



Full-Dose Sofosbuvir and Daclatasvir to Treat Hepatitis C Virus Infection in a 77-Year-Old Patient with Severe Renal Insufficiency

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Abstract

Introduction: Direct-Acting Antiviral agents (DAAs) have revolutionized the treatment of chronic Hepatitis C Virus (HCV) with Sustained Viral Response (SVR) achievable in more than 90% of all patients with few side-effects. This treatment is required to decrease the significant morbidity and mortality impact of the disease worldwide. We report a successful full dose sofosbuvir and daclatasvir treatment of HCV Infection in a patient with severe renal insufficiency.

Case Presentation: A 77-year-old male with a history of Chronic Kidney Disease (CKD) stage 4 was referred to our hospital for chronic HCV. The patient was treated by a combination of full dose sofosbuvir and daclatasvir without adverse effects or interaction between this regimen and other medications used by the patient. The patient's HCV load was undetectable at week 4, 8, 12 and a SVR was confirmed at week 48 post-treatment consistent with eradication of infection.

Conclusion: This report highlighted the effectiveness and safety of the association of sofosbuvir and daclatasvir to treat HCV in the elderly with severe CKD.

Keywords: Hepatitis C virus; Direct-acting antiviral; Chronic kidney disease; Elderly

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Received Date: 09 May 2020

Accepted Date: 21 May 2020

Published Date: 26 May 2020

Citation:

T Aatif, R Akka, M Sbaai. Full-Dose Sofosbuvir and Daclatasvir to Treat Hepatitis C Virus Infection in a 77-Year-Old Patient with Severe Renal Insufficiency. *Ann Clin Case Rep.* 2020; 5: 1841.

ISSN: 2474-1655

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Introduction

Hepatitis C Virus (HCV) is a leading cause of chronic liver disease, cirrhosis and hepatocellular carcinoma, and it is the most common indication for liver transplantation in many countries [1-3]. HCV is a major global health-care problem. The WHO estimates that HCV was infected up to 3% of the world's population, equating to more than 170 million carriers of virus worldwide [4]. HCV is a small, enveloped RNA virus allocated to a unique genus, designated *Hepacivirus*, within the family *Flaviviridae*. Six distinct genotypes are described and more than 90 sub-genotypes [5]. HCV genotype is a crucial predictor to determine Sustained Viral Response (SVR) rates (which indicate cure of HCV infection). It was first recognized in 1989 and different drugs were used in its treatment with limited success. Key therapeutic milestones were the introduction of Interferon (INF) in 1991, combination with Ribavirin (RBV) in 1998, PEGylation of INF (PEG-INF) in 2001 and emergence of the first Direct-Acting Antiviral agents (DAAs) Boceprevir and Telaprevir in 2011; second generation DAAs were licensed in 2013. All oral therapies have revolutionized the treatment of chronic HCV with SVR achievable in more than 90% of all patients with few side-effects; this differs from the therapeutic options historically which were characterized by their toxicity than treatment success [5-7]. Since HCV infection negatively impacts morbidity and mortality compared with non-HCV Chronic Kidney Disease (CKD) patients particularly on maintenance Hemodialysis (HD), effective treatment is especially pivotal for this patient group which it remains difficult [8]. In addition, clearance of the virus will increase the chance of getting a renal transplant, as HCV-infected patients demonstrate higher mortality, graft loss rates and episodes of rejection after renal transplantation [9]. However, the efficacy and safety profiles of DAAs therapy in severe CKD elderly patients are unclear [10]. Here we report a case of 77-year-old male patient with CKD stage 4 successfully treated with 12-week standard dose combination of Sofosbuvir and Daclatasvir.

