disease (CKD) stage V hemodialysed (HD) patients than in non-dialysed patients [14–16]. Over the last few years, the spread of HCV in hemodialysis centers has been decreasing, while the prevalence of chronic hepatitis C virus in these patients remains high [16].

In hemodialysis centers, the most frequent contamination is the inappropriate disinfection and cleaning of surfaces, inappropriate handling of equipment by hemodialysis (HD) center staff, inappropriate administration of parenteral drugs [17,18].

HCV natural history

Acute HCV infection affects 1/100,000 people in the general population per year. The infection is often asymptomatic (50%-90% of cases). In 20%-30% of cases, acute hepatitis disappears spontaneously, while in most cases acute hepatitis progresses to chronic hepatitis. Patients with chronic hepatitis show varying degrees of inflammation and fibrosis (often mild) [19,20].

Hepatic injury is mediated not necessarily by the cytopathic effect of the HCV virus, but by the HCV-induced cellular immune response [21].

About 10%-40% of patients with chronic HCV infection develop cirrhosis after twenty-thirty years, while 1%-23% patients develop hepatocellular carcinoma (HCC) [19-21].

Patients with cirrhosis have a 3% incidence of HCC per year, whereas the death incidence due to cirrhosis complications is 4% per year. Alcohol, smoking, metabolic syndrome, coinfection with HIV or other hepatotropic viruses contribute to the progression of fibrosis, while a major prognostic factor is older age [22].

The role of HCV infection genotype and viral load as risk factors for fibrosis progression is negligible [19-21]. Extrahepatic manifestations of chronic active HCV infection are: B cell lymphoma, ocular lesions, skin manifestations, sialadenitis, and vasculitis associated with cryoglobulinemia [21].

There are certain inherent disadvantages that makes the assessment of HCV natural history in dialysis patients difficult. With the levels of serum aminotransferase and Gamma-Glutamyl transpeptide within normal range, infection in hemodialysed chronic patients is often asymptomatic. Moreover, liver biopsy is

performed rarely in HD patients because of platelet dysfunction and risk of bleeding.

Studies often make a comparison between cases of HCV-related liver disease in otherwise healthy individuals and those undergoing dialysis. For instance, Okuda et al [23], compared renal patients undergoing dialysis while suffering from chronic HCV infections in pre-cirrhotic stages, and renal-disease free patients with HCV infections, of which 25% already progressed to liver cirrhosis. Ishida et al. [24] included data on HCV-infected patients from approximately 314 hemodialysis centers in Japan and found lower incidence rates for cirrhosis (8.6%) and liver cancer (1.8%), significantly lower than those in the renal-healthy general population (15 to 20% for cirrhosis and 5 to 28% for HCC). The prospective study by Nakayama et al [25] showed a significantly lower incidence rate for HCC in dialysis patients (0.6% among 1470 such patients, with 6-year follow-up), while in non-dialyzed patients the incidence was 1.2% per year. In the study by Ishida et al [24], cirrhosis and CHC incidence in patients with dialysis for over ten years was lower than in patients with dialysis for less than ten years. From these studies, we can see that there is an inverse correlation with the duration of dialysis.

Diagnosis of HCV infection in dialyzed patients

In patients infected with HCV, there was an increase in alanine aminotransferase (ALT), these tests being used in the general population for the detection of chronic liver disease. In HD patients, ALT has a poor diagnostic value because ALT tends to be below the baseline. Among the possible causes that could explain this phenomenon are: uremic toxins in patients' blood, vitamin B deficiency or some blood components capable of absorbing ultraviolet light [26]. For this reason, new ALT values were proposed, down to less than half (about 0.4 to 0.45 times) below the standard threshold [27].

In HD patients, serum ALT may be more useful for monitoring HCV infection. However, there are diagnostic tests in these patients, which enumerate enzyme-linked immune technology (EIAs) tests that are used to determine VHC antibodies, their specificity and sensitivity being high, especially those of third generation that are based on nuclear protein antigens of the virus 3, 4, 5. Although testing anti-HCV antibodies by EIA is a common method in the general population, this type of test remains significant only to exclude HCV infection in HD patients because their prevalence remains diminished and the proposed timeframe for antibody testing in these patients is 6-12 months [28].

Determining serological tests is not always relevant because they can have false negative results and cannot be used to distinguish between acute and chronic HCV infection. When anti-HVC EIA is negative, but suspicion of HCV infection remains, HCV RNA is determined using a polymerase chain reaction technique, a viral replication marker [28,29].

