REVIEW ARTICLE

Viral Hepatitis in Hemodialysis: An update

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ABSTRACT

Hepatitis outbreaks in hemodialysis (HD) patients and staff were reported in the late 1960s, and a number of hepatotropic viruses transmitted by blood and other body fluids have been identified. Hepatitis B virus (HBV) was the first significant hepatotropic virus to be identified in HD centers. HBV infection has been effectively controlled by active vaccination, screening of blood donors, the use of erythropoietin and segregation of HBV carriers. Hepatitis delta virus is a defective virus that can only infect HBV-positive individuals. Hepatitis C virus (HCV) is the most significant cause of non-A, non-B hepatitis and is mainly transmitted by blood transfusion. The introduction in 1990 of routine screening of blood donors for HCV contributed significantly to the control of HCV transmission. An effective HCV vaccine remains an unsolved challenge; however, pegylation of interferon-alfa has made it possible to treat HCV-positive dialysis patients. Unexplained sporadic outbreaks of hepatitis by the mid-1990s prompted the discovery of hepatitis G virus, hepatitis GB virus C and the TT virus. The vigilant observation of guidelines on universal precaution and regular virologic testing are the cornerstones of the effective control of chronic hepatitis in the setting of HD. Major recent advances in the viral diagnosis technology and the development of new oral, direct acting antiviral agents (DAAs) allow early diagnosis and better therapeutic response. The current update will review the recent developments, controversies and new treatment of viral hepatitis in HD patients.

Key Words: DAAs (Direct acting antiviral agents), Hemodialysis, Hepatitis B, Hepatitis C, Occult HBV, Viral hepatitis.

Introduction

It is well known that patients undergoing dialysis treatment, and in particular hemodialysis (HD), are at increased risk for contracting viral infections. This is due to their underlying impaired cellular immunity, which increases their susceptibility to infection. In addition, the process of HD requires blood exposure to infectious materials through the extracorporeal circulation for a prolonged period. Moreover, HD patients may require blood transfusion, frequent hospitalizations and surgery, which increase opportunities for nosocomial infection exposure.[1] The most frequent viral infections encountered in HD units are hepatitis B (HBV), hepatitis C (HCV) and, to a lesser extent, human immunodeficiency virus infection (HIV).

After the identification of HCV in 1989 and HEV in 1990, there were still unexplained cases of posttransfusion and "community-acquired" hepatitis, implying that cryptogenic hepatitis and cirrhosis may be related to viruses other than hepatitis A, B, C, D or E. By the mid-1990s, between 3% and 4% of anti-HCV-negative patients on chronic HD had elevated serum aminotransferase levels with no apparent etiology.[2,3] In 1995-1996, Simons et al.[4] and Linnen et al.[5] both from the United States, independently reported a group of putative agents that

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accounted for the unexplained non-A to non-E hepatitis. These viruses were named GB virus C (GBV-C) and hepatitis G virus (HGV). HGV was identified by molecular cloning with plasma from a patient originally identified by the CDC as having NANBH.[5]

In the current review, we will restrict our update to HBV and HCV only, and will discuss the most recent data of these viruses in HD.

HEPATITIS B VIRUS (HBV)

HBV infection is a substantial global health problem. It is estimated that more than two billion people worldwide have serological evidence of current or historical infection.[6]

Epidemiology of HBV

Hepatitis B is a blood-borne virus. Modes of infection include perinatal and through percutaneous or mucosal exposure to infected blood or body fluids.[7]There are considered to be more than 350 million people worldwide with chronic hepatitis B (CHB) infection.In dialysis units, both patient-to-patient and patient-to staff transmission of the virus have been recognized since the 1960s. In 1977, guidelines were published in the USA to reduce HBV infection in dialysis units.[9] The incidence of new hepatitis B infections in US dialysis patients subsequently fell from 6.2% in 1974 to 1% by 1980.[10] Testing of a vaccine began in the 1970s, and this came into widespread clinical use from the early 1980s.[11,12] This further reduced the risk of HBV infection in the dialysis setting. In addition to being at increased risk of infection, it has been demonstrated that HD patients are more likely to become chronic carriers of HBV than members of the general population.[13]

Occult Hepatitis B virus Infection (OBI)

