Early Acute Severe HCV Recurrence After Transplantation: From Universal Mortality to Cure

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Acute severe recurrence of hepatitis C virus (HCV) after solid organ transplant is associated with high mortality. Pegylated interferon and ribavirin are suboptimal in treatment of this severe form of recurrence. We report 4 cases of acute severe HCV recurrence (within 6 months after transplant), including 3 cases with fibrosing cholestatic hepatitis treated with sofosbuvir and ribavirin. All four patients achieved a rapid suppression of HCV RNA with a normalization of liver function tests within 4 weeks of starting therapy. All patients were HCV RNA negative at 12 weeks after stopping therapy. The combination was found to be safe as anemia was the only adverse effect, which developed in 2 patients (1 patient required blood transfusion, while another managed with erythropoietin). Sofosbuvir and ribavirin appear to be safe and efficacious in treatment of acute severe HCV recurrence after organ transplant. (J CLIN EXP HEPATOL 2017;7:28–32)

Hepatitis C virus (HCV)-related liver disease is the most common indication for liver transplantation in India and worldwide.^{1–3} Recurrence of hepatitis C is universal in patients who have circulating virus at the time of transplant.⁴ A proportion of patients (2–14%) who undergo liver or kidney transplant develop early severe recurrence (classically defined as within 6 months of transplant).^{5–7} The most aggressive form of HCV recurrence presents as cholestatic hepatitis (also called fibrosing cholestatic hepatitis [FCH]). Treatment of severe HCV recurrence with Pegylated Interferon (PEG-interferon) and ribavirin was associated with low response, high rate of adverse effects, and an associated mortality of up to 81%.^{8,9} However, with the introduction of sofosbuvir-based regimens, the outlook of severe HCV recurrence has dramatically changed. Recent reports suggest successful treatment of FCH with response rates and survival rates of 80–100% with the use of sofosbuvir-based regimens.^{10–14} We report 4 cases of acute severe HCV recurrence after transplantation including 3 with FCH (3 after liver transplant and 1 after kidney transplant),

and successful treatment of these patients with sofosbuvir and ribavirin.

CASE 1

Mrs. TQ, a 56-year-old female patient, presented with HCV-related end-stage liver disease in February 2015. She had decompensated liver disease with ascites, jaundice, and coagulopathy. Her Model for end stage liver disease (MELD) score was 25; she also gave a history of treatment with PEG-interferon and ribavirin in 2013 without response. She underwent living-related liver transplant (LRLT) for HCV-related liver disease in March 2015. Baseline HCV RNA was 3.2×10^6 IU/mL and HCV genotype was 1b (Table 1). Postoperative recovery was uneventful; she was discharged at the end of March with near normal liver function tests (LFTs). She was on triple immunosuppression with tacrolimus, mycophenolate, and tapering steroids. Steroids were stopped in May 2015.

In July 2015, she started having increasing aspartate aminotransferase (AST) and alanine aminotransferase (ALT). She presented to us again in August 2015 with jaundice, itching, and bilirubin of 2.92 mg/dL (normal < 1 mg/dL), AST 753 IU/L (normal 10–40 IU/L), ALT 629 IU/L (normal 10–40 IU/L), and gamma glutamyl transpeptidase (GGTP) 962 IU/L (normal < 50 IU/L). Doppler ultrasound of liver was normal and magnetic resonance cholangiopancreatography (MRCP) showed normal anastomosis with no dilatation of intrahepatic biliary radicals (IHBR). HCV RNA at presentation was $>10^8$ IU/mL. A liver biopsy was done that revealed 7 portal tracts, lobules showing disarray of lobular architecture, and prominent hepatocyte ballooning degeneration with several acidophilic bodies. Hepatocytes showed mild

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Abbreviations: HCV: hepatitis C virus; FCH: fibrosing cholestatic hepatitis; LRLT: living-related liver transplant; MMF: mycophenolate mofetil; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGTP: gamma glutamyl transpeptidase; MRCP: magnetic resonance cholangiopancreatography; IHBR: intrahepatic biliary radicals; LFT: liver function tests; POD: postoperative day; TND: target not detected

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Table 1 Baseline Characteristics.

