CASE REPORT

Successful treatment of hepatitis C, genotype 3, with sofosbuvir/ledipasvir in decompensated cirrhosis complicated by mixed cryoglobulinaemia

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SUMMARY

Advances in the treatment of chronic hepatitis C (HCV) have given HCV providers access to treatment regimens able to achieve sustained virological response (SVR or 'cure') in the majority of patients. 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 cryoglobulinaemia (CG)). This case outlines the successful eradication of GT-3 hepatitis C (HCV) in a patient with decompensated cirrhosis and renal failure secondary to mixed CG with DAA failure, using a 12-week course of sofosbuvir, ledipasvir and ribavirin. The achievement of SVR in this patient resulted in significant improvement in hepatic and renal function. Patients with decompensated cirrhosis and GT-3 disease remain a difficult to treat population, and the safety and efficacy of sofosbuvir, ledipasvir and ribavirin in this cohort require further study.

BACKGROUND

Advances in the treatment of chronic hepatitis C (HCV) with the recent 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 have not been studied in large cohorts (patients with cryoglobulinaemia (CG)).[1]

CASE PRESENTATION

This is a case of a 53-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 ~30 000) that had precluded interferon-containing antiviral therapy in the past. He was admitted to hospital with type-2 CG manifested by systemic vasculitis and renal failure with a kidney biopsy showing membroproliferative glomerulonephritis and a cryocrit of 5% (table 1). His model for end-stage liver disease (MELD) score at presentation was 26 with a Child-Pugh (CTP) score of 13 (class C).

TREATMENT

The patient was started on weekly plasma exchange (PLEX) and was listed for liver transplantation. Antiviral therapy with sofosbuvir (SOF) 400 mg daily and ribavirin (RBV) 200 mg every other day for 24 weeks with dose adjustments of RBV during treatment (table 1) was started. The patient's week 4 HCV RNA was positive but below the lower limit of detection. He was HCV RNA negative and CG negative by week 12, at which point PLEX was discontinued. During this DAA treatment regimen, his renal function as well as liver decompensation improved as reflected in improvement in the MELD and CTP score (table 1). The dose of RBV was increased over the course of treatment as the haemoglobin improved, however, the highest dose achieved was 200 mg twice daily.

The patient, unfortunately, relapsed 3 weeks after DAA discontinuation with a positive HCV RNA, recurrent CG and renal failure, requiring the reinitiation of PLEX and corticosteroids, and he was given two doses of rituximab (table 1). His renal function improved over a 1-month period (table 1), which then allowed the initiation of a second course of DAA therapy using SOF 400 mg and ledipasvir 90 mg (SOF/LDV) with RBV 600 mg twice a day for 12 weeks. Between weeks 0 and 4 of this regimen, there was an increase in the patient's diuretic doses (spironolactone/lasix) to control his ascites, in addition to a viral gastroenteritis associated with nausea, vomiting and diarrhoea resulting in an increase in his creatinine secondary to pre-renal azotemia between these two time points. During this second course of DAA therapy, a RBV dose of 600 mg twice daily was maintained throughout without the need for dose reduction.

OUTCOME AND FOLLOW-UP

This treatment was well tolerated and resulted in SVR12 in addition to improved hepatic and renal function (table 1) to the point where the patient has for the past 6 months been de-listed for liver transplantation.

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, cryoglobulinaemia and prior DAA failure, using SOF/LDV/RBV. A recent case series showed an SVR rate, using either SOF/RBV or SOF/Simeprevir, of 83% in 12 patients with HCV and

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Table 1 Clinical data during HCV antiviral treatment regimens

Rx Week Date	Cr (umol/L)	eGFR	INR	Bili T (umol/L)	Bili D (umol/L)	ALT (U/L)	Alb (g/L)	MELD	CTP Score	HCV RNA IU/mL	Cryocrit	Hg (g/L)	RBV mg
Antiviral therapy #1—SOF/RBV—24 weeks													
0 05/2014	222	27	1.9	61	14	135	27	26	13	4.11×10^5	5%	77	200 EOD
4 06/2014	107	63	1.5	54	–	33	42	16	9	<LLD*	–	93	400 EOD
12 08/2014	95	72	1.3	48	7	26	47	13	8	neg	Not detected	101	200 daily
24 11/2014	87	80	1.3	39	–	24	38	16	8	neg	–	127	200 BID
3 weeks post Rx 12/2014	278	21	1.4	39	–	229	38	25	10	1.45×10^5	15%	104	–
Antiviral therapy #2—SOF/LDV/RBV—12 weeks													
0 01/2015	152	40	1.4	61	10	92	39	19	10	–	–	116	600 BID
4 02/2015	170	37	1.3	115	10	28	34	22	10	–	–	117	600 BID
12 04/2015	118	57	1.3	130	8	18	35	19	10	–	–	99	600 BID
12 weeks post Rx 08/2015	131	51	1.2	34	5	20	36	14	8	Not detected	Not detected	117	–

*<LLD defined as below the linear range of the assay, which is <15 IU/mL.
BID, twice daily; Bili D, direct bilirubin; Bili T, total bilirubin; Cr, creatinine; CTP, Child-Turcotte-Pugh; Date, mm/yyyy; eGFR, estimated glomerular filtration rate (mL/min/1.73 m^2); EOD, every other day; HCV, hepatitis C; INR, international normalisation ratio; LLD, lower limit of detection; MELD, model for end-stage liver disease, RBV, ribavirin; Rx, treatment.

cryoglobulinaemia, one of whom had GT-3 disease.[2] These patients, however, had neither decompensated cirrhosis nor prior DAA exposure. There are limited clinical data on the use of SOF/LDV in patients with GT-3 disease and cirrhosis. Preliminary results from the ELECTRON-2 trial, presented in abstract form looking at SOF/LDV in GT-3 treatment-naïve patients including those with compensated cirrhosis, have suggested SVR rates of 100% and 64% with and without RBV, respectively.[3] A recent cohort study including data from the European Expanded Access Program (EAP) found an SVR rate in patients with CTP score ≥7 and GT-3 disease receiving 12 weeks of SOF/LDV/RBV to be 65%.[4] This cohort, however, did not have patients with previous DAA failure. It is uncertain in our case whether the achievement in SVR with SOF/LDV/RBV after failure with SOF/RBV was due to the LDV or to the ability to maintain adequate RBV doses with the secondary DAA regimen. In the EAP cohort, decompensated GT-3 patients receiving SOF/LDV without RBV had an SVR rate of only 40%.[4] The SOLAR-1 investigators have published data showing excellent SVR rates and safety with the use of SOF/LDV/RBV in patients with advanced cirrhosis (CTP B and C) and underlying GT-1 disease.[5] SVR in that cohort was also associated with improvements in hepatic function similar to what we observed in our case.

Although our patient's renal function improved overall after achieving SVR, it did not completely recover, with his eGFR remaining 51 mL/min/1.73 m^2 3 months after treatment discontinuation. 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.

The recent approval of daclatasvir has given clinicians an additional option to treat patients with decompensated GT-3 disease; however, coverage may limit its use, at least in the short term. Patients with decompensated cirrhosis and GT-3 disease 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, particularly for those with end organ damage due to cryoglobulinaemia.
- Sofosbuvir/ledipasvir 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 ribavirin 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 to end organ renal damage secondary to cryoglobulinaemia. Further work to evaluate the effect of DAAs on cryoglobulinaemia and long-term outcomes is required.

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Competing interests None declared.

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