Recently, with advanced HBV diagnostic tools, emerged the problem of occult HBV infection (OBI). OBI is defined as the presence of HBV-DNA without detectable HBsAg with or without hepatitis B core antibody (anti-HBc) or hepatitis B surface antibody (anti-HBs). Sensitivity and specificity improvement of polymerase chain reaction (PCR) methods with a detection limit of<10 IU/mL for HBV-DNA led to the identification of an increasing number of individuals carrying HBV-DNA as the only marker of infection. [14,15]

The clinical implications of occult HBV infection involve different clinical aspects. OBI harbors the potential risk of HBV transmission through HD, blood transfusion and organ transplantation. It can cause cryptogenic liver disease, acute exacerbation of CHB or even fulminant hepatitis, poor response to antiviral treatment and development of hepatocellular carcinoma(HCC). [16]

Occult HBV infection in HD patients

HD patients are at a high risk of acquiring parenterally transmitted infections, not only because of the large number of received blood transfusions, the invasive procedures that they undergo, low response to HBV vaccination and duration on dialysis but also because of their immunosuppressed state. [20] The prevalence of OBI in renal dialysis patients ranges between 0% and 58% in published reports. [17,18,19]

In an investigation on the prevalence of OBI in continuous ambulatory peritoneal dialysis (CAPD) and HD patients, 16.9% of HD patients and 9.8% of CAPD patients were HBV-DNA positive. Anti-HCV was negative and AST and ALT levels were normal in all of the HBV-DNA positive patients. They concluded that the prevalence of the occult HBV may be common in CAPD patients as in HD patients, and HCV positivity is not a contributing factor to occult HBV infection in dialysis patients.[21]

OBI and HCV infection

HCV infection suppresses the replication of HBV and also the expression of HBV surface protein in vitro and in vivo. [22,23] Therefore, HBsAg synthesis may be down-regulated by co-infection with HCV.[22,24] The presence of OBI in patients with chronic hepatitis C infection was frequently reported, [25] and suggested a co-incidence for HBV and HCV infection and mentioned a possible role for OBI in the chronic HCV-related liver disease.[25]

Prevention of HBV infection

Despite stringent measures, failures of infection control mechanism leading to isolated outbreaks of HBV infection in HD centers were still reported in the 1980s and 1990s.[26] Further preventive strategies that have been developed over the past 25 years include the increased availability of disposable

dialyzers, sophisticated machines and electronic fail-safe systems, the replacement of arterio-venous shunts with fistulae, durable synthetic grafts and cuffed indwelling venous catheters, the routine viral screening of blood donors and the launching of recombinant human erythropoietin in 1989 to substitute for or reduce the need for blood transfusion.[27] Hand washing after touching blood or body fluid and the use of gowns and face shields when exposure is anticipated. Furthermore, two additional strategies represent important milestones in the prevention of HBV infection in the dialysis setting: Active vaccination and segregation of HBV carrier.

Hepatitis B vaccination

Hepatitis B vaccine: In the 1970s, Krugman observed that HBsAg was immunogenic and that anti-HBs antibodies were protective against Hepatitis B.[28]Current recommendations state that dialysis patients should receive higher vaccine doses than individuals with normal renal function. As such, 40mg of Recombivax HB at 0,1 and 6 months or 40mg of Engerix B at 0,1,2 and 6 months should be administered. The best reported response rates to these schedules are <85% achieving seroprotection[29]

Management of chronic HBV infection

The primary goal of treatment should be complete eradication of the virus. Studies have showed that satisfactory responses to current anti-viral therapies were observed only in patients with certain well-defined clinical characteristics; the decision to start is, therefore, relying on the demonstration of active viral replication (HBeAg and/or serum HBV DNA detected by branched DNA or hybrid capture assays) and active liver disease (elevated serum ALT concentrations >1.5 times ULN and/or evidence of moderate/severe chronic hepatitis on liver biopsy).[30] Dialysis patients are used to having depressed baseline serum ALT levels, and their serum ALT levels could remain normal despite the presence of significant liver disease. The conventional cut-off value with serum ALT level >1.5 times ULN therefore might prove too high and not sensitive enough for the identification of HBV-infected dialysis patients with significant hepatic inflammation who otherwise warrant anti-viral treatment.

