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Case Report

Eradication of Combined Hepatitis B (HBV) and C (HCV) in Patients with Chronic Kidney Disease on Chronic Hemodialysis. A Case Study and Review of literatures

Ehab Mohamed Wahba Wafa, Mohammed Al-Homrany*, Dujana Mousa, Ali Alharbi, Amr Salah and Doaa Mosa

Diaverum AB-Clinic 9017, Khamis Mushait Dialysis Center, King Khaled Rd- Khamis Mushait General Hospital, Khamis Mushait, Kingdom of Saudi Arabia

Abstract

Hepatitis C Virus (HCV) infection is a global health threat. The available data suggest that HCV prevalence is about 2-3% of the world's population (130-170 million people). HCV is one of the few communicable disorder that continue to grow, with 47% increase in mortality over the last 2 decades. HCV is highly prevalent among chronic kidney disease subjects under hemodialysis and is important cause of morbidity and mortality in these patients.

The recently available combination therapy of Direct Antiviral Agents (DAA) (Ombitasvir, Paritaprevir and Ritonavir) in addition to Ribavirin have proven efficacy for dialysis patients infected with genotype 1b and 4 in several trials.

Co-infection prevalence of hepatitis C and hepatitis B virus in USA is 1.5-3% in the HCV only population and 3.7-11.3% in HCV with kidney involvement population, the latter is close to about a 10% co-infection prevalence in the general global population. Anti HCV treatment can cause reactivation of HBV during treatment and several severe comorbidites which requires strict supervision throughout therapy.

Our case report is a patient with combined HCV (geotype4) and HBV infection. She is under regular hemodialysis since two decades with failed trial of interferon therapy since few years.

Thanks to the available Direct Antiviral Agents (DAA): (Ombitasvir, Paritaprevir and Ritonavir) combination in addition to Ribavirin .This combination has eradicated both HCV and HBV without significant side effects or comorbidities. Quantitative PCR analysis has proven Rapid Virological Response after 3 months (RVR3) and Sustained Virological Response at one year of start of treatment (SVR12) unexpectedly.

We are fortunate with these results which stimulate us to go to randomized controlled trial as little is published on viral co-infection in dialysis population in particular as they are at a great risk of accelerated morbidity and mortality.

***Corresponding author:** Mohammed Al-Homrany, Consultant Nephrologist, Regional Medical Director, Diaverum, Abha, Kingdom of Saudi Arabia, Tel: +966 0172227288; E-mail: Mohammed.alhomrany@diaverum.com

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Introduction

Hepatitis C Virus (HCV) infection is a recognized public health concern with global implications that affects approximately 170 million individuals worldwide [1-3]. Infection with HCV is associated with an increased morbidity and mortality secondary to hepatic injury and associated complications [4].

The infection, however, can also affect other organs with significant extrahepatic manifestation. These include insulin resistance, cryoglobulinemic vasculitis, sicca syndrome, neurocognitive dysfunction, B-cell non-Hodgkin lymphoma and an increase in cardiovascular adverse events [3-6]. Patients with HCV infection are reported to have increased incidence of proteinuria and Chronic Kidney Disease (CKD) [4], associating essential cryoglobulinemia or idiopathic membrano-proliferative glomerulonephritis [6,7].

Patients with End Stage Renal Disease (ESRD) is suggested to have a higher prevalence of HCV infection due to greater blood product exposure and patient-to-patient transmission of disease within the dialysis clinics [7].

HCV causes B cell activation resulting in expansion of malignant cell lines or the production of unique antibodies that are of the IgM isotype and possess rheumatoid factor like activity [8,9]. As a consequence of these events, clinical syndromes including mixed cryoglobulinemia, lymphoproliferative disorders and glomerulonephritis with distinct histological patterns including membranous or membranoproliferative glomerulonephritis can be seen [3,4,10,11].

Circulating immune complexes formed due to HCV infection are trapped in the glomerular basement membrane and become clinically expressed as type 2 mixed cryoglobulinemia with resulting type1 membrano-proliferative Glomerulonephritis (GN), mesangial proliferative and focal proliferative GN, IgA nephropathy, membranous GN and polyarteritis nodosa [3,8,11].

Suppression of viral replication is necessary to interrupt immune-complex production and subsequent injury to the kidney. The VASCUVALDIC study described the use of sofosbuvir and ribavirin in 24 patients with HCV-vasculitis syndrome and cryoglobulinemia.

