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CASE REPORT

An HCV-positive recipient of an HCV-positive donor liver successfully treated before and immediately after liver transplant with daclatasvir, sofosbuvir, and ribavirin

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Key Clinical Message

This case suggests that initiation of HCV therapy immediately after liver transplantation with well-tolerated, all-oral regimens may achieve a virologic cure in HCV-positive recipients, thus preventing post-transplant HCV recurrence and associated disease progression. This strategy may broaden utilization of HCV-positive donor livers, potentially including HCV-negative transplant recipients.

Keywords

Daclatasvir, hepatitis C, liver transplantation, sofosbuvir.

Introduction

Hepatitis C virus (HCV) infection is a leading cause of chronic liver disease and a primary indication for liver transplant (LT) in Europe and the United States [1–3]. Recurrence of HCV infection is nearly universal among LT recipients with detectable HCV RNA at transplant and often leads to accelerated disease progression. Similarly, the use of HCV-positive donor livers in uninfected transplant recipients inevitably results in persistent infection [4]; consequently, HCV-positive donor livers are generally restricted to HCV-positive patients.

Recurrence of HCV infection after LT is associated with accelerated progression of liver fibrosis in the graft; 20–40% of patients with post-transplant HCV recurrence progress to cirrhosis within 5 years [5], compared with <5% of HCV-infected patients before LT [6]. In a recent study of nearly 60,000 LT recipients, rates of patient survival at 1, 5, and 10 years after transplant among HCV-positive versus HCV-negative patients were 83%, 63%, and 46% versus 84%, 70%, and 53%, respectively. Graft survival was 87%, 68%, and 51% versus 88%, 75%, and 54%, respectively [5], implying somewhat inferior patient and graft survival rates in HCV-positive recipients than HCV-negative ones.

Successful eradication of HCV infection before or after LT is vital to optimize patient outcomes. Clearance of the infection before LT is preferable to avoid the complications of treating transplant recipients; however, the timing of LT is driven primarily by clinical urgency and the availability of a donor liver, and a full course of treatment cannot always be completed before LT [7]. Therapy for HCV infection of LT recipients has improved markedly with the advent of all-oral combinations of direct-acting antivirals (DAAs). Studies have focused on patients with established post-transplant recurrence; in this situation, sustained virologic response (SVR; HCV RNA < lower limit of quantitation, target detected or target not detected) rates exceeding 90% have been reported with several oral regimens [8–11]. However, initiation of preemptive therapy immediately after LT with the aim of preventing HCV infection recurrence has not been studied in detail.

In the recent ALLY-1 study, 94% of patients with post-transplant recurrence achieved SVR12 following 12 weeks of treatment with the pangenotypic combination of daclatasvir (DCV; NS5A inhibitor), sofosbuvir (SOF; NS5B inhibitor), and ribavirin (RBV) [8]. The results suggested that this regimen was particularly useful in this setting, with a favorable safety profile and minimal drug–drug interactions with tacrolimus or cyclosporine [12–14]. This study also included a cohort of 60 patients with advanced cirrhosis and an anticipated need for LT. Among this group, three patients had treatment interrupted for LT and resumed treatment for a further 12 weeks immediately after LT; all three achieved SVR12. One of these patients received a transplant, an HCV-positive donor liver, after only 1 day of therapy. As in the other patients with treatment interrupted for LT, HCV RNA levels declined rapidly and SVR12 was achieved. This patient represents the first successful use of DCV, SOF, and RBV before and immediately after LT with an HCV-positive donor liver. This report describes this patient in detail and the potential implications of the findings with respect to LT in the setting of HCV infection.

Case History

The patient is a 63-year-old woman with a medical history of Child–Pugh class B cirrhosis due to HCV genotype 1a infection and a 2.4 × 1.8 cm hepatocellular carcinoma (HCC) in segment VIII seen by triphasic computed tomography scan. There was no evidence of vascular invasion or extrahepatic metastasis. She was listed for LT and treated with microwave and cryoablation of HCC with a satisfactory radiographic response. The patient was a prior null responder to peginterferon/RBV therapy. She enrolled in a phase 3 clinical trial of DCV + SOF + RBV for 12 weeks in patients with cirrhosis who may require LT. Patients with HCC within Milan criteria for transplant were eligible to participate.

At baseline, her biologic Model for End-Stage Liver Disease (MELD) score was 12 based on serum creatinine of 0.76 mg/dL, total bilirubin of 1.3 mg/dL, and international normalized ratio (INR) of 1.44. Serum alanine aminotransferase (ALT) was 54 IU/L, aspartate aminotransferase (AST) was 93 IU/L, albumin was 3.2 g/dL, and alpha-fetoprotein was 14.4 ng/mL. HCV RNA at baseline was 6.2 $\log_{10}$ IU/mL. Due to the patient's history of HCC, she was also listed with HCC exception points for LT.