Current treatment options for patients with CHB are interferons or antiviral therapy with nucleos(t)ide analogs (NAs) that target the viral polymerase.[31] The treatment of CHB in patients with CKD is based on nucleoside (lamivudine, telbivudine, entecavir) or nucleotide (adefovir, tenofovir) analogues (NAs). Entecavir and tenofovir represent the currently recommended first-line NAs for NA-naive CHB patients, while tenofovir is the NA of choice for CHB patients with resistance to nucleosides.[32]

HEPATITIS C VIRUS(HCV)

HCV Epidemiology

Hepatitis C is a liver disease caused by the HCV, the virus that can cause both acute and chronic hepatitis infection ranging in severity from a mild illness lasting a few weeks to a serious, lifelong illness. The HCV is a blood-borne virus and the most common modes of infection are through unsafe injection practices; inadequate sterilization of medical equipment in some health-care settings; and unscreened blood and blood products. One hundred and thirty to 150 million people globally have chronic hepatitis C infection.[33]There is currently no vaccine for hepatitis C; however, research in this area is ongoing.[33]

HCV infection in HD

Global magnitude of the problem The prevalence of HCV infection varies greatly among patients on HD from different geographic regions.[34] Wreghitt[35] described a range from 4% in the UK to 71% in Kuwait for HCV prevalence among a HD population.

Risk factors of HCV infection in CKD patients

Several factors are known to be associated with increased risk of HCV infection. A relatively large study in Brazil demonstrated that patients on HD for more than 3 years had a 13.6 fold greater risk of HCV positivity compared with subjects with less than 1 year of HD treatment.[37] Historically the number of blood transfusion received was consistently reported in the literature to be associated with an increased prevalence of HCV-positive dialysis patients. [38] Other risk factors include older age, [39,40] dialysis in multiple centers, [37,39,41] a history of organ transplantation, [42-44] hepatitis B infection,[43,45] HIV infection[40,46] and diabetes mellitus.[47,48]

HCV Diagnosis in HD Population

Routine serological testing for HCV infection among HD patients is currently recommended. [49,50] The rational is based on the following evidence:

a. HCV infection has a silent and subclinical course;
b. Liver biochemical tests are poor indicators of HCV infection among HD patients;
c. HCV infection is more prevalent among HD patients than in the general population;
d. Nosocomial transmission of HCV is a major problem in HD units and
e. Early identification of HCV-infected patients is essential.[50]

The current CDC recommendations for HCV screening in HD patients include testing for anti-HCV and serum ALT on admission, ALT every month and anti-HCV semiannualy. [49,50]

HCV Core Antigen

Recent advance in diagnosing early HCV infection is made by detecting the HCV core antigen (HCVcAg) that is present during the early stage of infection when anti-HCV seroconversion has not yet been established. HCVcAg testing permits the detection of an HCV infection about 1.5 months earlier than the HCV antibody screening tests and an average of only 2 days later than quantitative HCV RNA detection in individual specimens.[51] The efficacy of HCVcAg ELISA ranged from 81.9% to 95.9%. [52,53] The concentrations of HCVcAg and HCV RNA levels are significantly correlated. [53,54]

HCV prevention in HD

Nosocomial transmission of HCV in HD units is well established. [41,43,55-57]Lack of strict adherence to universal precautions by staff and sharing of articles such as multidose drugs might be the main mode of nosocomial HCV spread among HD patients. [57-61]

The CDC recommends that special precautions should be observed in dialysis units, including wearing and changing of gloves and water-proof gowns between patients, systemic decontamination of the equipment circuit and surfaces after each patient's treatment and no sharing of instruments (e.g., tourniquets, stethoscope, blood pressure cuff) or medications (e.g., multi-use vials of heparin) among patients.[62] The guidelines of the "Kidney Disease: Improving Global Outcome"(KDIGO) in 2008 recommend, as well, the adherence to the universal measures to prevent the HCV transmission in HD units[63]

Studies supporting isolation

In our personal experience in Medinah, Saudi Arabia, because of the high prevalence of HCV infection reaching 80% of our HD patients, we decided in 1996 to apply a complete isolation policy (separated rooms, machines and staff) of HCV-negative patients from HCV positive in addition to adherence to the universal precautions; in 2000, the prevalence of HCV-positive patients dropped to 40% and in 2006 this prevalence was 25%.[36] In our current experience in the UAE, the HCV isolation policy was applied in 1993, where the prevalence of HCV positivity was 40%, decreasing to 18.3% in 2002 and to 9.6% in 2014; we did not have any case of seroconversion during these 21 years (unpublished data).

