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CASE REPORT

Successful Treatment of Hepatitis C, Genotype 3, Treatment Failure (Sofosbuvir/Daclatasvir) with Sofosbuvir/Velpatasvir in Decompensated Cirrhosis Complicated by Renal Insufficiency

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Abstract

Clinical trials and real word data have proven that chronic hepatitis C (HCV) can be eradicated (sustained virological response SVR or 'cure') in the majority of patients by direct - acting antivirals (DAAs) . There are, however, groups of patients in whom HCV treatment outcomes with direct acting antivirals (DAAs) are suboptimal (genotype (GT) 3 patients, decompensated cirrhosis, renal failure) or have not been studied in large cohorts (patients with relapse to a previous DAAs treatment (failure)). This case outlines the successful eradication of GT-3 hepatitis C (HCV) in a patient with decompensated cirrhosis and renal failure secondary to diabetes after DAA failure, using a 24-week course of sofosbuvir, velpatasvir and ribavirin. The achievement of SVR in this patient resulted in significant improvement in hepatic function . Patients with decompensated cirrhosis and GT-3 disease remain a difficult to treat population, specially after first-line DAA failure and with chronic Kidney disease (CKD). The safety and efficacy of sofosbuvir, velpatasvir and ribavirin in this cohort require further study.

Background

Advances in the treatment of chronic hepatitis C (HCV) with the approval of direct acting antivirals (DAAs) has given HCV care providers access to treatment regimens able to achieve sustained virological response (SVR or 'cure') in the majority of patients, with minimal side effects. There are, however, groups of patients in whom HCV treatment outcomes with DAAs are suboptimal (genotype (GT) three patients, decompensated cirrhosis, renal failure) or patients with previous treatment DAAs failure and resistance [1]. Virologic failure to DAA-based therapies is associated with the selection or resistant viral isolates and retreatment with the same regimen has limited efficacy. Few data are available on yhe virological and clinical outcomes of advance liver disease patients with CKD, unfavorable genotype retreated after first line DAA failure.

Case Presentation

This is a case of a 50-year-old man with decompensated cirrhosis secondary to HCV GT-3, with a history of ascites, spontaneous bacterial peritonitis, non-bleeding oesophageal varices, hepatic encephalopathy and thrombocytopaenia (platelets -50,000) that had relapsed interferon-free antiviral therapy ended December 2015 (sofosbuvir/daclatasvir for 24 weeks).

The patient was young and highly motivated, but without therapeutic chances at the moment, decompensated, not suitable for regimens including PIs (even

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Table 1: Patient Clinical data before antiviral treatment regimen.

Parameter	Value	Normal Value
AST	109 U/L	17-59
ALT	74 U/L	11-66
eGFR	110	
INR	1.27	
Bilirubine	6.1 mg/dL	0.2-1.3
Albumine	3.5 mg/dL	4-4.76
Platelets	78.000	120.000/400.000
WBC	3.100	4.000/11.000

Table 2: Patient Clinical data 3 month after antiviral treatment regimen.

Parameter	Value	Normal Value
AST	33 U/L	17-59
ALT	30 U/L	11-66
eGFR	30	
INR	0.97	
Bilirubine	0.7 mg/dL	0.2-1.3
Albumine	3.95 mg/dL	4-4.76
Platelets	48.000	120.000/400.000
WBC	2.100	4.000/11.000

future) with good renal function (eGFR 110 by CKD-EPI) despite insulin treated diabetes, with no variants for sofosbuvir or NS3/4 reported but NS5A RAV (Y93H). He was treated with a schedule of Sofosbuvir/Velpatasvir plus ribavirin for 24 weeks supplied by Gilead for the purpose of a compassionate use. Ribavirin was poor tolerated and discontinuated soon. His clinical data are resumed (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4904391/table/BCR2016215293TB1/). His model for end-stage liver disease (MELD) score at presentation was 16 with a Child-Pugh (CTP) score of 11 (class C) (Table 1).

Treatment

The patient was started antiviral therapy in March 2017 and was listed for liver transplantation. At the time of starting the treatment, his height and weight were 168 cm and 100 kg, respectively. His viral load was 119829 IU/mL at baseline.

