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CASE REPORT

Antiviral treatment with sofosbuvir and simeprevir in a kidney transplant recipient with HCV-decompensated cirrhosis: viral eradication and removal from the liver transplant waiting list

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Summary

Hepatitis C positive kidney transplant (KT) recipients are a difficult-to-treat subpopulation. Interferon-based therapies are contraindicated (or at least not used) in KT patients, due to the risk of allograft rejection, its poor tolerability and the low rates of sustained virological response (SVR) achieved with these therapies. Nevertheless, the use of direct-acting antiviral drugs (DAAs) will certainly provide new opportunities for hepatitis C treatment in the KT setting. Here, we report the case of a KT recipient with decompensated cirrhosis who received antiviral therapy with sofosbuvir, simeprevir, and ribavirin during 24 weeks while awaiting liver transplantation. Hepatitis C was eradicated, and the patient was removed from the transplant list. Although there is no safety and efficacy data regarding the use of DAAs in the KT setting, this case suggests that KT recipients may benefit from the use of new antiviral drugs with high SVR rates and an excellent safety profile.

Introduction

Hepatitis C (HCV) is the leading cause of chronic liver disease in western world with approximately 170 million people infected. A wide range prevalence of HCV infection among hemodialysis (HD) patients is reported (1–90%), although currently these figures have fallen to 5% in the west world [1]. Survival rate of HCV-positive patients receiving HD is reduced as compared to HD patients without HCV infection [2]. Unfortunately, the applicability of antiviral therapy in this subpopulation is low (< 4%) due to the low rate of virological response achieved with interferon-based therapies in patients on HD and its poor tolerance [3].

HCV infection is highly prevalent in kidney transplant (KT) recipients (10% to 15%) and has a negative impact on post-transplant outcomes (higher risk of graft loss due to rejection and HCV-induced glomerular disease, lower survival rates, infections, post-transplant diabetes, cancer and rapid progression of liver fibrosis) [4]. Although the eradication of HCV infection is of paramount importance, KT recipients have always represented a difficult-to-treat population. Interferon-based therapies in these patients are associated with low rates of sustained virological response (SVR, 17–38%) and high risk of allograft dysfunction (51%) [5].

Currently, the use of direct-acting antiviral drugs (DAAs) has been a major step forward in the treatment of HCV infection [6]. The combination of sofosbuvir (SOF) and simeprevir (SMV) has shown high SVR rates (above 93%) in patients with mild or advanced fibrosis,

treatment-naïve or treatment-experienced patients [7]. The preliminary results from real-life cohorts using this regimen were recently presented [8]. In these studies, the combination of SOF and SMV with or without ribavirin (RBV) has also proved to be highly effective in patients with decompensated cirrhosis (SVR 75%) [8].

Here, we report the first case of a KT recipient with decompensated hepatitis C cirrhosis treated with all-oral antiviral combination.

Case report

This is a 48-year-old Caucasian female with chronic kidney disease (CKD) secondary to focal-segmental glomerulosclerosis and HCV-related cirrhosis (genotype 1b). While on HD (1999), interferon monotherapy was administered only for 3 months due to the onset of major depression. At that time, a liver biopsy showed signs of chronic hepatitis with fibrosis stage F1, and the hepatic venous pressure gradient measurement was 2 mmHg. Therefore, the patient underwent KT in 2000. Her clinical course progressed uneventfully during the following years. In 2012, she was referred to our Liver Unit because of the presence of signs of cirrhosis (platelet count 56 000/mm^3, total bilirubin 1.7 mg/dl, albumin 30 gr/L, INR 1.5), with a liver ultrasound showing a nodular liver with splenomegaly and ascites, and a transient elastography of 43.6 kPa. By the end of 2013, the patient was admitted to the hospital due to sepsis secondary to respiratory tract infection. In the context of infection, creatinine levels increased up to 1.4 mg/dl and liver function deteriorated with an increase in total bilirubin (3.9 mg/dl), INR (1.8), MELD (21 points), and Child–Pugh score (C, 10 points). Therefore, the patient was included into the waiting list to receive a liver transplantation (LT). To avoid hepatitis C recurrence after LT, it was decided to treat HCV infection with SOF 400 mg/day plus RBV 800 mg/day. Immunosuppression (IS) consisted on tacrolimus (1 mg/day). At week 4 of therapy, viral load was still detectable (38 IU/ml) and it was decided to add SMV 150 mg/day (at that time, there were no data on the lack of association between on-treatment viral kinetics and SVR rate). At week 8, viral load was undetectable and treatment

Table 1. Antiviral treatment summary.