Karkar et al. have reported a significant drop in the prevalence of HCV-positive patients from 57% to 29% after applying an isolation policy.[1] Mohamed et al. have reported similar results in decreasing the HCV-positive prevalence from 50% to 23% by the application of full isolation policy over a 5-year period from 2003 to 2008.[64]

Management of HCV infection

Treatment overview

Cumulative studies in the past two decades have shown that different genotypes respond differently to interferon (IFN)-based therapy, with genotypes 2 and 3 being the most easily cured and genotype 1 having the lowest cure rates with IFN-based regimens. With the approval of NS3/4 protease inhibitors (PIs) used in combination with pegylated IFN-alfa (PEG) and ribavirin (RBV; PEG+RBV), genotype 1b was found to have a higher barrier to resistance and thus was easier to cure than genotype 1a.[65] The genotypes have not been shown to differ in their progression to cirrhosis or in the development of liver cancer.[66]

Until 2011, the standard of care for the treatment of chronic HCV was PEG + RBV for 24-48 weeks, depending on HCV genotype. PEG and RBV represent nonspecific antivirals, of which the mechanisms of action in treating HCV were poorly understood. Response to therapy is gauged by rapid virologic response (RVR), which is defined as an undetectable serum HCV RNA 4 weeks into treatment. When the HCV RNA remains undetectable from 4 weeks to 12 weeks of therapy, it is called an extended RVR (eRVR). Cure is defined by sustained virologic response (SVR), a persistently negative HCV RNA 12 (SVR12) or 24 weeks (SVR24) after the completion of therapy. Virologic relapse is the recurrence of quantifiable levels of HCV RNA after the completion of treatment.[67]

Treatment of HCV in HD patients

At present, therapy for hepatitis C in patients with endstage renal disease is controversial and should be considered only in patients waiting for renal transplantation, those with significant liver disease and minimal comorbid conditions that may affect survival and in patients with acute hepatitis C. The therapeutic regimen varies with the severity of the kidney disease. Persons with creatinine clearance of more than 60 mL/min can be treated like those patients without kidney disease. Ribavirin (RBV) is cleared by the kidneys; therefore, HD patients have been treated with peg-IFN-α mono-therapy.[69] Because peg-IFN-α 2a is cleared through the liver and peg-IFN-α2b primarily through the kidneys, [68] there could be a theoretical accumulation of pegIFN-α 2b when used in HD, although HD does not appear to affect clearance.[70,71]

Although the current practice is to administer the full dose of peg-IFN-α, the recommended starting doses for this group are peg-IFN-α 2b at 1 μg /kg subcutaneously once weekly or peg-IFN-α 2a 135 μg subcutaneously once weekly. In the absence of RBV, SVR rates are substantially lower and careful patient selection and side effect management are important. Most studies used a 6-month post therapy SVR as the end point for successful therapy. Overall, 40% of HCV-treated patients had an SVR, including 31% for genotype 1, a rate greater than that reported for IFN monotherapy.[72]

The use of new Direct Acting Antivirals(DAAs), telaprevir and boceprevir, which are HCV protease inhibitors (PIs), showed no significant impact of renal dysfunction when these medications were used in patients with end-stage renal disease,[73] suggesting that both drugs might be used to treat HCV infection in this setting.[74] A recent study that included 36 treatment naive HCV genotype 1 HD patients showed that telaprevir containing triple therapy had superior efficacy than PEG-IFNα/RBV dual therapy, but was accompanied with more frequent and severe anemia.[74]

Conclusion:

Viral hepatitis continues to be a significant health problem in HD patients, in particular in the developing countries with limited resources. New diagnostic tools allow early diagnosis and better control of hepatitis in the dialysis units. Optimizing the HBV vaccination in predialysis care, the strict adherence to the universal precaution measures, segregation of HBV-positive patients in an isolated area and use of the modern therapies are the mainstay in controlling HBV infection in HD units. The issue is more complicated for HCV in the absence of specific vaccine, the nosocomial transmission of the virus, the controversy of isolation and the bad tolerance for the current available treatment. However, the recent development of DAA medications for HCV, the hard work to produce an anti-HCV vaccine and the strong emphasis on the adherence to the universal infection control precautions will give the hope for the cure and the control of HCV infection in this population of patients.

Conflicts of Interest: We have no conflict of interest.

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