If the anti-HCV EIA is positive in an HD patient, the next step is determining the viremia, which is useful for stratification of the patient prognosis prior to initiating antiviral treatment [29].

Blood collection to determine HCV RNA testing should be done before the HD session begins because the anticoagulant used during hemodialysis may influence the sample, and the HCV patient's RNA level may be diminished during the dialysis session [30].

For a more accurate evaluation of treatment response, duration and dose, besides the detection of RNA HCV, one must also determine HCV genotype, keeping in mind that genotypes 1, 4, 5 and 6 are more resistant to treatment, requiring a longer duration of treatment. According to a study in Turkey made on dialysis patients HCV genotype 1b is a specific marker [16].

Another study by Perez and co-workers [31] showed that genotype 1a is the most widespread subtype in dialysis patients, followed by genotype 1b and genotypes 3. This finding highlights the epidemiology of HCV infection, host factors and viral characteristics in patients with CKD stage V treated with HD [32].

Hepatic biopsy remains the gold standard for examining the degree of fibrosis produced by HCV infection and the elimination of other concomitant liver disorders [32].

The severity of hepatic lesions is not reflected by HCV viral load nor liver enzymes [33,34].

Enzymatic activity and the amount of HCV RNA can oscillate during hepatitis C virus infection, while fibrosis has a progressive and irreversible evolution. There are studies demonstrating that the stage of hepatic fibrosis, which is related to HCV, influences the morbidity of patients who are candidates for renal transplantation. In addition to that, the determination of the stage of hepatic fibrosis is essential for the HCV therapeutic strategy [35].

According to studies, up to 25% of HCV-infected patients show fibrosis or cirrhosis before liver biopsy [27].

Hepatic fibrosis is not an exclusion criterion for potentially renal transplant patients, but it is inevitable that these patients will not experience comorbidities and post-transplant complications [36].

Although liver biopsy remains essential in determining the degree of hepatic fibrosis, it has considerable limits, these being the number of bleeding during the invasive maneuver, as well as sampling and interpretation errors.

Anticoagulation during hemodialysis, coagulopathy, platelet dysfunction, thrombocytopenia, and antiplatelet therapy represent an additional risk of bleeding in these patients, therefore, transfemoral or transjugal biopsy pathway is recommended. It is noteworthy that although liver biopsy is performed correctly by an experienced physician and by a good pathologist who examines the evidence, there is still an error margin of up to 20% in the staging of liver disease [35,36].

Treatment

HCV infection has a strong impact on mortality in HD patients, so treatment of hepatitis C in these patients is difficult to establish. It is essential for HCV treatment to reduce liver-related mortality. Therefore, therapeutic success is considered the virological response in most studies. The most important virological response is the sustained viral response (SVR), which is defined as undetectable HCV RNA. SVR is measured by a susceptible test after therapy of more than 24 weeks. At the moment, treatment-associated toxicity induces symptoms such as fever, neutropenia, anemia, neuropsychiatric and disorders, as well as severe haemolysis, representing a major barrier to successful therapy. Moreover, even in the general population there was a need for a dose reduction in 35-42% of cases, while in 30% of cases a discontinuation was necessary [37,38].

Although SVR is easier in patients with renal disease, almost every treatment option available is associated with increased toxicity, as well as higher withdrawal rates [39].

On the other hand, taking into consideration the slow progression of liver disease, as well as the high toxicity of the treatment and co-morbidity, not all HD patients with HCV viral hepatitis should be treated. Treatment options for HD patients with HCV are in fact the same as for the general population. Thanks to a better understanding of the HCV viral cycle, new antiviral drugs have been made available, which are targeting enzymes specific to HCV as protease inhibitors, nucleoside and non-nucleoside inhibitors, showing partial or no recurrences and very high rates of respondents [40,41] with renal insufficiency and hemodialysis. No dose adjustments seem to be necessary for renal function, despite the fact that information on these new antiviral drugs is scarce. However, the next step in improving care in HCV hemodialysis patients should be combination trials of new oral antivirals.

Conclusions

HCV prevalence remains high, especially in Romania.

Dialysis patients, suffering from chronic renal disease are a special group, in which evolution, prognosis and treatment options for HCV-related liver disease remain problematic.

Different approaches are to be attempted, many ongoing studies showing promising data and good results.

Newly introduced treatment options for HCV will greatly change the prospect of these patients, especially in a resource-limited environment.

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Conflict of interests

The authors declare that they have no conflict of interests.

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