Date	Week 0	Week 4	Week 8	Week 12	Week 24	Week 12-Post Treatment
Sofosbuvir (mg)	400	400	400	400	400	0
Ribavirin (mg)	800	600	400	600	600	0
Simeprevir (mg)	–	–	150	150	150	0
HCV-RNA (IU/ml)	426.000	38	0	0	0	0
AST (UI/l)	81	33	29	32	28	30
ALT (UI/l)	62	16	19	25	21	18
ALP (UI/l)	387	279	285	319	154	129
GGT (UI/l)	34	34	30	30	30	31
Total bilirubin (mg/dl)	2.8	1	0.7	0.9	1	0.6
Albumin (g/l)	25	25	27	41	40	42
Prothrombin time (%)	39	55	58	61	65	78
Creatinine (mg/dl)	1.4		1			1.1
GRF (ml/min per 1.73 m^2)	41	55	57	50	>60	>60
Proteinuria (gr/24 hs)	0.9			1.6		6.6
MELD score	20		10			7
Hemoglobin (gr/dl)	105	96	88	98	91	110
EPO (mcg/week)	–	–	100	100	0	0
Platelets ($\times 10^9$)	30 000	31 000	46 000	57 000	59 000	60 000
White blood cells ($\times 10^9$)	1400	1400	2900	1800	1500	1900
Tacrolimus (ng/ml)	4.7	4.1	6.2	9.2	5.1	7.3
Tacrolimus doses (mg/day)	1		1.5	2.5	2.5	2.5
TE (kPa)	43.2				38	

AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma glutamyl transferase; MELD score, model for end-stage liver disease; TE, transient elastography. EPO (darbepoetin alfa) 100 microg every 3 weeks was administrated. GFR (glomerular filtration rate) was calculated by the formula of CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration).

was maintained until 24 weeks completion. After 12 of weeks of treatment discontinuation, SVR was achieved. The tolerance to antiviral therapy was good, except by the presence of anemia requiring RBV dose reduction and the administration of darbepoetin (100 mcg/week). No major adjustments in IS were needed. Liver function significantly improved during antiviral therapy: ascites disappeared, and bilirubin and albumin levels normalized (Table 1). This allowed the patient to be removed from the waiting list.

Discussion

Currently, KDIGO guidelines recommend that all HCV-positive patients under HD and awaiting KT should be assessed to receive antiviral therapy [9].Viral eradication is associated with a lower risk of liver fibrosis progression, lower incidence of extra-hepatic manifestations of HCV, and lower risk of allograft rejection. However, the applicability of interferon-based therapies in the KT setting is low.

The evidence regarding the use of DAAs in this difficult-to-treat subpopulation is still scarce, but the results are encouraging. The efficacy and safety of different antiviral combinations have been studied in patient with cirrhosis with SVR rates ranging between 60% and 100% according to the genotype and degree of liver dysfunction (Table 2) [8, 10–17].

Data on the efficacy and safety of DAA combinations in patients with severe renal impairment or HD are still scarce. Although the safety and efficacy of SOF have not been established in patients with CKD, no dose adjustment is required for patients with mild-to-moderate renal impairment, but its use in patients with a glomerular filtration rate (GFR) <30 ml/min is not recommended. Recently, the results of 2 trials evaluating interferon-free combinations in patients on HD were communicated. The C-SURFER trial evaluated the combination of Grazoprevir (a protease inhibitor) and Elbasvir (a NS5A inhibitor) in patients CKD stages 4 or 5 (76% of the patients were on HD). Ninety-nine percent of the 116 patients receiving antiviral therapy achieved SVR12 [18], and the tolerance to antiviral therapy was good in these complicated patients. The RUBY-I trial studied the combination of Paritaprevir/Ritonavir/Ombitasvir and Dasabuvir (with or without RBV) in 20 patients with CKD stages 4 or 5 (65% on HD). Most common adverse event was anemia, especially in patient receiving RBV. SVR4 is 100% in 10 patients who have reach post-treatment week 4 [19].