Case	Age	Sex	MELD baseline	Genotype	HCV RNA (IU/mL)	Prior Rx (PEG IFN + RBV)	Immunosuppression
1	56	F	25	1b	$>10^8$	Yes	Tacrolimus + MMF + steroid
2	50	M	20	1a	$>10^8$	Yes	Tacrolimus + MMF + steroid
3	52	F	15	1a	2.4×10^7	No	Tacrolimus + MMF + steroid
4	50	M	NA (kidney transplant)	1b	2.5×10^5	No	Tacrolimus + MMF + steroid

Figure 1 (a) Apoptotic hepatocytes (blue arrowhead) with ballooning degeneration (H&E 40 $\times$), (b) marked ballooning degeneration of hepatocytes with cellular cholestasis (H&E 20 $\times$), (c) portal tract showing bile ductular reaction (yellow arrowhead) (H&E 40 $\times$), and (d) Masson's Trichrome stain showing prominent perisinusoidal fibrosis (MT 40 $\times$).

macrovesicular steatosis and focal cholestasis. Portal tracts showed mild to moderate predominantly mononuclear inflammatory infiltrate with prominent bile ductular reaction. Masson's trichrome showed increased perisinusoidal fibrosis (Figure 1a–d).

She was diagnosed with FCH and was started on sofosbuvir and ribavirin on 26 August 2015. At 4 weeks after starting treatment, her LFTs were normal. HCV RNA was negative at 4 weeks. Treatment was continued for 24 weeks. She had a normal LFT and a negative HCV RNA at 12 weeks after stopping therapy.

CASE 2

Mr. EH, a 50-year-old male patient, underwent LRLT at another center in June 2015 for HCV-related end-stage liver disease. His MELD score at transplantation was 20; he also gave a history of treatment with PEG-interferon in 2014,

which had to be stopped after 12 weeks due to side effects. His baseline HCV RNA at transplant was 10^5 IU/mL and genotype was 1a. He was on triple immunosuppression with tacrolimus, mycophenolate, and steroids. His tacrolimus levels were maintained between 8 and 11 in the immediate post-transplant period at the center where the transplant was performed. He was discharged on post-operative day (POD) 20; at the time of discharge his bilirubin was normal but AST and ALT were in the range of 200–300. One month after transplant, ALT rose further to 850. Subsequently, his tacrolimus dose was further increased at the primary center.

He presented to us on 30 July 2015 with jaundice and malaise. His bilirubin was 6.74 mg/dL, AST was 362 IU/L, ALT was 605 IU/L, and GGTP was 460 IU/L. His tacrolimus level was determined, which was 26 ng/mL (Target level 5–8 ng/mL); HCV RNA at this time was $>10^8$ IU/mL. Doppler ultrasound of the liver revealed normal

vasculature, normal portal flow, and resistive index of hepatic artery, with no intra hepatic biliary radical dilatation (IHBRD). MRCP was also done, which was normal. He underwent a liver biopsy that showed mild lobular disarray and prominent ballooning degeneration of hepatocytes with several apoptotic hepatocytes. Foci of lobular inflammation and prominence of Kupffer cell were seen. Portal tracts showed mildly increased mononuclear inflammatory infiltrate with occasional eosinophils. There was no significant endothelitis and ductulitis. MT stain showed no significant fibrosis (Figure 2a–d).

He was started on sofosbuvir and ribavirin on August 3, 2015. As his renal functions were deranged at the time of starting therapy, ribavirin was started at 400 mg per day (adjusted according to creatinine clearance). He was continued on mycophenolate and steroids; tacrolimus was withheld for a few days. At the end of first week after starting treatment, the kidney functions normalized, tacrolimus was reintroduced, and ribavirin dose was increased to 800 mg per day. LFTs became normal at 3 weeks after starting therapy; HCV RNA at 4 weeks was negative (Table 2). He maintained normal liver functions

Figure 2 (a) Liver biopsy showing lobular disarray with hepatocyte ballooning (H&E 10 $\times$), (b) ballooning degeneration of hepatocytes (H&E 20 $\times$), (c) relatively quiet portal tract with scanty lymphocytes (H&E 40 $\times$), and (d) focally prominent Kupffer cells (yellow arrowhead).

Table 2 Treatment Characteristics.

Case	HCV RNA Week 4	HCV RNA Week 24	SVR4	SVR12	Side effects	Intervention
1	<15	TND	Yes	Yes	No	None
2	TND	TND	Yes	Yes	No	None
3	546 IU/mL (3 weeks)	TND	Yes	Yes	Anemia	Blood transfusions, erythropoietin
4	TND	TND	Yes	Yes	Anemia	Erythropoietin

and renal functions throughout the 6 months of treatment. HCV RNA was negative at the end of treatment as well at 12 weeks after stopping treatment.

CASE 3

Mrs. NK, a 52-year-old female patient, underwent LRLT in March 2015 for HCV-related liver disease. Her MELD score at the time of transplant was 15. She gave no previous history of treatment for HCV. Her baseline HCV RNA at the time transplant was 2.1×10^4 IU/mL and genotype was 1a. Her postoperative recovery was uneventful, and she was sent back to her native country 6 weeks after transplant. She was on triple immunosuppression with tacrolimus, mycophenolate, and steroids; steroids were stopped by July 2015.

