Case Report

Successful treatment of chronic hepatitis C in a hemodialysis patient

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Abstract

We present the first case of successful direct acting antiviral therapy of chronic hepatitis C in a hemodialysis patient in Serbia. The patient infected with genotype 1a has been successfully treated with Paritaprevir/Ritonavir/Ombitasvir/Dasabuvir and Ribavirin. There are only a few real world reports regarding this therapeutic option in hemodialysis patients.

Key words: chronic hepatitis C; hemodialysis; 3D regimen.


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Introduction

We are witnessing a revolution in chronic hepatitis C (CHC) therapy in the last few years. Direct acting antivirals (DAAs) provide shorter treatment duration with higher sustained virological response (SVR) rates, greater efficacy and safety, and less adverse events (AE) in comparison to interferon-based therapy [1]. DAAs can be used in patients with comorbidities, in which interferon-based therapy was unsuccessful or contraindicated [1]. Patients with chronic kidney disease (CKD), including those on hemodialysis (HD), can be treated successfully with DAAs [2]. We present a case of a young woman with CHC on HD successfully treated with the 3D regimen - Paritaprevir/Ritonavir/Ombitasvir and Dasabuvir.

Case Report

We present a case of 31 year-old female with CHC and stage 5 CKD. She was diagnosed with hypertension and CKD in 2003, when she was 18 years old. She didn't undergo a renal biopsy and the etiology of CKD remains elusive. Her average diuresis was less than 1.5 L/day when she became HD-dependent in 2008. Her current average diuresis is less than 50 mL/day and she has three four-hour HD sessions weekly. She had been diagnosed with CHC soon after she had started HD, so she was transferred to an isolation HD unit, along with other anti-HCV positive patients. Genotype 1 (GT1) HCV was determined, and the HCV RNA viral load was 2,265,000 copies/mL. She was treated with pegylated interferon-a2a (peg-IFN-a2a, 135 mcg SC once weekly) and ribavirin (200 mg PO 3 times per week) for 48 weeks during 2008/2009 and she tolerated the regimen well. Although HCV RNA was undetectable at the end of treatment (EOT), she experienced relapse during the 24-week follow-up period. During 2017 she underwent a reevaluation of CHC. A liver stiffness of 5.5 kPa, corresponding with minimal or no liver fibrosis (F0/F1), was identified by transient elastography. The HCV RNK viral load and GT were reassessed before DAAs treatment and were found to be 1,158,000 IU/mL and GT1a, respectively (COBAS HCV 4800, ROCHE Diagnostics, Branchburg NJ, USA).

She was treated with a 12-week 3D regimen consisting of 2 tablets taken once daily and each containing 75 mg of paritaprevir, 50 mg of ritonavir, and 12.5 mg of ombitasvir, together with a 250 mg tablet of dasabuvir taken twice daily, in combination with ribavirin (July - September 2017). Serum hemoglobin was 10 g/dL prior to DAAs therapy. The initial ribavirin dose was 200 mg 3 times per week after HD, with hemoglobin concentration monitoring before each dose. The patient received erythropoietin (20,000...
international units) twice per week through the entire course of the treatment, except on the few occasions in which the hemoglobin concentration exceeded 11g/dL. Ribavirin was not administered if serum hemoglobin was lower than 8.5 g/dL. She was also treated for hypertension with metoprolol 90mg, methyldopa 500 mg and ramipril 5 mg. All drugs taken as a single daily dose were administered after HD.

The treating clinicians actively evaluated the patient for AEs daily from the start of DAA therapy until 30 days after the EOT. The most important and serious AE observed during treatment was ribavirin-induced/exacerbated anemia. After the 5th dose of ribavirin (week 2 of antiviral therapy) there was a significant drop in the serum hemoglobin concentration to 8.3 g/dL, at which point ribavirin was interrupted. The patient subsequently received 2 pools of red blood cells (RBCs). After the hemoglobin concentration increased to 10.2 g/dL ribavirin was reintroduced during week 3 of therapy. From that point until EOT, the patient received 200 mg of ribavirin weekly. At week 7 since the beginning of therapy the patient had profuse menstrual bleeding and developed severe anemia, yet the treating physicians decided not to interrupt ribavirin because the bleeding ended on the day the hemoglobin concentration fell below 8.5 g/dL. Sure enough the hemoglobin concentration started to rise spontaneously after day 49 of therapy. Figure 1 illustrates the hemoglobin concentration dynamics in conjunction with RBC transfusions and ribavirin doses.

The patient complained of pruritus without any noticeable skin lesions, from the 4th to the 10th day (week 1-2) of DAA treatment. Pruritus was due to xerosis and it resolved with frequent moisturization. There were no other significant AEs.

The viral load was assessed at week 4 of antiviral treatment and was found to be <15 IU/mL. HCV RNA was undetectable at the EOT and after 12 weeks of follow-up (SVR12). The patient was transferred to a general HD unit for anti-HCV negative patients as soon as HCV RNA became undetectable.

