Case Report

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Hepatitis C Treatment with Sofosbuvir and Daclatasvir in an 83 Year Old Patient with Ischemic Vasculitis and End Stage Renal Disease on Hemodialysis

Apostolos Koffas[1,2], Nada Durica[1] and Patrick Kennedy[1,3]

1 The Liver Centre, The London Clinic, London, United Kingdom
2 NET Unit, ENETS Centre of Excellence, Royal Free Hospital, London, United Kingdom
3 Barts and The London School of Medicine and Dentistry, London, United Kingdom

Corresponding author: Apostolos Koffas

apostolos_koffas@hotmail.com

The Liver Centre, The London Clinic, 116 Harley Street, London W1G 7JL, UK

Tel: +4402079354444

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Abstract

Hepatitis C virus (HCV) was first identified just over 25 years ago, but in this timeframe we have moved from identifying the virus to being able to offer a cure for the infection, which represents a remarkable feat in clinical and scientific medicine. However, the path to today's treatment regimens was not straightforward. Interferon (INF), followed by the co-administration of Ribavirin and subsequently the pegylation of IFN represented the limited standard of care for many years; notable primarily for the significant systemic effects associated with IFN based therapy. The emergence of all-oral, IFN-free regimens with second generation direct acting antivirals (DAAs) in 2013 has revolutionized the hepatitis C treatment landscape with cure rates now exceeding 90% and significantly fewer side effects. Nevertheless, there remain difficult to treat cohorts, including those with end-stage renal disease (ESRD). Limited data exists on the optimal management of such individuals with DAAs; the current report presents the case of an 83-year-old female patient with refractory ischemic vasculitis and ESRD on hemodialysis with multiple other co-morbidities successfully treated with a 12-week combination of Sofosbuvir and Daclatasvir.

Keywords: Hepatitis C Virus; Direct Acting Antiviral Agents; Sofosbuvir; Daclatasvir; End Stage Renal Disease; Ischemic Vasculitis

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Introduction

An estimated 130-150 million people are chronically infected with Hepatitis C Virus (HCV) worldwide [1]. HCV represents a leading indication for liver transplantation globally; the complications of chronic infection include cirrhosis and hepatocellular carcinoma and accounts for approximately 500,000 deaths per year [2,3]. There are six distinct genotypes described and more than 90 sub-genotypes [2]. HCV, previously described as non-A non-B, was first recognized in 1989 and many different drugs have been used in its management with limited success. Key therapeutic milestones were the introduction of Interferon (INF) in 1991, combination with Ribavirin in 1998, pegylation of INF (PEG-INF) in 2001 and the emergence of the first Direct-Acting Antiviral (DAA) agents Boceprevir and Telaprevir in 2011; second generation DAAs were licensed in 2013. Approval of all-oral therapies have revolutionized the treatment of chronic HCV with sustained virological response (SVR) achievable in more than 90% of all patients with few side-effects; this differs dramatically from the limited therapeutic options historically which were characterized more by their toxicity than treatment success [2,4,5].

In 2013 Sofosbuvir and Simeprevir were FDA approved as the first all-oral therapies to be used in clinical practice, followed by Daclatasvir, Ledipasvir and Ombitasvir/Paritaprevir/Ritonavir. The primary objective of antiviral therapy is viral eradication. Response rates for all-oral, INF-free regimens of DAAs reported SVRs between 82% and 100% [6,7]. Despite this, difficult to treat groups remain including those with end stage renal disease (ESRD) and/or hemodialysis patients, where limited data exist. HCV treatment in renal failure is complicated by increased mortality rates, associated anemia and polypharmacy; moreover, limited data exist on the safety and utility of DAAs in this population. ION-1, ION-3, PEARL III and IV, SAPPHIRE and TURQUOISE II are

the landmark studies that led to the development of the current guidelines, but no data exist on how best to manage subjects with a creatinine clearance <30 ml/min [2,8-10].

Here we report on the HCV management of an 83 year-old female with a complex medical history including ESRD on dialysis and refractory ischemic vasculitis. Following careful consideration, a combination of Sofosbuvir and Daclatasvir were selected in the absence of any clear guidance or robust data on the management of HCV in renal failure and an SVR at 12 weeks post completion of treatment was achieved.

Case Report

An 83 year-old lady was referred to The London Clinic Liver Centre for the management of her chronic HCV. The patient's medical history included refractory ischemic vasculitis, ESRD, prior renal transplantation with graft failure in 2014, systemic hypertension, cerebrovascular disease, chronic atrial fibrillation and hypothyroidism; the patient had limited mobility and was wheelchair bound. She was on renal replacement therapy and required hemodialysis thrice weekly. Her medications included Atorvastatin, Diltiazem, Metoprolol, Aranesp, Escitalopram, Lansoprazole, Levothyroxine, Folic acid, Alfacalcidol, Apixaban, Prednisolone 13 mg daily, Mycophenolate Mofetil 1 gm of mg twice daily and Cyclosporine 25 mg twice daily.

Investigated for her neurological decline; characterisation of her vasculitis proved inconclusive and thus any treatment administered was empirical. However, her condition appeared refractory to both immunosuppressive agents and corticosteroids, which prompted consideration for treatment with Rituximab. The role of the chronic HCV in the vasculitis was a subject of debate. There were also concerns about treatment with Rituximab in the context of her chronic HCV and any underlying liver disease. Assessed from a chronic HCV perspective, she was deemed non-cirrhotic and eradication of her HCV was clinically indicated in the context of her vasculitis and limited treatment options.