Antiviral therapy with sofosbuvir (SOF) 400 mg/velpatasvir (VEL) 100 mg daily and ribavirin (RBV) 800 mg for 24 weeks with dose adjustments of RBV during treatment was started. The patient's week 4 HCV RNA was negative (below the lower limit of detection). He was HCV RNA negative and transplanted negative at week 12, at which point therapy was discontinued for one week. During this DAA treatment regimen, his renal function as well as liver decompensation improved as reflected in improvement in the MELD and CTP score. The dose of RBV was decreased over the course of treatment and as the haemoglobin does not improved, RBV was stopped.

The patient, after transplantation was immunosuppressed with tacrolimus, restarted SOF/VEL after 1 week of DAA discontinuation with still negative HCV RNA, but his creatinine started to rise (2.5 mg/dl), requiring SOF/VEL dose reduction that was given 4 days a week, tacrolimus was stopped and he was given everolimus.

His renal function improved over a 1-month period, which then allowed the end of DAA therapy. Between weeks 0 and 4 of this regimen, there was an increase in the patient's diuretic doses (spironolactone/furosemide) to control his ascites, in addition to albumin supplementation.

Outcome and Follow-Up

This treatment was well tolerated and resulted in SVR12 in addition to improved hepatic and renal function (Table 2). Patient is still virus negative.

Discussion

To the best of our knowledge, this is the first report of successful HCV eradication in a patient with decompensated cirrhosis with underlying GT-3 disease, CKD and prior DAA failure, Y93H resistence mutant, using SOF/VEL/RBV.

Failure to daclatasvir/sofosbuvir in GT3 was associated with a strong increase of Y93H, which was also shown in the approval study [2].

Second-generation NS5A inhibitors showed improved activities against GT3 isolates harboring Y93H and recently also GT3-sensitive PIs were approved. SVR rates after a rescue treatment with sofosbuvir plus a second-generation PI like voxilaprevir or pibrentasvir are now available [3,4]. However PI use in decompensated patient is controindicated, and retreatment of GT3 failure patients harbouring Y93H remain a challenge. Sofosbuvir Velpatasvir for longer duration (24 weeks) and the addition of ribavirin may increase treatment efficacy in difficult-to-treat patients. In GT3-infected patients with decompensated cirrhosis, SVR rates to velpatasvir/sofosbuvir were substantially lower compared with the group that additionally received ribavirin [5] Moreover, a recent study suggested that the addition of ribavirin to retreatment regimens, like daclatasvir or velpatasvir plus sofosbuvir, could increase SVR rates [6] Thus, the addition of ribavirin may be an option for rescue treatments in difficult to-treat GT3-infected patients Our patient poorly tolerated ribaviran and had to stop this drug. He missed a week of therapy without consequences (as was recently described in SIMPLIFY study) [7].

Although our patient's renal function, with his eGFR declining to 28 mL/min/1.73 m^2, forced to a reduced sofosbuvir schedule in the last 3 months of treatment,

SVR was achieved. This patient also had underlying comorbid diabetes, which may have played a role. As SOF is renally cleared, it is therefore also possible that he acquired SOF-induced renal insufficiency. Recent data from the HCV-TARGET cohort showed that 15% of patients started on SOF-based DAA regimens with a baseline estimated glomerular filtration rate (eGFR) ≤ 45 mL/min/1.73 m^2 experienced worsening renal function while on treatment [6]. This supports the need for close monitoring of patients with renal insufficiency, while on SOF-based HCV regimens, by experienced providers.

Patients with decompensated cirrhosis and GT-3 disease and RAVs remain a difficult to treat population, and the safety and efficacy of SOF/LDV/RBV in this cohort require further study.

Learning Points

Despite advances in the treatment of hepatitis C, there remain a few important difficult to treat populations with limited data to guide treatment decisions (decompensated, previous DDAs failure, CKD).

Sofosbuvir/velpatasvir has shown to be effective and relatively safe in patients with hepatitis C genotype 1 decompensated cirrhosis, however, data in genotype 3 is limited and requires further study.

This case demonstrates the efficacy and safety of sofosbuvir with velpatasvir based direct acting antiviral (DAA) regimens in patients with decompensated cirrhosis and genotype 3.

On treatment, viral suppression and sustained virological response appear to provide sustained improvement. Further work to evaluate the effect of DAAs on long-term outcomes is required.

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Footnotes

Contributors

Both authors were involved in the management of the patient described in the case report. Marco Distefano wrote the first draft of the manuscript, which was reviewed and approved by Vito Di Marco.

Competing interests

None declared.

Patient consent

Obtained.

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