**Discussion**

HCV infection is one of the most important causes of chronic liver diseases, liver cirrhosis and hepatocellular carcinoma, as well as liver-related...
Patients with CKD stages 4-5 have a higher prevalence of HCV infection compared to the general population. The prevalence of HCV infection among HD patients varies widely, ranging from 5% to approximately 40%, depending on the geographic region. Thus, these patients still represent a high risk group for the acquisition of HCV infection [5-7]. Prevalence of anti-HCV positive patients among those on HD in Serbia was found to be high, but showing tendency to decrease (31-23%) [8].

HCV infection is associated with significant morbidity and mortality in HD patients, especially due to cardiovascular diseases [9,10]. In addition, various histological types of glomerulopathies are associated with HCV infection (membranoproliferative glomerulonephritis is the most common). Therefore, patients with stages 4 and 5 of CKD have to be considered priority patients for HCV therapy. Achieving a SVR could also slow the progression of CKD stages 1-3 [11,12].

The introduction of DAAs offers new therapeutic avenues for previously difficult-to-treat patients, including those with ESRD. Furthermore, DAAs could lead to eradication of HCV infection among them. The 3D regimen, grazoprevir / elbasvir and glecaprevir / pibrentasvir are all drugs with a predominant hepatic metabolism and excretion and as such are ideal in the CKD setting [13,14]. Thousands of patients were treated with the 3D protocol worldwide, but few reports deal with HD patients, and most present a relatively small number of cases. Glecaprevir / pibrentasvir achieved high SVR12 rates and was well tolerated in three difficult-to-treat patient subgroups with limited treatment options (DAA-experienced patients, patients with CKD) [15]. Grazoprevir / elbasvir has also been demonstrated to be an efficacious and safe option in HD patients [16]. Unfortunately, DAAs are very expensive, and their price is an issue in both developed and developing countries.

Peg-IFN with ribavirin is still the most common therapeutic option in Serbia. Few Serbian hemodialysis patients were treated with these medications, with modest results, so the majority remains treatment naïve. Interferon based therapy is neither effective (a SVR rate of 40-58%) nor safe (a 26.9% withdrawal rate due to side-effects) in patients with end stage renal disease (ESRD) [17,18]. Sofosbuvir / ledipasvir, grazoprevir / elbasvir and 3D regimen were approved for clinical use in Serbia during 2016/17. Thus far just 23 patients were treated with DAAs in Serbia, all of them with the 3D regimen. Only one of them was on HD.

It is important to emphasize that co-administration of ribavirin is recommended for infection with GT1a HCV, which poses an additional challenge in ESRD patients due to preexisting anemia and their limited ability to excrete ribavirin [2,13]. The Ruby-I study analyzed the 3D regimen in treatment-naïve GT1 patients with stage 4-5 CKD, 14 of which were HD patients. Results were encouraging with SVR12 rate of 90%. Anemia was the main AE and it was considered a consequence of ribavirin treatment [2]. Here, ribavirin was interrupted if hemoglobin concentrations fell below 10g/dL which is a more conservative approach than ours was.

Data from Spain showed that all HD patients with GT1 and 4 achieved SVR regardless of DAA regimen [19]. In 15 cases, ribavirin was co-administrated with DAAs and anemia was found to be the most important AE. Ribavirin treatment should be interrupted if hemoglobin levels fall by more than 2g/dL or to less than 8.5g/dL, which is exactly what happened in the case presented here [2,13]. It is interesting that treatment discontinuation and blood transfusion were not necessary in a cohort of Spanish patients which had no significant drop in hemoglobin concentration because they had received high doses of erythropoietin. It poses a reasonable preventive measure for ribavirin-induced/exacerbated anemia in patients on HD [19]. Although blood transfusion and erythropoietin were permitted in the Ruby-I study, ribavirin treatment had to be discontinued in nine GT1a infected patients. Ribavirin was reintroduced in three patients after improvement of hemoglobin concentrations, and the same was done in the Serbian patient.

Ribavirin should be used with 3D regimens and grazoprevir/elbasvir in GT1a and GT4 patients with ESRD with individual dose modification [13]. Although this could be challenging in patients with cirrhosis, Ponziani et al. showed that the 3D regimen is effective and well tolerated in patients with GT1 and GT4 on HD and with compensated cirrhosis, including those requiring administration of ribavirin [20].

Ribavirin is minimally eliminated by HD, and doses should be individually adjusted based on careful hemoglobin concentration monitoring. Recommended ribavirin doses range from 200mg per week to 200 mg daily [21]. There are patients, as the one presented here, who tolerate only minimal ribavirin doses (200 mg per week), but still benefit from them.
Conclusion

Patients with ESRD are not difficult-to-treat CHC patients anymore. The 3D regimen is safe, well tolerated and associated with high SVR rates in this setting. The benefits of ribavirin therapy can be reaped safely in HD patients if adequate AE monitoring is implemented. Cooperation between nephrologists and infectologists is essential for successful CHC treatment of HD patients.

References


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