She presented back to our center in September 2015 with a history of jaundice and itching since 4 weeks. Her bilirubin at presentation was 3.6 mg/dL, AST was 245 IU/L, ALT was 109 IU/L, and GGTP was 1353 IU/L. Doppler of liver and MRCP were normal. HCV RNA was 2.4×10^7 IU/mL. She underwent a liver biopsy that showed perisinusoidal fibrosis with ballooning of hepatocytes and apoptotic cells. The portal inflammation was scanty and she had significant cholestasis. She was diagnosed as FCH and started on sofosbuvir 400 mg/day and ribavirin 1 g/day on 9 September 2015.

Her LFTs started improving; by the end of 3 weeks of treatment, her bilirubin had improved to 1.9 mg/dL, AST and ALT were normal, and GGTP was 377 IU/L. Her HCV RNA was 546 IU/mL at 3 weeks. She was sent to her country on treatment. At around 6 weeks of treatment, she was admitted in a hospital in her country because of severe fatigue and weakness. Her LFTs at admission were normal but hemoglobin was found to be 3.5. Ribavirin was stopped and she received 4 blood transfusions. Two weeks after this, ribavirin was added at a dose of 600 mg per day along with erythropoietin and iron supplements. She continued on this dose for a total of 24 weeks. At the end of treatment, her LFTs were normal and HCV RNA was negative. She achieved SVR 12 and maintained normal LFTs.

CASE 4

Mr. PPS, a 50-year-old male patient, underwent liver-related kidney transplant in May 2015. He was diagnosed

HCV positive at the time of transplant. His HCV RNA was 2.8×10^5 IU/mL at transplant and genotype was 1b. Liver functions at transplant were normal, and fibrosis assessment by transient elastography showed no fibrosis. There was no previous history of treatment with interferons. Renal functions were normal after kidney transplant, and he was discharged on POD 12.

He presented with jaundice and itching in September 2015. At the time of presentation, his bilirubin was 12.2 mg/dL, AST/ALT was 104/66 IU/L, and GGTP was 2254 IU/L. His renal functions were normal at presentation. He underwent a liver biopsy that showed features characteristic of FCH (minimal inflammation, hepatocyte ballooning, and dropout along with significant cholestasis and perisinusoidal fibrosis).

The patient was started on sofosbuvir 400 mg/day and ribavirin 1 g/day on October 8, 2015. At 4 weeks of treatment, the patient had a bilirubin of 2.6 with normal AST, ALT, and GGTP. HCV RNA was negative at 4 weeks. The patient had a drop in hemoglobin that was managed with erythropoietin and iron supplements; no blood transfusions were required. The patient also developed severe herpes zoster at 3 weeks after starting therapy. Tablet acyclovir was given for 2 weeks along with pain relief medications. At the end of 24 weeks of treatment, the patient had a normal LFT and RFT. HCV RNA was negative at end of treatment, at 4 weeks, as well as 12 weeks after stopping treatment.

DISCUSSION

Acute severe recurrence including FCH has been reported in 5–10% of the patients undergoing transplantation for HCV-related liver disease. Early HCV recurrence is a severe disease and invariably used to be fatal in the interferon era. Despite early diagnosis and timely treatment, the prognosis used to be grim. With the advent of Directly acting antivirals (DAAs), the treatment of this aggressive form of HCV disease has radically changed. We report 4 cases of acute severe recurrence (3 with FCH) that were successfully treated with sofosbuvir and ribavirin. To our knowledge, this is the first report from the Indian subcontinent on the use of DAAs in this disease.

FCH after liver transplant has been reported as early as in first month after liver transplant.¹⁵ The median time to

presentation of FCH has been reported as 7.6 months after transplant.⁷ In our series, all four cases presented within 6 months after transplant. Three of four patients had itching as a predominant symptom (all 3 with FCH had itching). The liver enzyme was cholestatic in 3 patients with FCH, and the fourth patient had predominantly hepatocellular injury with high AST/ALT. There was a precipitous drop in HCV RNA in all patients; 3 out of 4 patients had negative HCV RNA at 4 weeks. One patient had a low HCV RNA at 3 weeks (546 IU/mL, Case 3). All patients completed 24 weeks of therapy and achieved SVR12 after stopping therapy.