Patients were treated with Direct-Acting Antiviral Agents (DAAs) for 24wk and achieved a Sustained Viral Response at week12 (SVR12) of 74% with minimal side effects [12]. The less common presentation of an active vasculitic syndrome due to the cryoglobulinemic syndrome requires a targeted aggressive treatment strategy against the ongoing endothelial inflammatory process. Recommended therapy include high dose corticosteroids, rituximab and therapeutic plasma exchange in addition to appropriate DAA therapy to eradicate viral replication [12-15].

HCV-infected patients have an increased risk for the development of CKD and proteinuria [4,16]. Furthermore, emerging data suggests that the rate of CKD progression to ESRD is greater than the non-infected patients[16]. Furthermore HCV-infected patients with CKD stages Ⅰ, Ⅱ and Ⅲ a should be considered for DAA therapy targeting to slow the progression of CKD. HCV-infected patients with CKD stages Ⅲb, Ⅳ and Ⅴ will require a more individualized approach depending on the renal replacement therapy options being considered.

In the ESRD patient, it is estimated that 5%-10% of the United States dialysis population is infected with HCV [17]. Many studies have demonstrated that HCV infection is associated with an increased risk of mortality and worse clinical outcomes in ESRD patients [3,18-21]. The increased morbidity and mortality associated with HCV infection may be due to the multiple HCV-associated extrahepatic manifestations and complications [4,19]. An increased cardiovascular risk attributable to HCV infection has been demonstrated in the ESRD patient [19].

As for dialysis-related HCV infection HCV infection is widely spread in dialysis units where hygienic measures are suboptimal. In certain units, the prevalence of infection exceeds 80%. Not only does this negatively impact on patient survival, and subsequent transplant outcomes, but it also generates a reservoir that disseminates infection to the community [13,14].

In an updated report from The Dialysis Options and Practice Patterns Study data, it was concluded that HCV infection in ESRD patients was associated with an increased risk of death and hospitalization, anemia and worse quality of life scores for physical function, pain, vitality and mental health [22]. Consequently, successful treatment is suggested to deliver a positive impact on outcomes. Hsu et al. [23], reported that IFN-based therapy increased survival in HCV-infected. The authers further reported that ESRD patients receiving IFN plus ribavirin obtained improved renal and cardiovascular outcomes compared to those who were untreated [24].

In a metanalysis of 24 prospective studies, including 529 HCV +ve patients on hemodialysis who were treated with Interferon-Alpha (IFN-α), it was shown that mono therapy resulted in a Sustained Viral Response at 48 weeks (SVR48) in only 39% of cases [25]. Better outcomes (SVR48 of 50-60%) were achieved by a combination of Peg-interferon and reduced doses of ribavirin [26]. Survival was significantly improved in treatment responders, with a hazard ratio for death of 0.47 compared to untreated patients according to the DOPPs data including 4589 HCV-infected patients [26]. Despite this remarkable advantage, only 1% of patients on regular dialysis and 3.7% of those on the transplant waiting list actually received treatment during the Interferon era [27]. This trend will undoubtedly change with the introduction of DAAs, which currently achieve a SVR12 of 100% with Paritaprevir/ Ritonavir+ Ombitasvir [28] or 84.6% with RBV-free Simeprevir +1/2 dose sofosbuvir [29].

The viral genotype is an important determinant of response to treatment. The choice of treatment protocol must be based on genotype-specific Randomized Controlled Trials (RCTs). Since HCV genotypes are globally dispersed on geographical basis, it is presumed that patients in the same community share the same genotype, which justifies the adoption of country-specific guidelines. Whenever there is paucity of RCTs on a particular genotype, it makes sense to extrapolate data on pangenotypic drugs from other genotype studies [30,31].

The Japan Society of Hepatology (JSH) guidelines for the management of HCV infection recommends combination therapy with Daclatasvir and Asunaprevir (DCV/ASV) as interferon-free Direct-Acting Antiviral Agents (DAAs) for dialysis patients with chronic infection of HCV genotype 1b (HCV/1b) in Japan. This therapy has several flaws compared to the more updated regimen of Ombitasvir, Paritaprevir and Ritonavir (OBV/PTV/r). This recently available combination therapy with (OBV/PTV/r) is not contraindicated in patients with chronic renal failure and has more safety profile and shorter treatment period than that with DCV/ASV, and was recently reported to show a Sustained Virological Response at 12 weeks after treatment (SVR12) [32-34].