Table 2. DAAs regimens in cirrhotic patients.

Therapeutic regimen	Respond to previous INF based therapy	*N* (cirrhotics)	Duration (weeks)	Genotype	Patient characteristics	SVR 12
OBV/PTV/RTV + DSV	TN/TE (TURQUOISE-II) [16]	208/172	12–24	1a/1b	CP-A	92% and 96% (12 and 24 weeks, respectively)
SOF/LDV ± RBV	TN (ION-1) [11]	66	12–24 ± RBV	1a/1b	CP-A	97% and 100% ± RBV (both 12 and 24)
	TE (ION-2) [10]	70	12–24 ± RBV	1a/1b	CP-A	82-86% 12 weeks(± RBV) and 100% 24 weeks (± RBV)
	TN/TE (SIRIUS) [17]	513	12-24 ± RBV	1	CP-A	96% and 97% (12 and 24 weeks, respectively)
	TN/TE (SOLAR-1) [8]	99	12–24 + RBV	1/4	CP-B/C (Score 7-12)	87% and 89% (12 and 24 weeks, respectively)
SOF + SMV	TN/TE (OPTIMIST-2) [13]	50/53	12	1	CP-A	88% and 79% (TN and TE, respectively)
SOF + SMV ± RBV	TN/TE (TARGET2.0) [8]	180	12	1	CP-A	87% and 75% (previous decompensation)*
SOF+DAC+RBV	TN/TE (ALLY-1) [15]	60	12	1-6	CP-A/B/C	92%, 94%, and 56% (CPA, B, and C, respectively).
Grazoprevir + Elbasvir ± RBV	TN/TE (C-WORTHY) [8]	123/48	12–18	1	CP-A	90% to 97% and 91% to 100% (TN and TE, respectively) †
SOF + RBV	(TARGET) [8]	26	12	2	MELD>10	81%
SOF + RBV	TN/TE (VALANCE) [12]	13/45	24	3	CP-A	92% and 60% (TN and TE, respectively)
SOF + DAC	TN and TE (ALLY-3) [14]	22/8	12	3	CP-A	73% and 63% (TN and TE, respectively)

TN, treatment naïve; TE, treatment experienced; CP, Child–Pugh.
*SVR4.
†Either ±RBV or 12/18 weeks.

In the kidney transplant setting, current treatment options are limited as well. Recently, the results of a real-life cohort including 15 KT recipients undergoing antiviral therapy with SOF-based regime during 12 weeks have been presented. Ten out of the 12 (83%) patients with available data achieved SVR12 and 2 patients relapsed. Two patients experienced worsening proteinuria, and no patient develops rejection [20]. These very preliminary data suggest that the efficacy of antiviral therapy in KT recipients would probably be similar to other patient populations. However, the use of these drugs will be affected by some characteristics related to KT itself: (i) kidney function might be abnormal in some patients, limiting the administration of SOF-based therapies, (ii) there are potential drug–drug interactions (DDI) between immunosuppressive drugs and some DAAs (cyclosporine should not be co-administrated with SMV, and in combination with Paritaprevir/Ritonavir, both Tac and cyclosporine doses need to be reduced). Dose adjustments must be frequently monitored with scheduled through levels, especially in KT patients which are at higher risk of allograft rejection as compared to LT recipients.

Despite the scarcity of information, interferon-free antiviral therapy seems to be an excellent approach. It might improve liver function, reverse clinical decompensations, and it might allow the withdrawal of the patients from the LT waiting list [6]. Clearly, the experience with DAAs in patients awaiting LT and KT recipients is limited. While awaiting the results of clinical trials, real-life experiences, like the one reported here, provide some light into the use of interferon-free combinations in difficult-to-treat populations in great need of HCV eradication and suggest that antiviral therapy with DAAs should be considered in KT recipients.

Authorship

MB and MC: has drafted the manuscript. MCL, XF, JMC and NE: has made the critical revision.

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