Investigations and Treatment

The patient started treatment with DCV 60 mg daily, SOF 400 mg daily, and RBV 600 mg daily. On the same day (day 1), a potential liver graft became available from a 21-year-old donor who was chronically infected with HCV genotype 1a. Biopsy of the donor liver indicated mild perivenular and periportal fibrosis and minimal steatosis. HIV nucleic acid testing of the donor was negative. The patient was aware that the liver allograft was from an HCV-positive donor and understood the possible risks and benefits of the transplant; informed consent was obtained before the surgery. Pathological examination of the explanted liver confirmed complete ablation of HCC with no vascular or lymphatic invasion.

The initial immunosuppressive regimen comprised tacrolimus with a goal plasma trough level of 8–10 ng/mL, mycophenolate mofetil 1 gm twice daily, and prednisone taper. Other concomitant medications included furosemide, pantoprazole, valganciclovir, and lorazepam. The patient received blood transfusions intraoperatively. Treatment with DCV, SOF, and RBV was resumed within 1 day after transplant, and 12 weeks of treatment were completed. On the fourth day of treatment, the dose of RBV was reduced to 400 mg daily due to grade 1 anemia. Moderate hepatic artery stenosis based on noninvasive resistive indices was observed and treated with aspirin.

Outcome and Follow-up

Serum HCV RNA was 2.9 $\log_{10}$ IU/mL on the day after LT, below the lower limit of detection (<25 IU/mL) within 2 weeks, and undetectable by week 4. HCV RNA remained undetectable through the end of treatment and post-treatment follow-up (Table 1). Liver biochemistries normalized by week 6 (AST, 18 IU/L; ALT, 24 IU/L; alkaline phosphatase, 84 IU/L; total bilirubin, 0.3 mg/dL; albumin, 4.9 g/dL); at the 5-month follow-up visit, total bilirubin was 0.2 mg/dL, AST was 17 IU/mL, ALT was 22 IU/mL, and alkaline phosphatase was 105 IU/mL.

Discussion

Historically, recurrent HCV infection after LT has been difficult to manage and is associated with a high risk of accelerated disease progression in the grafted liver, potentially leading to graft failure, retransplant, or death. Treatment with interferon-based regimens has provided generally low efficacy and is difficult to manage due to frequent adverse events (AEs). The recent emergence of interferon-free, combinations of DAAs has been of enormous benefit in this regard [15]; however, preemptive postoperative treatment to prevent HCV infection recurrence has not been explored extensively with oral DAA regimens. The potential benefits are substantial, such as prevention of disease progression in the grafted liver, reduced need for retransplantation, and simplified patient

Table 1. Clinical, biochemical, and virologic features before and after transplant according to DCV + SOF + RBV treatment.

Parameter	Baseline	Post-transplant day 1	Week 4	Week 12	Post-treatment week 4	Post-treatment Week 24
HCV RNA, IU/mL	log 6.2	log 2.9	Undetectable	Undetectable	Undetectable	Undetectable
AST, IU/L	93	87	24	19	20	17
ALT, IU/L	54	71	43	22	35	22
Total bilirubin, mg/dL	1.3	0.7	0.3	0.3	0.2	0.2
Alkaline phosphatase, IU/L	208	68	118	69	107	105
Albumin, g/dL	3.2	4.2	4.7	4.7	4.5	3.7
INR	1.44	1.07	0.95	0.95	0.99	0.9
Hemoglobin, g/dL	13.5	11.2	10.4	9.5	10.3	10.8
Creatinine, mg/dL	0.76	0.57	1.08	1.41	1.46	1.26

Undetectable, HCV RNA <LLOQ, TND.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; DCV, daclatasvir; HCV, hepatitis C virus; INR, international normal ratio; LLOQ, lower limit of quantitation; RBV, ribavirin; SOF, sofosbuvir; TND, target not detected.

care. Previously, evaluation of preemptive therapy with peginterferon showed no benefits with respect to HCV infection recurrence, patient survival, or graft survival, and patients experienced frequent treatment-related AEs [16]. However, the greatly improved efficacy and safety profiles that oral DAA regimens have shown in treatment of post-transplant recurrence suggest that early initiation of therapy should be revisited.

Here, we report a novel approach of starting antiviral therapy before and continuing immediately after LT. The combination of DCV + SOF with RBV was highly efficacious, despite the patient being viremic at transplant and receiving an HCV-positive donor liver. Viral load decreased rapidly, becoming undetectable by week 4 after transplant and remaining undetectable through 24 weeks of post-treatment follow-up. There was no need to adjust the immunosuppressive regimen due to HCV treatment, and treatment-related AEs were limited to mild anemia that resulted in reduction of the RBV dose.