Initial laboratory investigations at assessment revealed the following; hemoglobin 92 g/L, white blood count 10.6 × 10^9, platelets 186 × 10^9, ESR 65 mm/h, normal coagulation, creatinine 274 umol/L (GFR 14 ml/min), serum albumin 26 g/L, ALT 42 IU/L, AST 55 IU/L, bilirubin 22.4 umol/L, GGT 171 IU/L, ALP 66 IU/L, CRP 51.5 mg/L. Genotype 1A HCV was confirmed with a quantitative HCV RNA of 2.6 × 10^6 IU/ml. Routine imaging confirmed unremarkable appearances of the liver and transient elastography (Fibroscan) revealed a median liver stiffness of 6.7 kPa, excluding any significant fibrosis. While considered for treatment with DAAs, her established ESRD represented a major challenge in light of the paucity of data on the safety and efficacy of DAAs in ESRD patients. An additional challenge was the significant polypharmacy and the necessity for drug and dose optimization; for example, due to a lack of data on interactions between DAAs and Apixaban, she was switched to Tinzaparin prior to the initiation of antiviral therapy (Warfarin was excluded on the basis of erratic INRs in the past).

Following discussion in multi-disciplinary meeting involving her neurologist and renal physician, a 12-week combination regimen was initiated in June 2015. Her management consisted of Sofosbuvir 400 mg dosed three times per week (post-dialysis), Daclatasvir 60 mg once daily and Ribavirin 200 mg once daily. No immediate complications were reported following the initiation of treatment and the DAAs appeared well-tolerated. During the second week of treatment, the patient was admitted to hospital with sepsis and was managed with intravenous antibiotics. Her recovery was complicated by the development of a large femoral subcutaneous hematoma and the patient was discharged after a week of in-patient care. Ribavirin was stopped to avoid further compromise of her full blood count and associated anemia. Subsequently she was on Sofosbuvir 400 mg three times per week and Daclatasvir 60 mg once daily.

She completed 12 weeks of treatment without any further complications on the 26th of August 2015. End of treatment (EOT) blood tests showed hemoglobin 128 g/L, white blood count 7 × 10^9, platelets 240 × 10^9, ESR 79 mm/h, INR 1.1, creatinine 413 umol/L (GFR 14 ml/min), serum albumin 32 g/L, ALT 28 IU/L, AST 22 IU/L, bilirubin 6.7 umol/L, GGT 172 IU/L, ALP 70 IU/L, CRP 21.4 mg/L. HCV RNA was undetectable at week-2 on-treatment and remained undetectable throughout treatment. HCV RNA was confirmed to be negative at week 4, 8 and 12 post-treatment consistent with eradication of her HCV.

Discussion

HCV causes a spectrum of liver disease ranging from mild disease to cirrhosis, hepatocellular carcinoma and death; it is the leading indication for liver transplantation worldwide [2,3]. In 2013 DAAs were first licensed for the management of HCV resulting in SVRs varying between 82% and 100%, a significant improvement in treatment outcomes when compared to the pre-DAA era [6,7]. Nevertheless, difficult to treat subgroups of patients remained owing to a lack of data on pharmacokinetics, safety and efficacy of the DAAs in certain populations, such as patients with ESRD and/or renal replacement therapy. To the best of our knowledge limited data existed on the use of DAAs in this population at the time this patient was considered for treatment with the exception of sporadic case reports or small studies [8-11].

In the current report, the case presented is that of an elderly patient with Genotype 1A non-cirrhotic HCV who was treatment naïve with ESRD (GFR<30 ml/min/1.73 m^2) on renal replacement therapy. The American Association for the Study of Liver Disease recommends a combination of Paritaprevir/Ritonavir/Ombitasvir with Dasabuvir with or without Ribavirin in this hepatitis C subgroup, although recognized that these recommendations are based on limited safety and efficacy data [11,12].

Notably, the medical history in this case included other significant co-morbidities and maintenance polypharmacy with limited data on potential drug interactions with the DAAs. Although not reported, potential interactions between DAAs and Apixaban or any of the newer oral anticoagulants needed to be considered and prompted a switch to low molecular weight heparin with regular anti-factor X monitoring.

As per current guidelines for treatment naïve, non-cirrhotic Genotype 1A patients, she was initially considered for treatment with a combination regimen comprising Sofosbuvir, Daclatasvir and Ribavirin. Daclatasvir was administered at the recommended dose of 60 mg per day since no dose adjustment is required in patients with severe renal disease [13]. Sofosbuvir is administered at a dose of 400 mg per day in individuals with normal renal function; the same dose in combination with Simeprevir was administered with good tolerability and treatment outcome in a study involving 17 patients with genotype 1 Hepatitis C with End-Stage Renal Disease on hemodialysis or GFR <30 mL/min [14]. Half-dose Sofosbuvir (plus Simeprevir) in patients with ESRD was studied by Ram et al. [15]. This case however, represents a unique challenge given the patient's age, significant co-morbidities including refractory vasculitis and polypharmacy. Sofosbuvir (400 mg thrice weekly) was dosed post-dialysis and while Ribavirin was co-administered initially, this was discontinued shortly after commencement of treatment on the development of gram-negative septicemia and worsening anemia. She completed the 12-week course on Sofosbuvir and Daclatasvir without further complications and minimal side effects. Laboratory tests at weeks 4, 8 and 12 post-treatment confirmed undetectable HCV RNA.

Successful eradication of hepatitis C using DAAs in this elderly patient with ESRD on renal replacement therapy, ischemic vasculitis and other significant co-morbidities was achieved without immediate complications and excellent tolerability. This case alongside encouraging results from small studies and other sporadic reports underline the necessity for large studies to be conducted in HCV patients with ESRD to inform treatment decisions. The challenges faced with this case highlight the complexities of treatment in a real-world situation, but simultaneously reinforce the potency of the DAAs and the potential to achieve HCV cure even in difficult to treat patients.

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