The European Association for the Study of the Liver (EASL) Guidelines recommend ombitasvir/paritaprevir/ritonavir plus ribavirin as an option in treatment-naive and-experienced patients with chronic HCV genotype 4 infection without cirrhosis or with compensated cirrhosis [35]. This recommendation applies both to patients with HCV genotype 4 monoinfection and patients co-infected with HCV genotype 4 and HIV [35].

Ombitasvir/paritaprevir/ritonavir plus ribavirin is also one of the options recommended in American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA) guidelines for use in treatment-naive and -experienced patients with chronic HCV genotype 4 infection [36]. The ombitasvir/paritaprevir/ritonavir dosage does not need to be adjusted in patients with renal impairment, in the elderly or based on gender, bodyweight, race or ethnicity [37].

In addition to the constraints of using DAAs in CKD Stages IV/V, drug analyzability is an additional factor to consider upon selecting suitable treatment for patients on regular dialysis. Dialyzability depends on the drug's molecular size and configuration, its protein binding, electrostatic charge and other less significant factors. It is possible to predict drug dialyzability by physical and pharmacokinetic studies, yet clinical trials remain crucial for a final conclusion [30].

Some precautions are also taken when treating patients with a HCV and Hepatitis B Virus (HBV) co-infection. The co-infection prevalence in the USA revealed by Solid et al. [38], is 1.5-3.0% in the HCV-only population, and 3.7-11.3% in HCV with kidney involvement population (that is close to about a 10% co-infection prevalence in the general global population [39]). It is noteworthy, that this substantial proportion of patients has an increased risk not only of more rapid liver disease progression, but also of HBV reactivation in case of anti-HCV treatment [40,41], which requires strict monitoring throughout therapy.

Case Report

A 67 years old female was receiving hemodialysis due to chronic renal failure secondary to adult polycystic kidney disease. Dialysis

was started since 22 years. She was hypertensive since her last pregnancy which antedates dialytic therapy by few years. She had negative virus serology for HBV, HCV and HIV and was dialyzed in the clean area for around three years, then she was shifted to isolation area for seven years due to virus infection (?HBV, ?HCV).

Ten years after start of dialysis, she was transferred to a central hospital for dialysis where virological studies revealed co-infection of B and C virus and genotypic analysis revealed HCV genotype 4.

The source of infection was not determined and antiviral treatment was started at that time using Interferon without response.

One year ago, the patient received antiviral therapy, which is the recent available combination therapy: Ombitasvir (12.5mg), Paritaprevir (75mg) and Ritonavir (100mg) (Viekirax) in combination with Ribavirin, for treatment of HCV. Viekirax is a new drug combination of Direct Antiviral Agents (DAAs) and is not contraindicated in chronic renal failure patients [33,34] and have shown Sustained Virological Response (SUR12) in HCV genotype 1b and genotype 4 [32]. The patient received 12 weeks of DAA treatment on twice daily basis.

On treatment, regular assessments included standard laboratory testing: Serum HCV&HBV PCR testing and symptoms directed physical examination. Adverse Events (AEs) were evaluated at early visit during treatment. Only sense of nausea and abdominal discomfort which disappeared on completion of the drug course (12 weeks). Clinical laboratory testing were performed regularly after the end of treatment period up to one year.

PCR testing for both HCV and unexpectedly HBV revealed negative PCR (Quantitative analysis), signifying complete eradication (RVR3 and SVR12) of both viruses without significant side effects nor complications.

Discussion

This case showed significant antiviral activity of DAA in eradication of both HCV genotype G-4 in addition to chronic HBV infection.

HBV and HCV co-infection as in our case report constitute a significant challenge: Liver injury, including the risk of hepatocellular carcinoma even in serologically silent HBV infection, as the extent of liver damage is more aggressive [30].

Little is published on renal pathology of this co-infection, yet patients on regular dialysis often have it, and are therefore at a great risk of accelerated mortality. The risk depends on the dominant virus, being greater when HBV dominates. Treatment should receive top priority, using oral drugs (DAAs) rather than interferon-based protocols, addressing both viruses simultaneously [30].

In our case report, eradication of both viruses with SVR [12], occurred fortunately enough without side effects or morbidities.

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