The most important finding in this series was that this regimen was very well tolerated. Only significant side effect in these patients was anemia. One patient had drop in hemoglobin to 3.5 g/dL requiring blood transfusions. However, this patient could not undergo surveillance for hemoglobin as advised as she had moved to her native country. Once diagnosed, she did very well with reduced dose ribavirin and erythropoietin combination and maintained good hemoglobin through the remaining therapy duration. Another patient had hemoglobin below 10 g/dL, but was managed with erythropoietin, iron supplements, and lower dose ribavirin. The other two patients did not develop significant anemia, and no erythropoietin was required for them. One patient at the start of therapy had high serum creatinine, which was ascribed to high tacrolimus levels. The renal dysfunction improved as tacrolimus dose was decreased. Normal renal functions were maintained throughout the duration of therapy.

Sofosbuvir and ribavirin combination has been used to treat FCH with a success rate of 80%.^{10,11} Recently, combination of sofosbuvir and daclatasvir or ledipasvir with or without ribavirin has been used in this condition with a 96–100% success rate.^{12–14} In our series, all patients achieved SVR 12 on 24 weeks treatment of sofosbuvir and ribavirin. We conclude that a combination of sofosbuvir and ribavirin for 24 weeks results in a high cure rate of severe HCV recurrence including FCH after solid organ transplant.

CONFLICTS OF INTEREST

The authors have none to declare.

REFERENCES

1. Merion RM. Current status and future of liver transplantation. *Semin Liver Dis.* 2010;30:411–421.
2. Verna EC, Brown Jr RS. Hepatitis C virus and liver transplantation. *Clin Liver Dis.* 2006;10:919–940.
3. Wadhawan M, Kumar A, Gupta S, et al. Post-transplant biliary complications: an analysis from a predominantly living donor liver transplant center. *J Gastroenterol Hepatol.* 2013;28(6):1056–1060.
4. Garcia-Retortillo M, Forns X, Feliu A, et al. Hepatitis C virus kinetics during and immediately after liver transplantation. *Hepatology.* 2002;35:680–687.
5. Narang TK, Ahrens W, Russo MW. Post-liver transplant cholestatic hepatitis C: a systematic review of clinical and pathological findings and application of consensus criteria. *Liver Transpl.* 2010;16:1228–1235.
6. Cimsit B, Assis D, Caldwell C, et al. Successful treatment of fibrosing cholestatic hepatitis after liver transplantation. *Transpl Proc.* 2011;43:905–908.
7. Satapathy SK, Sclair S, Fiel MI, et al. Clinical characterization of patients developing histologically-proven fibrosing cholestatic hepatitis C post-liver transplantation. *Hepatol Res.* 2011;41:328–339.
8. Calmus Y, Duvoux C, Pageaux G, et al. Treatment of recurrent HCV infection following liver transplantation: results of a multicenter, randomized, versus placebo, trial of ribavirin alone as maintenance therapy after one year of PegIFN alpha-2a plus ribavirin. *J Hepatol.* 2012;57:564–571.
9. Verna EC, Abdelmessih R, Salomao MA, et al. Cholestatic hepatitis C following liver transplantation: an outcome-based histological definition, clinical predictors, and prognosis. *Liver Transpl.* 2013;19:78–88.
10. Forns X, Charlton M, Denning J, et al. Sofosbuvir compassionate use program for patients with severe recurrent hepatitis C after liver transplantation. *Hepatology.* 2015;61:1485–1494.
11. Issa D, Eghtesad B, Zein NN, et al. Sofosbuvir and simeprevir for the treatment of recurrent hepatitis C with fibrosing cholestatic hepatitis after liver transplantation. *Int J Org Transplant Med.* 2016;7(1):38–45.
12. Leroy V, Dumortier J, Coilly A, et al. Efficacy of sofosbuvir and daclatasvir in patients with fibrosing cholestatic hepatitis C after liver transplantation. *Clin Gastroenterol Hepatol.* 2015;13:1993–2001.
13. Forns X, Mutimer D, Manns M, et al. Ledipasvir/sofosbuvir with ribavirin for the treatment of fibrosing cholestatic hepatitis C after liver transplantation. *J Hepatol.* 2015;62:S623.
14. Manns M, Samuel D, Gane EJ, et al. Ledipasvir and sofosbuvir plus ribavirin in patients with genotype 1 or 4 hepatitis C virus infection and advanced liver disease: a multicentre, open-label, randomised, phase 2 trial. *Lancet Infect Dis.* 2016;16(6):685–697.
15. Murakami K, Kawagishi N, Ishida K, et al. Fibrosing cholestatic hepatitis developing within one month after living donor liver transplantation for chronic hepatitis C-related cirrhosis: a case report. *Transpl Proc.* 2014;46:995–998.