Case Presentation

B. E. a 77-year-old male referred to our hospital for chronic HCV. The patient's medical history

included gout, urinary lithiasis and CKD stage 4 with an estimated glomerular filtration rate (eGFR=19 ml/min/1.73 m²). His medications included amlodipine 10 mg daily, allopurinol 100 mg daily, calcium 1000 mg daily and levothyroxine 50 g daily. The patient had previously received PEGylated interferon and Ribavirin within reached SVR. Initial laboratory investigations at assessment revealed the following: hemoglobin 119 g/L, white blood count 8.18 × 10⁹, platelets 226 × 10⁹, normal coagulation, Fasting Blood Sugar (FBS) 1.06 g/L, creatinine 264 μmol/L (eGFR=19 ml/min/1.73 m²), serum albumin 31 g/L, ALT 16.5 IU/L, AST 27.7 IU/L, bilirubin 5 μmol/L, GGT 14 IU/L, ALP 81IU/L, CRP 8.26 mg/L. The patient tested negative for the human immunodeficiency virus and we confirmed genotype 1A HCV with a quantitative HCV RNA of 3.4910⁷ IU/ml (7.54 Log IU/ml) (Real-time PCR technique on Cobas TaqMan; Kit HCV Test, v2.0 HPS). There was no evidence of cirrhosis. A recent abdominal ultrasound scan indicated a liver of normal size and shape and no focal lesion. We did not perform a liver biopsy because the patient refused to conduct it. We calculated Fibrosis-4 score (FIB-4), the result was of 2.23, which was predictive of a low fibrosis stage [11]. This case was challenging because the age of patient, the costs of the new medications, the drug interactions with DDAs and the CKD stage 4, which represented a major challenge in the light of the paucity of data on the safety and efficacy of DAAs in CKD stages 4-5-including dialysis patients. The options were discussed with the patient, and he agrees to take the regimen. Following discussion in multi-disciplinary meeting involving his gastroenterologist and nephrologist, a combination regimen was initiated in October 2015, consisting of standard dose sofosbuvir (400 mg) and daclatasvir (60 mg) once daily for 12 weeks. No immediate complications were reported following the initiation of treatment and the DAAs appeared well-tolerated. He completed 12 weeks of treatment without any further complications on the 11th of January 2016. End blood tests showed hemoglobin 115 g/L, white blood count 8.36 × 10⁹, platelets 210 × 10⁹, normal coagulation, FBS 1.04 g/L, creatinine 254 μmol/L (eGFR=20 ml/min/1.73 m²), serum albumin 34 g/L, ALT 20 IU/L, AST 19 IU/L, bilirubin 4 μmol/L, GGT 49 IU/L, ALP 92 IU/L, CRP 6.2 mg/L. HCV RNA was undetectable throughout treatment. HCV RNA was confirmed to be negative at the week 4, 8, 12 and 48 post treatments consistent with eradication of his HCV.

Discussion

Recent advances in the treatment of chronic HCV infection have resulted in the availability of several new DAAs with significantly improved efficacy and tolerability relative to PEG-INF and RBV. Major progress has been made over the last 2 decades in the treatment of HCV infection among the general population. SVR rates increased progressively from 7% to 10% with INF alone, increased to 25% with INF and RBV, and increased to 40% to 50% with PEG-INF and RBV. SVR rates rose further to 60% to 70% with the addition of protease inhibitors and eventually to >95% with the current DAAs. Importantly, DAAs regimens are for shorter duration (mostly 12 weeks), are INF-free and are thus found to have much improved tolerance [12]. We should propose treatment with DAAs to any patient with renal impairment in order to reduce the progression of the liver disease, especially after transplantation; reduce the risk of renal-related morbidity and mortality; reduce the risks of diabetes, cardio or cerebrovascular disease and improve well-being [13]. Elderly patients with chronic HCV infection and CKD remain a challenging population to manage, with limited treatment options available. DAA represents a major advancement in the treatment of elderly patients

with CKD and HCV infection. Here we report the case of 77-year-old male with chronic HCV infection and CKD stage 4 treated successfully by a combination of a full dose of sofosbuvir and daclatasvir without side effects. Among the currently approved DDAs, sofosbuvir a nucleotide polymerase inhibitor (NS5B inhibitor), is the only one that has significant renal elimination. The other currently approved DDAs (simeprevir, ledipasvir, daclatasvir, paritaprevir/ritonavir, ombitasvir, dasabuvir, grazoprevir and elbasvir) are not eliminated by the kidneys and thus do not need dose adjustment, even in severe CKD or in Hemodialysis (HD) patients [14,15]. The recommended dose of 400 mg sofosbuvir is not approved in patients on CKD 4-5 (mostly HD) owing to concerns of accumulating metabolites with potential cardiovascular and hepatobiliary toxicity [16]. In effect, sofosbuvir is metabolized to the active metabolite GS461203 which acts intracellularly and subsequently to the inactive metabolite GS331007, which is the predominant metabolite, would accumulate in patients on HD, potentially leading to toxicity. Lowering the dose is not desirable, as sofosbuvir is a pro-drug and potentially could lead to lower levels of the active metabolite GS461203 and lower effectiveness [16,17]. Indeed, Gane et al. [18] report in ten genotype 1 HCV infected patients with a creatinine clearance <30 ml/min using sofosbuvir 200 mg daily showed low efficacy (SVR 40%). These results suggest that standard doses of sofosbuvir 400 mg might be necessary to achieve SVR in CKD stages 4-5 including dialysis patients, but the tolerability is unknown. In our case we opted for full dose sofosbuvir with no adverse effects or interaction between this regimen and other medications used by the patient.

In summary, successful eradication of HCV using DAAs in elderly patient with severe CKD can be achieved with an excellent tolerability. The challenges encountered in this case highlight the complexities of treatment in a real-world situation, but at the same time encourage the eradication of HCV to decrease morbidity and mortality in CKD elderly patients.

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