Two other case reports of HCV treatment immediately after LT are consistent with our findings. One patient achieved SVR after treatment with SOF and RBV before, during, and after transplant [17]; two patients co-infected with HIV and HCV were treated successfully with SOF + RBV and SOF + DCV, respectively, with treatment initiated during the anhepatic phase [18]. Neither of these reports indicated the HCV serostatus of the liver donors, but both support the concept that early initiation of therapy after transplant can be beneficial. However, with some regimens, drug–drug interactions between ritonavir or HCV NS3 protease inhibitors and calcineurin inhibitors may preclude treatment initiation until immunosuppressive regimens have been stabilized [14]. Differences in regimen safety profiles may also influence utility during the early post-transplant phase. Further study is needed to establish the optimal timing for initiating treatment after LT with each available regimen.

This approach reduces the need to strategize whether and when HCV therapy should be initiated in patients listed for LT. Potentially, patients can initiate HCV treatment while awaiting a liver, and treatment can be resumed immediately after transplant, without experiencing HCV recurrence, if the treatment duration pretransplant is considered insufficient. A recent study suggested that suppression of HCV RNA before transplant improves survival [19]; however, some transplant groups have been cautious about initiating treatment before transplant because of concern that treatment may reduce MELD scores and the associated priority for receiving a liver, potentially extending the risk of experiencing life-threatening hepatic events. Our data do not address this consideration; further study is needed to assess the risk/benefit of treatment in patients listed for transplant.

A key aspect of the patient described in this report is the achievement of SVR12 despite receiving a liver from an HCV-positive donor. Although data suggest little difference in outcomes for HCV-positive patients receiving HCV-positive versus HCV-negative donor livers [5, 20], a higher proportion of HCV-positive than HCV-negative donor livers are not transplanted. From 2002 to 2012, the proportion of unused HCV-negative livers was about 9% in most years, but the annual proportion of unused HCV-positive livers was generally twofold to threefold higher [21]. Furthermore, HCV-positive donor livers are seldom used in HCV-negative recipients to avoid infecting the patient during transplant. However, if the result achieved in the present case can be confirmed in a larger prospective study, this may have the effect of increasing the pool of usable donor livers. Ultimately, eliminating the risk of establishing chronic HCV infection after transplant may open the door to use of HCV-positive donor livers in HCV-negative recipients.

With initiation of treatment immediately after transplant, the chosen therapy should be effective for treating

the HCV genotypes infecting both the donor and the recipient. In this regard, the pangenotypic combination of DCV with SOF and RBV can theoretically be used to treat all HCV infections; most other DAA regimens studied in the post-transplant setting have restricted genotypic coverage.

Overall, these results highlight several topics that require prospective study in larger patient cohorts:

1 What is the optimal paradigm for treatment with oral regimens to consistently achieve SVR12 in patients receiving HCV-positive donor livers?
2 Do HCV resistance polymorphisms that may be carried by an HCV-positive donor liver have any impact on treatment efficacy?
3 Does the duration of therapy before LT have an impact on treatment efficacy?
4 Is early initiation of therapy after transplant compatible with the range of postoperative complications that are typically encountered?

In conclusion, this case introduced the concept that treatment with DCV + SOF + RBV before and continuing immediately after LT can prevent HCV infection recurrence, allowing the patient to achieve SVR, even with an HCV-positive donor liver. The results suggest several topics for prospective studies to confirm these findings and optimize treatment parameters to achieve the greatest benefit for patients.

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Authorship

FP, EL, JAG, JG, KS, and ESS were all contributors to the study design/conception, and data acquisition, analysis and interpretation.

Conflict of Interest

F. Poordad served on advisory committees or review panels for Abbott, Achillion, Bristol-Myers Squibb, Inhibitex, Boehringer Ingelheim, Pfizer, Genentech, Idenix, Gilead, Merck, Vertex, Salix, Janssen, and Novartis and received grant/research support from Abbott, Anadys, Achillion, Bristol-Myers Squibb, Boehringer Ingelheim, Genentech, Idenix, Gilead, Merck, Pharmasset, Vertex, Salix, Tibotec/Janssen, and Novartis. E. Lawitz served on advisory committees or review panels for AbbVie, Achillion, BioCryst, Biotica, Enanta, Idenix, Janssen, Merck, Novartis, Santaris, Theravance, and Vertex; received grant/research support from AbbVie, Achillion, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Idenix, Intercept, Janssen, Merck, Novartis, Presidio, Roche, Santaris, and Vertex; and served as a speaker for Gilead, Kadmon, Merck, and Vertex. J. Gutierrez served on advisory committees or review panels for AbbVie, Bristol-Meyers Squibb, Gilead, and Janssen and served as a speaker for AbbVie, Bristol-Meyers Squibb, Gilead, and Janssen. J. Guerrero and K. Speeg have no conflicts of interest to declare. E. Swenson is an employee of Bristol-Myers Squibb.

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